Supplemental Table 1

AALL0434 Treatment Plan from Winter SS, Dunsmore KP, Devidas M, et al. Improved Survival for Children and Young Adults With T-Lineage Acute Lymphoblastic Leukemia: Results From the Children's Oncology Group AALL0434 Methotrexate Randomization. *J Clin Oncol.* 2018;36(29):2926-2934.

Phase and Regimen	Drug	Dose	Schedule
Induction all arms*	IT cytarabine	Age adjusted†	At diagnostic lumber puncture or day 1
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 22
	Prednisone	30 mg/m^2/dose twice a day	Days 1-28
	Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
	Pegaspargase	2,500 U/m^2	Day 4, 5, or 6
	IT-MTX	Age adjusted†	Days 8, 29 (CNS3: + days 15, 22)
Consolidation (arms A and C)	Cyclophosphamide	1,000 mg/m^2	Days 1, 29
	Cytarabine	75 mg/m^2	Days 1-4, 8-11, 29-32, 36-39
	Mercaptopurine	60 mg/m^2	Days 1-14, 29-42
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 15, 22, 43, 50
	Pegaspargase	2,500 U/m^2	Days 15, 43
	IT-MTX	Age adjusted†	Days 8, 15, 22,29 (HR); days 1, 8 (CNS3); days 1, 8, 15, 22 (all others)
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 15 (arm A)
	TRT§	24 Gy (persistent disease only)	Completed before day 15
Consolidation + nelarabine (arms B and D)	Cyclophosphamide	1,000 mg/m^2	Days 8, 50
	Cytarabine	75 mg/m^2	Days 8-11, 15-18, 50-53, 57-60
	Mercaptopurine	60 mg/m^2	Days 8-21, 50-63
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 22, 29, 64, 71
	Pegaspargase	2,500 U/m^2	Days 22, 64
	IT-MTX	Age adjusted†	Days 15, 22, 57, 64 (omit day 22 for CNS3)
	Nelarabine	650 mg/m^2	Days 1-5, 43-47
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 22 (arm B)
	TRT§	24 Gy (persistent disease only)	Completed before day 15
Interim maintenance C-MTX (arms A and B)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Every 10 days × 5 doses/days 1, 11, 21, 31, 41
	IV-MTX‖	100 mg/m^2	Every 10 days × 5 doses/days 1, 11, 21, 31, 41
	Pegaspargase	2,500 U/m^2	Days 2, 22
	IT-MTX	Age adjusted†	Days 1, 31
Interim maintenance HDMTX (arms C and D)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 15, 29, 43
	IV-MTX	5,000 mg/m^2	Days 1, 15, 29, 43
	Leucovorin	15 mg/m^2	42, 48, 52 hours post-IV-MTX
	Mercaptopurine (oral)	25 mg/m^2	Days 1-56
	IT-MTX	Age adjusted†	Days 1, 29
Delayed intensification (arms A and C)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 43, 50
	Pegaspargase	2,500 U/m^2/dose	Day 4 or 5 or 6 and 43
	Dexamethasone	5 mg/m^2/dose twice a day	Days 1-7, 15-21
	Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
	Cytarabine	75 mg/m^2/d	Days 29-32, 36-39
	Cyclophosphamide	1,000 mg/m^2	Day 29
	Thioguanine	60 mg/m^2/d	Days 29-42 (omit for patients receiving CRT)
	IT-MTX	Age adjusted†	Days 1, 29, 36
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 50 (arm C)
Delayed intensification + nelarabine	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 50
	Pegaspargase	2,500 U/m^2/dose	Day 4 or 5 or 6 and 50
	Dexamethasone	5 mg/m^2/dose twice a day	Days 1-7, 15-21
	Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
	Cytarabine	75 mg/m^2/d	Days 36-39, 43-46
	Cyclophosphamide	1,000 mg/m^2	Day 36
	Thioguanine	60 mg/m^2/d	Days 36-49 (omit for patients receiving CRT)
	IT-MTX	Age adjusted†	Days 1, 36, 43
	Nelarabine	650 mg/m^2	Days 29-33
	CRT‡	12 Gy (18 Gy for CNS3)	Start on day 50 (arm D)
Maintenance¶ (12-week cycles)	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 29, 57
	Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 29-33, 57-61
	Mercaptopurine (oral)	75 mg/m^2/d	Daily/days 1-84
	MTX (oral)	20 mg/m^2/dose	Weekly
	IT-MTX	Age adjusted†	Days 1 (and 29 first four cycles; LR only)
Maintenance + nelarabine¶	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 57
	Prednisone	20 mg/m^2/dose twice a day	Days 1-5, 57-61
	Mercaptopurine (oral)	75 mg/m^2/d	Days 1-28, 36-84
	MTX (oral)	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50, 57, 64, 71/weekly—omitted while taking nelarabine
	IT-MTX	Age adjusted†	Day 1
	Nelarabine	650 mg/m^2	Days 29-33 (first three cycles arms B and D)

NOTE. Treatment arms: A (C-MTX), B (C-MTX + nelarabine), C (HDMTX), D (HDMTX + nelarabine).

Abbreviations: C-MTX, Capizzi-style escalating intravenous methotrexate; CRT, cranial radiation therapy; HDMTX, high-dose methotrexate; HR, high risk; IT, intrathecal; IV, intravenous; LR low risk; MTX, methotrexate; TRT, testicular radiation therapy.

*Induction failure (M3 at day 29) begin arm D consolidation as soon as possible. IT therapy is not held during the concomitant administration of CRT.

†IT cytarabine: 1-1.99 years, 30 mg; 2-2.99 years, 50 mg; ≥ 3 years, 70 mg. IT-MTX: 1-1.99 years, 8 mg; 2-2.99 years, 10 mg; 3-8.99 years, 12 mg; ≥ 9 years, 15 mg.

‡CNS1 or 2: 1.5 Gy/d × eight fractions; CNS3 in 1.8 Gy/d × 10 fractions for intermediate risk and HR participants only.

§For biopsy-proven, persistent disease only: 2 Gy/d for 12 fractions.

‖IV-MTX: 100 mg/m^2 (dose escalated by 50 mg/m^2 every 10 days for a total of five doses, adjusted for toxicity).

¶Total duration of treatment from start of interim maintenance: female patients with T-cell acute lymphoblastic leukemia, 2 years; male patients with T-cell acute lymphoblastic leukemia, 3 years.

Supplemental Table 2: **AALL1231 Treatment summary** adapted from Teachey DT, Devidas M, Wood BL, et al. Children's Oncology Group Trial AALL1231: A Phase III Clinical Trial Testing Bortezomib in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia and Lymphoma. *J Clin Oncol*. 2022:JCO2102678.

Phase and Regimen	Drug	Dose	Schedule
Induction Arm A	IT cytarabine	Age adjusted*	At diagnostic LP OR Day 1
No Bortezomib Arm	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 22
	Dexamethasone	3 mg/m^2/dose twice a Day	Days 1-28
	Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
	Pegaspargase	2,500 units/m^2	Days 4, 18
	IT-MTX	Age adjusted*	Days 8, 29 (CNS3: + Days 15, 22)
Induction Arm B	Bortezomib	1.3 mg/m^2	Days 1, 4, 8, 11
Bortezomib Arm	IT cytarabine	Age adjusted*	At diagnostic LP OR Day 1
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 22
	Dexamethasone	3 mg/m^2/dose twice a Day	Days 1-28
	Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
	Pegaspargase	2,500 units/m^2	Days 4, 18
	IT-MTX	Age adjusted*	Days 8, 29 (CNS3: + Days 15, 22)
Consolidation	Cyclophosphamide	1,000 mg/m^2	Days 1, 29
All patients	Cytarabine	75 mg/m^2	Days 1-4, 8-11, 29-32, 36-39
	Mercaptopurine (oral)	60 mg/m^2	Days 1-14, 29-42
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 15, 22, 43, 50
	Pegaspargase	2,500 units/m^2	Days 15, 43
	IT-MTX	Age adjusted*	Days 1, 8, 15, 22 (Omit Days 15, 22 for CNS3)
	TRT#	24 Gy (persistent disease only)	Completed before end of phase
Interim maintenance C-MTX@	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 11, 21, 31, 41
All patients	IV-MTX†	100 mg/m^2	Days 1, 11, 21, 31, 41
	Pegasparagase	2,500 units/m^2	Days 2, 22
	IT-MTX	Age adjusted*	Days 1, 31
Interim maintenance HDMTX@	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 15, 29, 43
IR only	IV-MTX	5,000 mg/m^2	Days 1, 15, 29, 43
	Leucovorin	15 mg/m^2	42, 48, 54 hours post IV-MTX
	Mercaptopurine (oral)	25 mg/m^2	Days 1-56
	IT-MTX	Age adjusted*	Days 1, 29
Intensification Block 1@	Dexamethasone	10mg/m^2/dose twice a day	Days 1-5
VHR only	IV-MTX	5,000 mg/m^2	Day 1
	Leucovorin	15 mg/m^2	42, 48, 54 hours post IV-MTX
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 6
	Cyclophosphamide	200 mg/m^2 Every 12 hours	Days 2-4 (5 doses)
	Cytarabine	2000 mg/m^2 Every 12 hours	Day 5 (2 doses)
	Pegaspargase	2,500 units/m^2	Day 6
	IT-MTX/HC/ARAC	Age adjusted*	Day 1
	Filgrastim	5 mcg/kg	Daily from Day 7 until WBC >3000/μl

Intensification Block 2@	Dexamethasone	10mg/m^2/dose twice a day	Days 1-5
VHR only	IV-MTX	5,000 mg/m^2	Day 1
	Leucovorin	15 mg/m^2	42, 48, 54 hours post IV-MTX
	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 6
	Ifosfamide	800 mg/m^2 Every 12 hours	Days 2-4 (5 doses)
	Mesna	300 mg/m^2	0, 4, 8 hours post Ifosfamide
	Daunorubicine	30 mg/m^2	Day 5
	Pegaspargase	2,500 units/m^2	Day 6
	IT-MTX/HC/ARAC	Age adjusted*	Day 1
	Filgrastim	5 mcg/kg	Daily from Day 7 until WBC >3000/μl
Intensification Block 3@	Dexamethasone	10mg/m^2/dose twice a day	Days 1-5
VHR only	Cytarabine	2,000 mg/m^2 Every 12 hours	Days 1-2 (4 doses)
	Etoposide	100 mg/m^2 Every 12 hours	Days 3-5 (5 doses)
	Pegaspargase	2,500 units/m^2	Day 6
	IT-MTX/HC/ARAC	Age adjusted*	Day 5
	Filgrastim	5 mcg/kg	Daily from Day 7 until WBC >3000/μl
Delayed intensification Arm A	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 43, 50
No Bortezomib Arm	Pegaspargase	2,500 units/m^2/dose	Day 4, 18, 43
	Dexamethasone	5 mg/m^2/dose twice a Day	Days 1-7, 15-21
	Doxorubicin	25 mg/m^2/Day	Days 1, 8, 15
	Cytarabine	75 mg/m^2/Day	Days 29-32, 36-39
	Cyclophosphamide	1,000 mg/m^2	Day 29
	Thioguanine (oral)	60 mg/m^2/Day	Days 29-42
	IT-MTX	Age adjusted*	Days 1, 29, 36
Delayed intensification Arm B	Bortezomib	1.3 mg/m^2	Days 1, 4, 15, 18
Bortezomib Arm	Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 43, 50
	Pegaspargase	2,500 units/m^2/dose	Day 4. 18, 43
	Dexamethasone	5 mg/m^2/dose twice a Day	Days 1-7, 15-21
	Doxorubicin	25 mg/m^2/Day	Days 1, 8, 15
	Cytarabine	75 mg/m^2/Day	Days 29-32, 36-39
	Cyclophosphamide	1,000 mg/m^2	Day 29
	Thioguanine (oral)	60 mg/m^2/Day	Days 29-42
	IT-MTX	Age adjusted*	Days 1, 29,36
Maintenance‡ (12-week cycles)	Vincristine	1.5 mg/m^2 (2 mg max)	Days 1, 29, 57
All patients	Dexamethasone	3 mg/m^2/dose twice a Day	Days 1-5, 29-33, 57-61
	Mercaptopurine (oral)	75 mg/m^2/Day	Daily/Days 1-84
	Methotrexate (oral)	20 mg/m^2/dose	Weekly (Omit Day 1. Omit Day 29 for first four cycles if SR and first two cycles if IR).
	IT-MTX	Age adjusted*	Day 1 (and Day 29 first 4 cycles if SR and Day 29 first 2 cycles if IR)
	CRT##	12 Gy for VHR CNS1/2 T-ALL 18 Gy for CNS3 T-ALL and T-LL	First cycle of maintenance

Supplement #3 Number of Lumbar Punctures by Treatment Group

Study AALL0434

Risk Group	LR	LR	LR	LR	IR	IR	IR	IR	IR	IR	IR	IR	HR	HR	HR	HR	HR	HR	HR	HR
Treatment Arm	A	A	C	C	A	A	B	B	C	C	D	D	A	A	B	B	C	C	D	D
Sex	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Total LP+ ITC	29	25	29	25	25	21	25	21	25	21	25	21	25	21	25	21	25	21	25	21

Study AALL1231

Risk Group	SR	SR	SR	SR	IR	IR	IR	IR	VHR	VHR	VHR	VHR
Treatment Arm	A	A	B	B	A	A	B	B	A	A	B	B
Sex	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Total LP+ITC	29	25	29	25	29	25	29	25	28	24	28	24

*Neither LR on AALL0434 or SR on AALL1231 received pCRT

*Only CNS-3 IR pts on AALL1231 received CRT (18 Gy during 1st 4 weeks of Maintenance

*Patients on Arms A and B on AALL0434 received CRT in Consolidation

*Patients on Arms C and D on AALL0434 received CRT in Delayed Intensification

*VHR patients on AALL1231 received CRT during first 4 weeks of maintenance

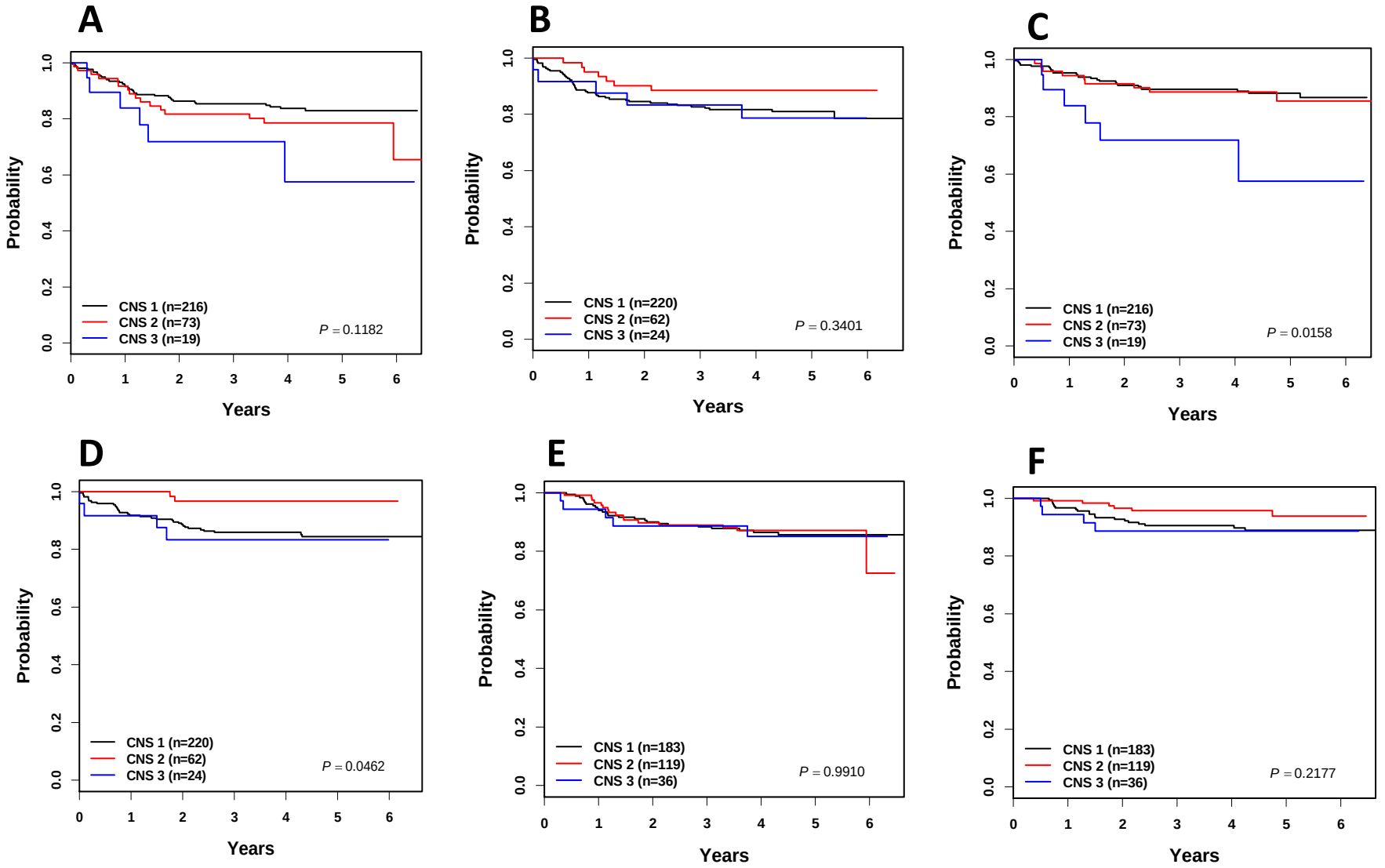
*VHR patients on AALL1231 received Triple Intrathecal Therapy three times, once with each intensification block

Supplemental Table 4

Multivariable Cox regression analysis on EFS

	Hazard Ratio and 95%CI	P-value
Age	1.00 (0.98-1.02)	0.591
sex (ref=male)	1.16 (0.91-1.46)	0.227
Race(ref=white)-black	1.02 (0.75-1.40)	0.891
-other	1.08 (0.70-1.66)	0.728
Ethnicity(ref=Not Hispanic or Latino)	1.18 (0.86-1.63)	0.300
WBC(ref=<50k/ul)	1.47 (1.17-1.84)	0.001
MRD EOI(ref=<0.01%)	2.73 (2.20-3.40)	<0.0001
CNS Status (ref=CNS 1)		
CNS 2	1.04 (0.80-1.37)	0.759
CNS 3	1.80 (1.28-2.52)	0.001

Supplement 5: AALL1231 EFS and OS by treatment arm and CNS Status.



(A) Arm A; Without Bortezomib; 4-year EFS: CNS-1, 2 and 3 (83.7%±3.0%, 78.6%±5.8%, 57.5%±18.7%), p=0.118 (B) Arm B; With Bortezomib; 4-year EFS: CNS-1, 2 and 3 (81.8%±3.1%, 88.5%±5.0%, 78.7%±9.4%), p=0.34 (C) Arm A; Without Bortezomib; 4-year OS: CNS-1, 2 and 3 (89.6%±2.5%, 88.7%±4.5%, 71.9%±17.1%), p=0.0158 (D) Arm B; With Bortezomib; 4-year OS: CNS-1, 2 and 3 (85.9%±2.8%, 96.7%±2.8%, 83.3%±8.8%), p=0.0462 (E) Intermediate Risk (IR) patients only; Overall 4-year EFS: CNS-1, 2, and 3 (86.5%±3.0%, 87.1%±3.7%, 85.2%±7.5%), p=0.99 (F) Intermediate Risk (IR) patients only; Overall 4-year OS: CNS-1, 2, and 3 (90.6%±2.6, 95.7%±2.2%, 88.7%±6.8%), p=0.218.

Activated: 01/22/07
Closed: 7/25/14
Version Date: 03/24/16
Amendment: 11

CHILDREN'S ONCOLOGY GROUP

AALL0434

Intensified Methotrexate, Nelarabine (Compound 506U78; IND # 52611) and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia (ALL) or T-cell Lymphoblastic Lymphoma

A Groupwide Phase III Study

IND sponsor: National Cancer Institute

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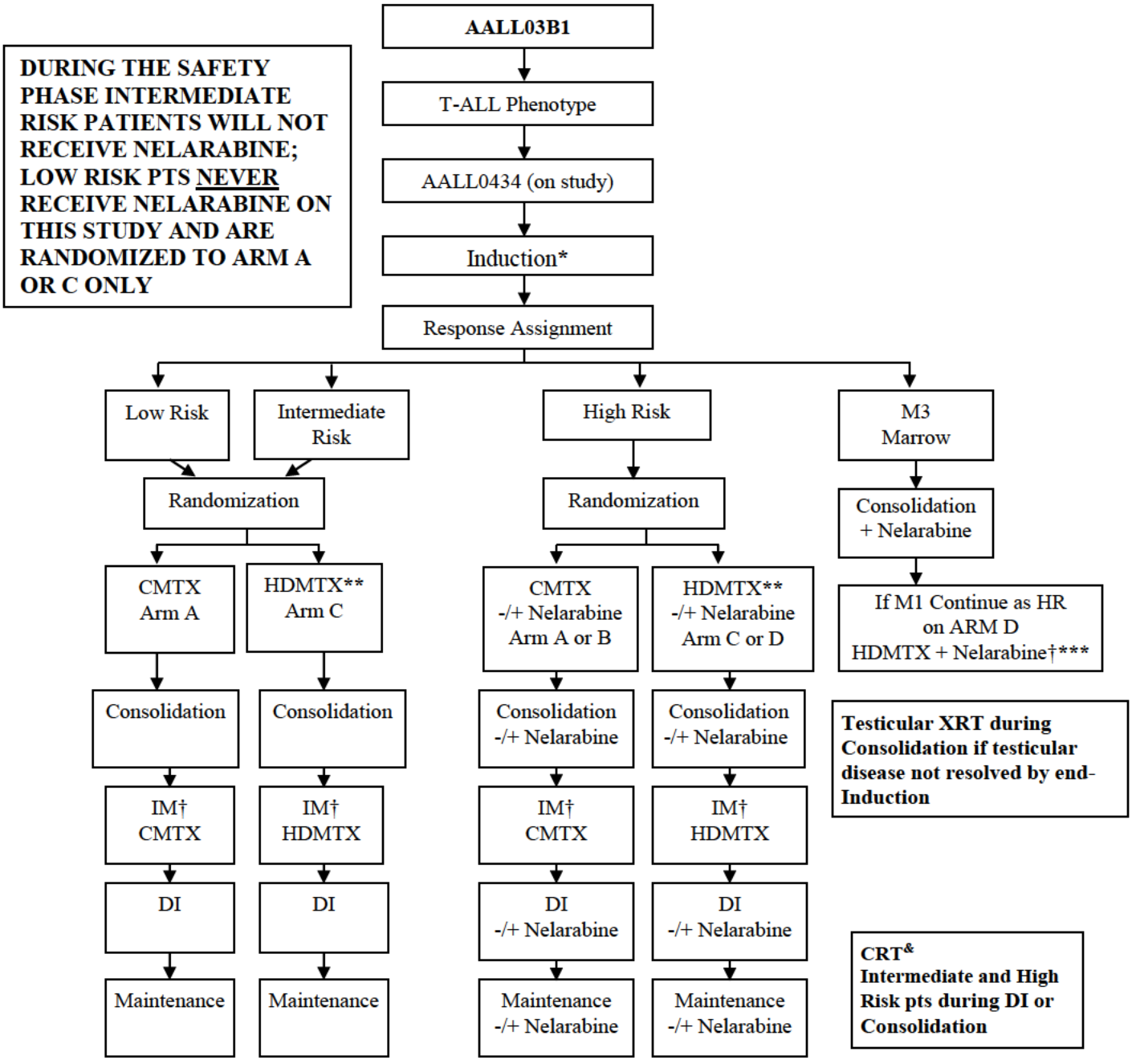
ABSTRACT

AALL0434 is a COG group-wide Phase III study designed for patients with T-lineage acute lymphoblastic leukemia (T-ALL) or T-lineage lymphoblastic lymphoma (T-NHL) from 1-30 years of age. Although event free survival (EFS) and overall survival continue to increase for children and young adults with T-ALL, "On-Treatment" relapses in the central nervous system (CNS) and bone marrow compartments continue to be common causes of treatment failure. There is evidence that both Nelarabine (Compound 506U78) and high dose methotrexate (HDMTX) are effective in preventing relapse in T-ALL. To specifically address the early treatment failures associated with T-ALL, this study will test the safety and efficacy of these two therapeutic interventions. The study utilizes a 2 x 2 factorial design with augmented intensity BFM backbone. After a Day 29 risk assignment has been determined, patients will become eligible for treatment assignment or randomization. Patients will be randomized to receive Capizzi style methotrexate without leucovorin rescue (plus PEG Asparaginase) versus high dose methotrexate with leucovorin rescue during the two month Interim Maintenance phase of therapy. A safety phase was conducted, during which only the High Risk patients were randomized to receive or not receive Nelarabine. During the subsequent efficacy phase of the study (which is now open), Intermediate Risk patients will also be randomized to receive or not to receive Nelarabine at a dose of 650 mg/m^2/day for 5 days during the Consolidation, Delayed Intensification and Maintenance phases of therapy. All patients will receive only one Delayed Intensification course and all Intermediate and High Risk patients will receive prophylactic cranial radiation (1200 cGy) either during Consolidation (if randomized to treatment Arm A (CMTX) or Arm B (CMTX + Nel) or Delayed Intensification (if randomized to treatment Arm C (HDMTX) or Arm D (HDMTX + Nel). All Intermediate and High Risk patients classified as CNS3 will be assigned to receive HD MTX on either Arm C (HDMTX) or Arm D (HDMTX + Nel) and receive cranial radiation therapy (CRT) (1800 cGy) during Delayed Intensification. T-NHL patients will be enrolled in a separate stratum and will receive the same common Induction therapy given to the T-ALL patients. T-NHL patients will be classified as Standard or High Risk, based upon flow cytometry studies performed on diagnostic bone marrow samples, an approach piloted in the recently completed lymphoblastic lymphoma study (COG A5971). Patients with $\geq$ 1% disease in the marrow at diagnosis or any level of steroid pre-treatment will be designated as High Risk and, at the end of Induction, will be randomized to either Arm A (CMTX) or Arm B (CMTX + Nel). Patients with < 1% disease in the marrow at diagnosis will be non-randomly assigned to Arm A (CMTX). Patients who fail to achieve at least a radiologic partial response (PR) at the end of Induction (Induction Failures) will be non-randomly assigned to Arm B (CMTX + Nel). T-NHL patients will receive treatment for a total of 2 years from the start of Interim Maintenance, regardless of gender, and without prophylactic cranial irradiation. T-ALL patients with testicular leukemia will be assigned to receive HDMTX on either Arm C (HDMTX) or Arm D (HDMTX + Nel), and will receive testicular radiation therapy (TRT) (2400 cGy) during Consolidation therapy, if testicular disease does not resolve by the end of Induction therapy. T-NHL patients with CNS3-positive disease and testicular disease patients will not be eligible for this study, as only CMTX-based therapy will be offered to T-NHL patients. Low Risk patients, who are NCI standard risk by age and WBC, with no testicular disease at diagnosis, CNS1 and rapid early responders (RERs) with an M1 marrow by Day 15, and minimal residual disease (MRD) < 0.1% on Day 29, have an excellent outcome and therefore will not receive Nelarabine in either the safety or efficacy phases; nor will they receive CRT.

EXPERIMENTAL DESIGN SCHEMA: T-ALL SAFETY PHASE (COMPLETED)



* Induction evaluation = Day 8 BMA; if not M1 then repeat on Day 15.
Evaluation of BMA and MRD on Day 29.
** Patients with CNS3 and/or testicular disease at Dx will be assigned to HDMTX arms
***Patient may also be taken off study for alternate therapy, including BMT
†Patients must be M1 at end-Consolidation to continue on therapy
RER = M1 marrow on Day 8 and < 0.1% MRD on Day 29 OR
M2/M3 marrow on Day 8 and M1 marrow on Day 15 and
< 0.1% MRD on Day 29.
SER = M2/M3 on Day 15 OR positive MRD on Day 29.
Low Risk = NCI SR by age & WBC count; RER, M1 on Day 15 and MRD < 0.1% on Day 29; CNS 1 status; and no testicular disease at diagnosis.
Intermediate Risk = RER or SER with MRD < 1% on Day 29; any CNS status.
High Risk = M2 at end of Induction or MRD ≥ 1% on Day 29; any CNS status.

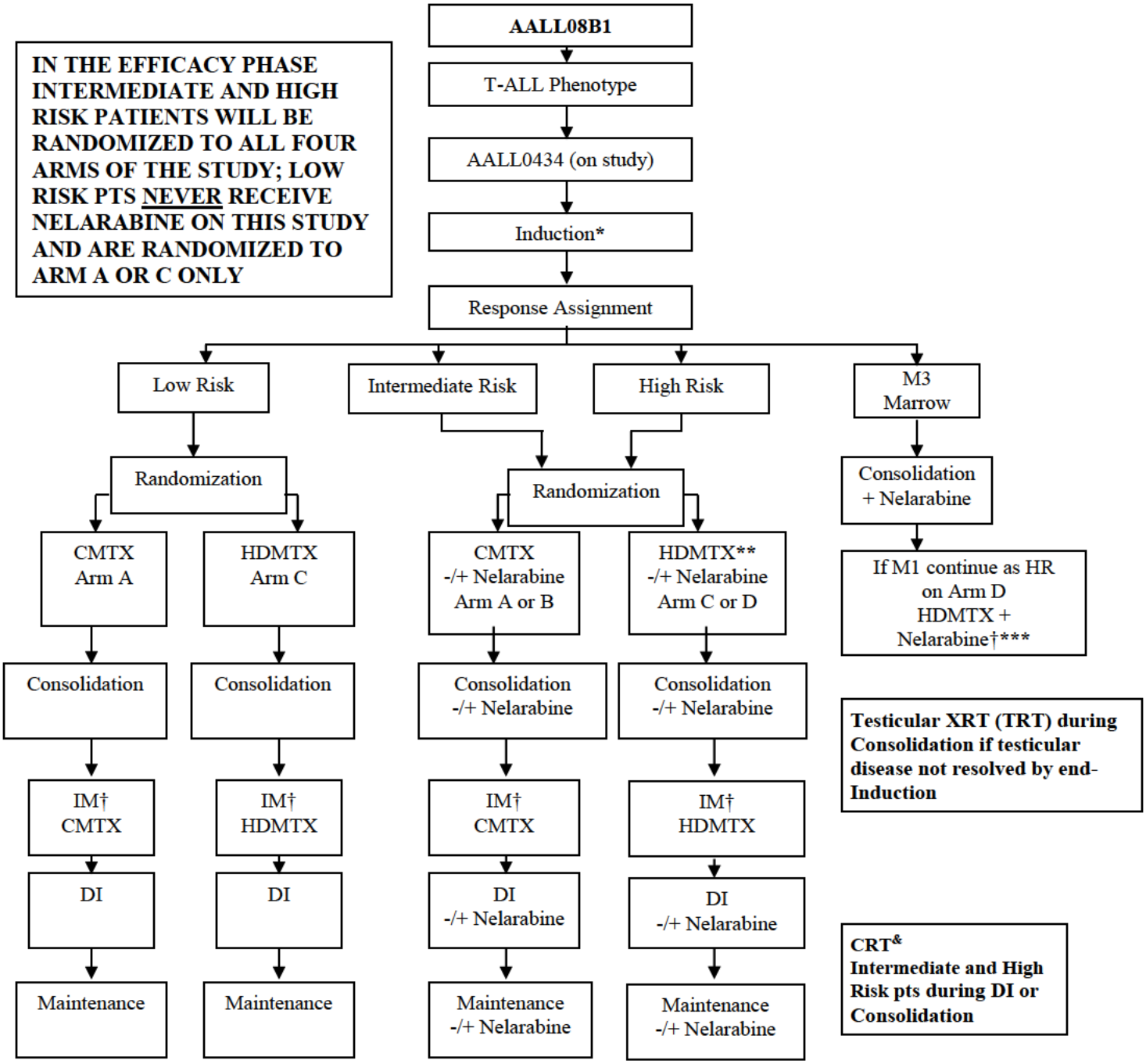
CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
IM = Interim Maintenance
DI = Delayed Intensification

Patients with a prior seizure disorder will not receive Nelarabine.

& CRT = cranial radiation (See Section 14.0 for details).

The safety phase ends when the 1st 20 High Risk pts to receive Nelarabine have been evaluated per Section 10.2.

EXPERIMENTAL DESIGN SCHEMA: T-ALL EFFICACY PHASE (OPEN)



* Induction evaluation = Day 8 BMA; if not M1 then repeat on Day 15.
Evaluation of BMA and MRD on Day 29.

** Patients with CNS3 and/or testicular disease at Dx will be assigned to HDMTX arms

***Patient may also be taken off study for alternate therapy, including BMT

†Patients must be M1 at end-Consolidation to continue on therapy

RER = M1 marrow on Day 8 and < 0.1% MRD on Day 29 OR
M2/M3 marrow on Day 8 and M1 marrow on Day 15 and
< 0.1% MRD on Day 29.

SER = M2/M3 on Day 15 OR positive MRD on Day 29.

Low Risk = NCI SR by age & WBC count; RER, M1 on Day 15 and MRD < 0.1% on Day 29; CNS 1 status; and no testicular disease at diagnosis.

Intermediate Risk = RER or SER with MRD < 1% on Day 29; any CNS status.

High Risk = M2 at end of Induction or MRD ≥ 1% on Day 29; any CNS status.

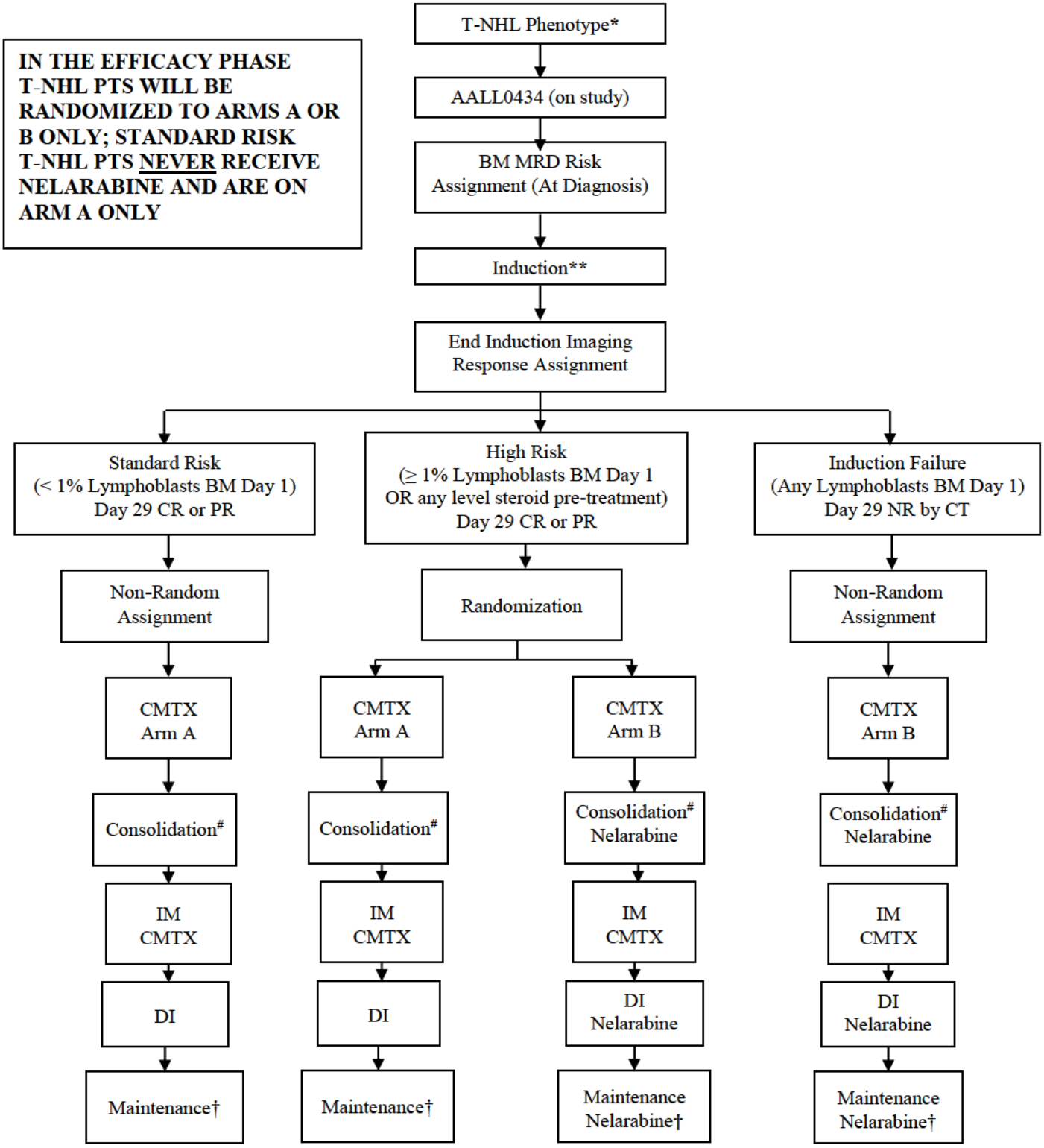
CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
IM = Interim Maintenance
DI = Delayed Intensification

Patients with a prior seizure disorder will not receive Nelarabine.

& CRT = cranial radiation (See Section 14.0 for details).

EXPERIMENTAL DESIGN SCHEMA: T-NHL EFFICACY PHASE

IN THE EFFICACY PHASE T-NHL PTS WILL BE RANDOMIZED TO ARMS A OR B ONLY; STANDARD RISK T-NHL PTS NEVER RECEIVE NELARABINE AND ARE ON ARM A ONLY



***Patients with testicular disease or CNS3 disease are ineligible for this study.** T-NHL patients do not receive cranial radial therapy on any arm of this study.

**Induction evaluation = Day 29 bone marrow (if positive at diagnosis); end of Induction imaging (computed tomography (CT) ± bone scan as indicated per Section 7.2).

End of Consolidation evaluation: BM and CT ± bone scan as indicated per Section 7.1. **Patients who are not PR at end of Consolidation are off protocol therapy.** † Maintenance will be two years from the start of IM for both boys and girls. **Patients with a prior seizure disorder will not receive Nelarabine.**

CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
IM = Interim Maintenance
DI = Delayed Intensification

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Main Clinical Objectives

1.1.1
To determine, through randomization, the relative safety and efficacy of the addition of Nelarabine (Compound 506U78) to augmented BFM therapy (Regimen C, CCG-1961).

1.1.2
To determine the relative safety and efficacy of high dose methotrexate (5 g/m^2) with leucovorin rescue compared to escalating methotrexate without leucovorin rescue plus Pegaspargase (Capizzi I) delivered during Interim Maintenance.

1.1.3
To gain preliminary data on the use of Nelarabine in patients with High Risk T-cell lymphoblastic lymphoma and its effect on long-term survival.

1.2 Secondary Clinical Objective

1.2.1
To determine the relative safety and efficacy of withholding radiation in patients with Low Risk T-ALL, while treating Intermediate and High Risk patients with 1200 cGy of prophylactic cranial radiation.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration via Remote Date Entry (RDE)

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN).*

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

3.1.2 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206), emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a 'Time of Need' registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

3.1.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

3.1.4 Timing

PATIENTS WITH T-ALL MUST BE ENROLLED ON COG AALL08B1 BEFORE TREATMENT ON COG AALL0434 BEGINS (with the exception of the first dose of intrathecal chemotherapy and/or selected cases for which there has been steroid pretreatment). **PATIENTS THAT BEGIN PROTOCOL THERAPY FOR LEUKEMIA, PRIOR TO ENROLLMENT ON AALL08B1, ARE INELIGIBLE FOR BOTH AALL08B1 AND COG ALL THERAPEUTIC TRIALS**.

PATIENTS WITH T-NHL ARE INELIGIBLE FOR AALL08B1 AND CAN ENROLL DIRECTLY ON AALL0434. EVERY EFFORT SHOULD BE MADE TO ACQUIRE AS MUCH TISSUE AS POSSIBLE. SPECIFIC INSTRUCTIONS REGARDING TISSUE SUBMISSION ARE OUTLINED IN SECTIONS 15 & 16.

All patients:

Informed consent: Except for administration of intrathecal cytarabine or allowable steroid pretreatment (defined below), *informed consent/parental permission* MUST be signed before protocol therapy begins.

Study enrollment: Study enrollment for AALL0434 must take place within *five* (5) calendar days of beginning protocol therapy. If enrollment takes place *before* starting therapy, the date protocol therapy is projected to start must be no later than *five* (5) calendar days after enrollment.

Eligibility studies: Patients must meet all eligibility criteria prior to the start of protocol therapy or enrollment, whichever occurs first. Unless otherwise indicated in the eligibility section, all clinical and laboratory studies to determine eligibility must be performed within 7 days prior to the start of protocol therapy or enrollment, whichever occurs first.

Initiation of systemic protocol therapy: Systemic induction chemotherapy, with the exception of steroid pretreament as outlined below, must begin within 72 hours of the first dose of intrathecal chemotherapy

3.1.5 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.1.6 Randomization

Randomization/assignment of post-Induction treatment will take place through the eRDE system after Day 29 risk status has been assigned. For all patients, post-Induction randomization via the RDE Late Randomization CRF should be done PRIOR to starting Consolidation therapy.

T-ALL PATIENTS:
For T-ALL patients, there are four treatment arms in this study. They are identified as follows:

Arm A: Capizzi MTX without Nelarabine (CMTX);
Arm B: Capizzi MTX with Nelarabine (CMTX + Nel);
Arm C: High Dose MTX without Nelarabine (HDMTX); and
Arm D: High Dose MTX with Nelarabine (HDMTX + Nel).

During the safety phase (completed), ONLY High Risk T-ALL patients were randomized to receive Nelarabine.

During the efficacy phase (now open), both High and Intermediate Risk T-ALL patients will be included in the Nelarabine randomization. Low Risk T-ALL patients do not receive Nelarabine on this protocol.

T-NHL PATIENTS:
For T-NHL patients, treatment will be restricted to 1 of 2 arms:

Arm A: Capizzi MTX without Nelarabine (CMTX)
Arm B: Capizzi MTX with Nelarabine (CMTX + Nel)

Patients classified as Standard Risk for T-NHL will be non-randomly assigned to Arm A (CMTX). Patients classified as High Risk for T-NHL will be randomized to either Arm A (CMTX) or Arm B (CMTX + Nel). Please see Section 3.3.5 for details regarding T-NHL risk classification.

3.2 Patient Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

INCLUSION CRITERIA

3.2.1 Classification Study

T-ALL patients must be enrolled on AALL08B1 prior to treatment and enrollment on AALL0434.

3.2.2 Age

Patients must be greater than 1.00 and less than 31 years of age.

3.2.3 Diagnosis

Patients must have newly diagnosed T-cell acute lymphoblastic leukemia (T-ALL) or T-lineage lymphoblastic lymphoma (T-NHL) Stage II-IV (see Appendix VIII). B-lineage lymphoblastic lymphoma will not be eligible for this study. A diagnosis of T-ALL is established when leukemic blasts lack

myeloperoxidase or evidence of B-lineage derivation (CD19/CD22/CD20), and express either surface or cytoplasmic CD3 or two or more of the antigens CD8, CD7, CD5, CD4, CD2 or CD1a. If surface CD3 is expressed on all leukemic cells, additional markers of immaturity, including TdT, CD34 or CD99 will be assessed for expression. Cases with uncertain expression will receive additional review within the appropriate COG reference laboratory.

T-NHL PATIENTS:
For T-NHL patients with tissue available for flow cytometry, the criterion for diagnosis should be analogous to T-ALL. For tissue processed by other means (i.e. paraffin blocks), the methodology and criteria for immunophenotypic analysis to establish the diagnosis of T-NHL defined by the submitting institution will be accepted.

3.2.4 Prior Therapy Restrictions

Patients shall have had no prior cytotoxic chemotherapy with the exception of steroids and/or IT cytarabine.

IT chemotherapy with cytarabine is allowed prior to registration for patient convenience. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. (Note: The CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in Section 3.3.) Systemic chemotherapy must begin within 72 hours of this IT therapy.

Patients diagnosed as having T-NHL or T-ALL with respiratory distress or hyperleukocytosis may require steroids prior to the initiation of additional systemic therapy. They are eligible for AALL0434 and will be stratified according to Section 3.3.5 below, based on the initial CBC. Steroid pretreatment may alter the risk group assessment. If the T-ALL patient's clinical status precludes a lumbar puncture within 48 hours of the initiation of steroid therapy, T-ALL patients CANNOT be classified as Low Risk and will be Intermediate or High Risk based on the results of the Day 29 marrow as above. Patients with T-NHL who receive steroid pre-treatment will be classified as High Risk. The dose and duration of previous steroid therapy should be carefully documented.

For the management of airway compromise, patients who have received emergent chest irradiation up to 600 cGy will be eligible for this study.

3.2.5 Concomitant Medications Restrictions

Patients with a prior seizure disorder requiring anti-convulsant therapy are not eligible to receive Nelarabine. In addition, patients with pre-existing Grade 2 (or greater) peripheral neurotoxicity, as determined prior to Induction treatment by the treating physician or a neurologist, are not eligible to receive Nelarabine. These restrictions in eligibility are designed to prevent excessive Nelarabine-induced central and peripheral neurotoxicity in at-risk patients. For the purposes of this study, this includes any patient that has received **anticonvulsant therapy to prevent/treat seizures in the prior two years**.

EXCLUSION CRITERIA

3.2.6 Pregnant/Lactating Females

Pregnant or lactating females are ineligible. The medications used in this protocol may put the fetus at risk, and may cross into the breast milk and put the infant at risk.

3.2.7 Patients with Down syndrome

Patients with Down syndrome are ineligible to enroll onto this study.

3.2.8 For T-NHL patients the following additional exclusion criteria apply:

- B-Precursor lymphoblastic lymphoma
- Morphologically unclassifiable lymphoma
- Absence of both B-cell and T-cell phenotype markers in a case submitted as lymphoblastic lymphoma
- CNS3-positive (see Section 3.3.2 for details) or testicular involvement

REGULATORY

3.2.9
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.10
All institutional, FDA, and NCI requirements for human studies must be met.

3.2.11
For details regarding obtainment of Nelarabine, please see Section 6.11.

3.3 Definitions

3.3.1 Hematological Parameters

INITIAL WBC: The first WBC at the treating COG institution. If prior therapy (i.e. steroids) or IV hydration has been administered then the initial WBC prior to therapy and/or hydration should be used.

INITIAL PLATELET COUNT: The first platelet count at the treating COG institution, or the count before transfusion of platelets if transfused prior to arrival.

INITIAL HEMOGLOBIN: The first hemoglobin at the treating COG institution, or the hemoglobin prior to intravenous fluid or red cell transfusions, whichever occurred first.

ABSOLUTE NEUTROPHIL COUNT (ANC): Total WBC count multiplied by the percentage of (neutrophils + bands).

3.3.2 Definitions of Extramedullary Disease

CNS LEUKEMIA AT DIAGNOSIS:

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs).

CNS 2: In CSF, presence of < 5/μL WBCs and cytospin positive for blasts or ≥ 5 μL WBCs with negative Steinherz Bleyer algorithm.

- CNS 2a: < 10/μL RBCs; < 5/μL WBCs and cytospin positive for blasts;
- CNS 2b: ≥ 10/μL RBCs; < 5/μL WBCs and cytospin positive for blasts; and
- CNS 2c: ≥ 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).

CNS3: In CSF, presence of ≥ 5/μL WBCs and cytospin positive for blasts and/or clinical signs of CNS Leukemia.
(Note: Clinical CNS criteria appear below in CNS 3c):

- CNS 3a: < 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts;
- CNS 3b: ≥ 10/μL RBCs, ≥ 5/μL WBCs and positive by Steinherz/Bleyer algorithm (see below); and
- CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

T-NHL DEFINITION OF CNS3-POSITIVE DISEASE
Elevated CSF WBC (≥ 5 cell/μL) and a cytocentrifuge preparation demonstrating lymphoma cells. CNS lymphoma may also be diagnosed when the CSF WBC is normal but clinical signs of CNS involvement are present:

- Cranial nerve palsy (if not explained by extra cranial tumor)
- Clinical spinal cord compression
- Isolated intracerebral mass

CNS3-POSITIVE T-NHL PATIENTS ARE NOT ELIGIBLE FOR THIS STUDY

METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES:
If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/μL and blasts, the following algorithm should be used to distinguished between CNS2 and CNS3 disease:[46]

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \quad \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/μL blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = 60/μL; CSF RBC = 1500/μL; blood WBC = 46000/μL; blood RBC = 3.0 X 10^6/μL:

$$\frac{60}{1500} = 0.04 > 2X \quad \frac{46000}{3.0 \times 10^6} = 0.015$$

TESTICULAR LEUKEMIA AT DIAGNOSIS: Unilateral or bilateral testicular disease. Biopsy is required if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass.

T-NHL PATIENTS WITH TESTICULAR DISEASE ARE NOT ELIGIBLE FOR THIS STUDY.

3.3.3 Definitions of Bone Marrow Involvement

BONE MARROW STATUS:
M1: < 5% lymphoblasts
M2: 5 - 25% lymphoblasts
M3: > 25% lymphoblasts.

BONE MARROW MRD STATUS FOR T-ALL PATIENTS*****
Negative: < 0.1% detectable leukemia cells
Positive-Intermediate: ≥ 0.1%-1% detectable leukemia cells
Positive-High: > 1% detectable leukemia cells
***** The definitions for MRD negative, positive-intermediate and positive-high listed above, contribute to the classification of marrow results on Day 29 for all patients and the end of Conslidation for patients who were M2 or M3 or positive-high (MRD > 1%) on Day 29.

BONE MARROW MRD STATUS FOR T-NHL PATIENTS
The MRD status of T-NHL patients will be assessed at diagnosis and patients will be risk-stratified as described in Section 3.3.5.

3.3.4 Definitions of Early Response to Treatment

T-ALL PATIENTS:
RAPID EARLY RESPONDER (RER): M1 marrow on either Day 8 or 15, and M1 marrow with negative MRD status (< 0.1%) on Day 29.

SLOW EARLY RESPONDER (SER): M2 or M3 marrow on Day 15 OR positive MRD status Day 29. M1/M2 marrow on Day 29.

T-NHL PATIENTS:
T-NHL patients will not be classified based on early response to treatment for risk assignment. Patients who fail to respond (< PR; see Section 11.3) will be considered Induction failures.

3.3.5 Definitions of Risk Stratification

T-ALL PATIENTS:
LOW RISK T-ALL: NCI Standard Risk by age (1.00 – 9.99 years) and WBC (initial ≤ 50,000/µL); RER, M1 on Day 15 and M1 marrow with MRD < 0.1% on Day 29; CNS 1 status and no testicular disease at diagnosis.

INTERMEDIATE RISK T-ALL: RER or SER, M1 marrow with MRD < 1% on Day 29; any CNS status.

HIGH RISK T-ALL: M2 marrow and/or MRD ≥ 1% on Day 29; any CNS status.

INDUCTION FAILURE T-ALL: M3 marrow on Day 29.

T-NHL PATIENTS:
STANDARD RISK T-NHL: < 1% disease in the bone marrow at diagnosis detected by central lab flow cytometry.
HIGH RISK T-NHL: ≥ 1% disease in the bone marrow at diagnosis detected by central lab flow cytometry or any level of steroid pre-treatment.

INDUCTION FAILURE T-NHL: Failure to achieve PR, CR or Cr_u at end of Induction therapy (see Section 11.3).

NO RESPONSE (NR) FOR T-NHL: see Section 11.3.

UNFAVORABLE CHARACTERISTICS:

PHILADELPHIA CHROMOSOME POSITIVE (Ph+)
a) *BCR-ABL1* (formerly known as *BCR-ABL*) fusion transcript determined by FISH or RT-PCR
b) t(9;22)(q34;q11) determined by cytogenetics

T-ALL patients entered onto AALL0434 who are later found to meet eligibility criteria for the AALL0622 Ph+ ALL study (or successor) should immediately be taken off protocol therapy prior to Day 15 of Induction therapy.

T-NHL patients entered onto AALL0434 who are later found to meet the criteria for Ph+ T-NHL will be ineligible for post-Induction therapy on AALL0434 and should be removed from protocol therapy at the end of Induction.

STEROID PRETREATMENT:

Risk Assessment based on steroid pretreatment for T-ALL patients. Please **note**: This is different from patients with B-precursor ALL.

Patients receiving steroids within the week preceding diagnosis, prior to the diagnosis of T-ALL:

i. Patients who have received less than 48 hours of oral or IV steroids during the week immediately prior to diagnosis will be stratified according to the schema outlined above if the results of a CBC obtained prior to the initiation of steroid therapy are available. The pre-steroid CBC and age will be used to determine risk assignment.

ii. If the patient has received > 48 hours of oral or IV steroids, whether or not a CBC is available prior to therapy, they will be categorized as an SER and assigned to the Intermediate Risk group provided their Day 29 BM is M1 and MRD < 1%. If Day 29 BM is M2 or contains > 1% MRD the patient will be considered to be High Risk. Note that on this trial, SER status does not determine treatment assignment.

iii. In the absence of presteroid CBC patients will be considered Intermediate Risk unless their Day 29 BM is M2 and/or their MRD is > 1%. These later patients fall into the High Risk category.

Patients who have received steroids within one month of diagnosis (e.g. week -4 to week -1):

i. Patients who receive less than 48 hours of steroids will not have risk assignment changed.

ii. Patients who receive > 48 hours in weeks -4 to -1 will be assigned to the Intermediate or High Risk category depending on the Day 29 bone marrow status.

Any T-NHL patient with a history of steroid pre-treatment in any of the parameters listed above will be categorized as High Risk.

3.3.6 Definitions of Relapse

T-ALL and T-NHL PATIENTS
Any recurrence of disease whether in marrow or extramedullary site. Relapse should be histopathologically confirmed.

CNS Relapse: Positive cytomorphology and ≥ 5 WBC/µL OR positive cytomorphology with CSF WBC 0-4/µL on two successive occasions one month apart. If any CSF evaluation shows positive cytomorphology and < 5 WBC/µL, a second CSF evaluation is required in 4 weeks. Identification of leukemic clone in CSF by flow cytometry (CD2, CD3, CD34, or the same T-cell immunophenotypic markers that were identified at diagnosis) or FISH for diagnostic karyotypic abnormality is encouraged.

Testicular Relapse: Must be documented by testicular biopsy if the testicular relapse is isolated. Biopsy is not mandated if the marrow is also involved.

Bone Marrow Relapse: Patients with an M3 marrow at any point after Day 29.

T-NHL PATIENTS ONLY
Progressive disease: Greater than 25% increase in the size of any lesions or appearance of new lesion(s).

4.0 TREATMENT PLAN

4.1 Overall Treatment Plan

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

All T-ALL and T-NHL patients will receive the same Induction sequence. Subsequent therapy will be dependent on risk assignment, as detailed below in Table 3. Since treatment assignment is in part dependent on Day 29 MRD status for T-ALL, a radiation oncology consultation should be considered for all T-ALL patients during Induction. As specified below, Low Risk T-ALL patients (NCI std. risk, CNS1 with RER) do not receive radiation treatment and will, therefore, not require a radiation oncology consultation; **however, Intermediate and High Risk T-ALL patients may be randomized to an arm that includes CRT at Week 8 from the start of Induction therapy (Week 3 of Consolidation)**. No T-NHL patients will receive CRT. T-NHL patients with CNS3-positive and/or testicular disease are not eligible for this study.

4.1.1 Risk Assignment

Low Risk T-ALL: These patients will be randomized ONLY to Arm A (CMTX) and Arm C (HDMTX) and will NOT receive Nelarabine in either the safety or efficacy phases. They must meet the following criteria: Age 1.00-9.99 years and initial WBC count less than 50,000/μL, without testicular disease at diagnosis, CNS1 status; RER with an M1 marrow by Day 15; and MRD < 0.1% on Day 29. **Low Risk patients will NOT receive CRT. Pretreatment with steroids may preclude Low Risk status (see Section 3.3).**

Intermediate Risk T-ALL: These patients are neither Low Risk, nor High. They will be eligible for the Nelarabine randomization during the efficacy phase (which is now open), but did not receive Nelarabine during the safety phase (which is now closed). **All Intermediate Risk patients will receive CRT during either Consolidation (if randomized to Arm A (CMTX) or Arm B (CMTX + Nel) or Delayed Intensification (if randomized to Arm C (HDMTX) or Arm D (HDMTX + Nel); those with CNS3 status will be assigned to HDMTX on either Arm C (HDMTX) or Arm D (HDMTX + Nel) and receive 1800 cGy rather than the 1200 cGy prophylactic CRT dose during Delayed Intensification**. Patients with testicular disease at diagnosis will be assigned to HDMTX on either Arm C (HDMTX) or Arm D (HDMTX + Nel), and may receive TRT during Consolidation, depending on response.

High Risk T-ALL: These patients will be eligible to receive Nelarabine during both the safety and efficacy phases. These patients, **regardless of other features**, will have a morphologic M2 marrow or MRD ≥ 1.0% at the end of Induction. All High Risk patients will proceed directly to Consolidation, without waiting for count recovery at end-Induction. Given their high risk for subsequent failure, the remission status of these patients will be monitored carefully. They will have peripheral blood sent at start, mid and end-Consolidation for MRD determination and marrow sent at end Consolidation for both morphology and MRD. Patients must have attained an M1 marrow by morphology at the end of Consolidation to continue on study. **All High Risk patients will receive CRT during either Consolidation (if randomized to Arm A (CMTX) or Arm B (CMTX + Nel) or Delayed Intensification (if randomized to Arm C (HDMTX) or Arm D (HDMTX + Nel); those with CNS3 status will be assigned to HD MTX on either Arm C (HDMTX) or D (HDMTX + Nel) and will receive 1800 cGy rather than the 1200 cGy prophylactic CRT dose during Delayed Intensification**.

Patients with testicular disease at diagnosis will be assigned to HDMTX on either Arm C (HDMTX) or Arm D (HDMTX + Nel) and may receive TRT during Consolidation, depending on response.

Induction Failures T-ALL: Patients with an M3 marrow on Day 29 will be non-randomly assigned to Arm D (HDMTX + Nel). These patients should proceed directly to Consolidation after the Day 29 marrow without waiting for count recovery to occur. They will receive at least 1 block of Consolidation therapy. Prior to the 2nd course of Nelarabine exposure during Consolidation therapy (Day 43), the patients are to have a bone marrow evaluation by local morphologic assessment. Bone marrow and peripheral blood samples will also be sent for MRD analysis. If M3 status is again observed, the patient is taken off protocol therapy. If the patient has an M1 or M2 marrow, they will continue with the second block of Arm D (HDMTX + Nel) Consolidation therapy. If the patient has an M1 marrow at end of two blocks of Consolidation therapy (ten weeks), they may remain on Arm D (HDMTX + Nel) of the study. These patients may also be taken off protocol therapy to receive alternate therapies, such as stem cell transplantation, at investigator discretion. Peripheral blood and bone marrow samples for MRD are required at end-of-Consolidation.

Standard Risk T-NHL: Patients with < 1% disease in the bone marrow at diagnosis by central lab flow cytometry. These patients are NOT eligible for the Nelarabine randomization and will be non-randomly assigned ONLY to Arm A (CMTX).

High Risk T-NHL: Patients with ≥ 1% disease in the bone marrow at diagnosis by central lab flow cytometry or any level of steroid pre-treatment. These patients are eligible for the Nelarabine randomization and will be randomized to either Arm A (CMTX) or Arm B (CMTX + Nel). **There will be no CRT during Consolidation.** T-NHL patients who are CNS-positive or who have testicular disease are not eligible for this study.

Induction Failures T-NHL: Patients who fail to achieve at least a PR (see Section 11.3) at the end of Induction. These patients will be non-randomly assigned to Arm B (CMTX + Nel). Patients who do not attain at least a PR (see Section 11.3) by the end of Condolidation therapy will be removed from protocol therapy at that time.

Table 3

T-ALL Risk Status	**NCI Risk Status**	**Day 15 Induction Response; Day 29 MRD**	**CNS Status**
Low Risk (Must meet **all** criteria **and** not have testicular disease at diagnosis, and pre-treament with steroids may preclude Low Risk status)	Standard Risk (Age 1.00-9.99 yrs and initial WBC less than 50,000/µL)	M1 (RER) Day 8 or 15 and M1 marrow with MRD < 0.1% on Day 29	CNS1
Intermediate Risk	Standard	Steroid pre-treated, SER or CNS3 or testicular disease but M1 with 0.1 to 0.99% MRD on Day 29	Any
	High	RER or SER; M1 with < 1% MRD on Day 29	Any
High Risk	Standard or High	M2 marrow at **end** of Induction or MRD ≥ 1% on Day 29	Any
Induction Failure	Standard or High	M3 marrow at **end** of Induction	Any
T-NHL Risk Status	**Baseline BM MRD**	**Day 29 Induction Response**	**CNS Disease**
Standard Risk	< 1%	CR, CR_u, PR	None
High Risk	≥ 1% or steroid pre-treated	CR, CR_u, PR	None
Induction Failure	Either	Failure to achieve PR, CR or CR_u (see Section 11.3)	None

Testicular Disease: T-ALL patients with testicular involvement at diagnosis will not receive irradiation if testicular disease has resolved completely at the end of Induction (biopsy is required if there is any uncertainty regarding the clinical response). Those patients with persistent testicular disease at end Induction, based on clinical and/or biopsy findings, will receive radiation during Consolidation (2400 cGy to bilateral testes). T-NHL patients with testicular disease are not eligible for this study.

4.1.2 Randomization

After a risk assignment has been determined for each patient with T-ALL or T-NHL, the patient will become eligible for treatment randomization. Randomization will also be determined by whether or not patients have T-ALL vs. T-NHL.

4 treatment regimens (for patients with T-ALL):
Arm A Augmented BFM with Capizzi MTX, no Nelarabine (CMTX)
Arm B Augmented BFM with Capizzi MTX plus Nelarabine (CMTX + Nel)
Arm C Augmented BFM with High Dose MTX, no Nelarabine (HDMTX)
Arm D Augmented BFM with High Dose MTX plus Nelarabine (HDMTX + Nel)

2 treatment regimens (for patients with T-NHL):
Arm A Augmented BFM with Capizzi MTX, no Nelarabine (CMTX)
Arm B Augmented BFM with Capizzi MTX plus Nelarabine (CMTX + Nel)

4.1.2.1 Safety Phase Randomization (closed)

During the safety phase of the AALL0434 trial only the High Risk patients received Nelarabine. High Risk patients were randomized to all four arms of the study. Toxicity data for the High Risk cohort receiving Nelarabine were assessed following administration through Week 43 of the study. If additional data were required to assess toxicity in High Risk patients who received Nelarabine, a second assessment would have occurred prior to the completion of the third year of the study (see Section 10.2). Completion of the analysis of these data ended the safety phase. Grade 2 and greater neurotoxicity was monitored closely during the safety phase. During this phase, Low Risk and Intermediate Risk patients were randomized to either Arm A (CMTX) or Arm C (HDMTX) and did not receive Nelarabine. NOTE: During the safety phase analysis, High Risk patients continued to be randomized to all four treatment arms.

4.1.2.2 Efficacy Phase Randomization (open)

Analyses of toxicity data have been completed for the initial cohort of High Risk T-ALL patients randomized to receive Nelarabine, and the study has been approved to move into the efficacy phase as Nelarabine has been deemed safe. The efficacy of Nelarabine will be determined by randomized treatment assignment. During the efficacy phase of this study, Intermediate Risk and High Risk T-ALL patients (as defined in Table 3) will be randomized to any one of the 4 treatment arms as shown in Table 4. Low Risk T-ALL patients will not receive Nelarabine and thus will only be randomized to either Arm A (CMTX) or Arm C (HDMTX) (Table 4). High Risk T-NHL patients (as defined in Table 3) will be randomized to one of two treatmemt arms, as shown below in Table 4. Standard Risk T-NHL patients will not receive Nelarabine and thus will be non-randomly assigned to Arm A (CMTX).

Table 4

Intermediate or High Risk T-ALL	Augmented BFM	Augmented BFM/Nelarabine
Capizzi-Style Methotrexate	**A**	**B**[§]
High Dose Methotrexate	**C**[%]	**D**[§ # %]
High Risk T-NHL	Augmented BFM	Augmented BFM/Nelarabine
Capizzi-Style Methotrexate	**A** (NO CRT/TRT)	**B**[§ #] (NO CRT/TRT)
Low Risk T-ALL*	Augmented BFM	
Capizzi-Style Methotrexate	**A**	
High Dose Methotrexate	**C**[%]	
Standard Risk T-NHL*	Augmented BFM	
Capizzi-Style Methotrexate	**A** (NO CRT/TRT)	

§ Children with an anti-convulsant-dependent seizure disorder or those who have Grade 2 or greater peripheral neuropathy will NOT be assigned to Nelarabine

* Children with Low Risk T-ALL or Standard Risk T-NHL will NOT receive Nelarabine or cranial XRT

% T-ALL patients with CNS3 and/or testicular disease at diagnosis will be ASSIGNED to receive HD MTX

T-ALL patients with a Day 29 M3 marrow status will be ASSIGNED to receive HD MTX with Nelarabine; T-NHL patients who fail to achieve at least a PR at the end of Induction (see Section 11.3) will be ASSIGNED to receive CMTX with Nelarabine.

See Section 7.0 for baseline studies to be obtained prior to starting Induction therapy.

4.1.2.3 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. **Therefore, all dosing is to be determined by the patient's actual weight. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with administering chemotherapy doses based on actual body weight should not enroll obese patients on this protocol.

4.2 **INDUCTION** (All patients)
All treatment arms will receive common Induction therapy.

Intrathecal Cytarabine: IT
Given at time of diagnostic lumbar puncture OR Day 1.

Age-based dosing:

Age (yrs)	Dose
1 – 1.99	30 mg
2 – 2.99	50 mg
≥ 3	70 mg

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1, 8, 15 and 22

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

PrednISONE: PO*****
30 mg/m^2/dose BID (i.e., 60 mg/m^2/day, divided BID) on Days 1-28 (do not taper)

***** May give IV: substitute methylprednisolone IV at a ratio of 4 mg for each 5 mg of predniSONE

DAUNOrubicin: IV push
25 mg/m^2/dose on Days 1, 8, 15 and 22

Administer at a concentration of 5 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DAUNOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Pegaspargase: IM (or IV over 1-2 hours)
2500 International units/m^2/dose **x 1 dose** on Day 4 [**OR** 5 **OR** 6]

For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Days 8 and 29 (CNS3 T-ALL patients also receive IT MTX on Days 15 & 22). The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose

1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

The therapy delivery map (TDM) for Induction is on the next page.

Following completion of Induction, the next course (Consolidation, Section 4.3 or 4.4) starts on Day 36 or when blood count parameters are met (whichever occurs later). See below for additional details regarding risk group assignment and randomization.

Criteria to begin Consolidation

Once risk assignment occurs, patients must complete and sign informed consent specific to post-Induction therapy for the appropriate risk group and then undergo randomization. Consolidation for Arm A (CMTX) and Arm C (HDMTX) is in Section 4.3; Consolidation for Arm B (CMTX + Nel) and Arm D (HDMTX + Nel) is in Section 4.4.

If patient has T-ALL with M1 marrow and MRD < 1% as determined by the COG Reference Lab (Low and Intermediate Risk T-ALL), randomize and proceed to Consolidation at Day 36 or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later).

If patient has Standard Risk T-NHL (< 1% disease in the bone marrow at diagnosis), proceed to Consolidation on Arm A (CMTX) (Section 4.3) at Day 36 or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later).

If patient has High Risk T-NHL (≥ 1% disease in the bone marrow at diagnosis or any level of steroid pre-treatment), randomize and proceed to Consolidation at Day 36 or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later).

High Risk T-ALL

If the Day 29 marrow is M2 (5%-25% blasts) and/or the central COG reference lab determines MRD ≥ 1%, then the patient is defined as High Risk. High Risk patients should be randomized as soon as possible and begin Consolidation therapy (as randomized) as soon as possible and should not wait until Day 36 or for count recovery to occur.

Induction Failure T-ALL

If the Day 29 marrow is M3 (≥ 25% blasts), then patient is an Induction Failure. Study chair should be notified. The patient will be non-randomly assigned to Arm D (HDMTX + Nel) and should begin Consolidation therapy as soon as possible and should not wait until Day 36 or for count recovery to occur. Patients with Induction Failure must sign the appropriate consent form before Consolidation therapy begins.

Induction Failure T-NHL

If the Day 29 evaluation reveals that the patient's response status is NR or progressive disease (see Section 11.3) then patient is an Induction Failure. Please notify the study chair. The patient will be non-randomly assigned to Arm B (CMTX + Nel) and should begin Consolidation therapy as soon as possble and should not wait until Day 36 or for count recovery to occur. Patients with Induction failure must sign the appropriate consent form before Consolidation therapy begins.

4.2.1 INDUCTION (All arms)

All treatment arms will receive common Induction therapy.

Patient name or initials

DOB

This Course lasts 5 weeks (35 days) and this Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) / Dose 1 – 1.99 / 30 mg 2 – 2.99 / 50 mg ≥ 3 / 70 mg	Given at time of diagnostic lumbar puncture (LP) **OR** Day 1	May give prior to randomization **Note age-based dosing**	a. Hx/PE b. Weight (BSA) c. CBC/diff/platelets d. BM eval e. CSF cell count, cytospin f. PB for host polymorphisms (T-ALL only) g. PB for MRD (T-ALL only) h. Bilirubin, ALT, BUN, creatinine i. Varicella titers j. TPMT genotype (see Section 5.9) T-NHL only: k. Chest/abdomen/pelvis CT l. Bone scan m. Diagnostic biopsy/cytology **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV Push Over 1 min+	1.5 mg/m^2/dose	Days 1, 8, 15 & 22	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
PrednISONE (PRED)	PO (may give IV*)	30 mg/m^2/dose BID	Days 1-28 (no taper)	Total daily dose: 60 mg/m^2/day, divided BID *For IV substitution see Sec 4.2	
DAUNOrubicin (DAUN)	IV Push Over 15 min	25 mg/m^2/dose	Days 1, 8, 15 & 22	See Section 4.2 for administration guidelines	
Pegaspargase (PEG-ASP)	IM (or IV over 1-2 hours)	2500 International units/m^2 **x 1 dose**	Day 4 [**OR** 5 **OR** 6]	For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 8 & 29 (CNS3 T-ALL also Days 15 & 22)	**Note age-based doing**	

Therapy Delivery Map **Ht** cm **Wt** kg **BSA** m^2

Date Due	Date Given	Day	IT ARAC mg	VCR mg	PRED mg	PRED mg	DAUN mg	PEG-ASP IU	IT MTX mg	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		1	mg	mg	___mg	___mg	mg			a, b, c, d, e, h, i, j, (k, l, m)*	
		2									
		3									
		4						___IU			
		5						**(1 dose)**			
		6									
		7									
		8		___mg			___mg		___mg	a, c, d$^{\beta}$, e, g^	
		9									
		10									
		11									
		12									
		13									
		14								l*	
		15		___mg			___mg		___mg#	a, c, d$^{\beta}$, e#	
		16									
		17									
		18									
		19									
		20									
		21									
		22		___mg			___mg		___mg#	a, c, e#	
		23									
		24									
		25									
		26									
		27									
		28									
		29							mg	a, c, d^$^{\alpha}$, e, f$^{\beta}$, g^, (k, l)*	
		36	**Start next course (Consolidation, Sec 4.3. or 4.4) on Day 36 or when blood count parameters are met (whichever occurs later).**								

^ See Section 7.1 for details # CNS3 T-ALL patients **ONLY** * T-NHL patients only (see Section 7.2 for details, including exceptions)

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4.3 **CONSOLIDATION Arms A (CMTX) and C (HDMTX)** (NO Nelarabine) Weeks 6-13
This Consolidation course is for patients randomized or assigned to either treatment arm WITHOUT NELARABINE (Arms A and C).

Criteria to begin Consolidation
Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). **Once Consolidation therapy has begun, interruptions for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) should occur only at Day 29**. Once the Day 1 or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated.

T-ALL patients who are High Risk with MRD > 1% and/or M2 marrow on Day 29, should be randomized and proceed directly to Consolidation without waiting for count recovery.

Patients with Induction failure should proceed directly to Consolidation without waiting for count recovery.

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Days 1^{++} or 29^{++}, 8, $15^{\#}$ and $22^{\#}$

$^{++}$if High Risk T-ALL or T-NHL: omit Day 1 and give on Day 29 instead i.e, patients should receive IT MTX on Days 8, 15, 22, and 29.
$^{\#}$if CNS3 T-ALL: omit Days 15 & 22 i.e, patients should receive IT MTX on Days 1 & 8 only.
All other patients receive IT MTX on Days 1, 8, 15 and 22.
The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Cyclophosphamide: IV (over 30 minutes)
1000 mg/m^2/dose on Days 1 and 29. Reduce urine specific gravity to ≤ 1.015 prior to administering cyclophosphamide and give IV fluids to maintain urine output. Furosemide may be given at a dose of 0.25 – 0.5 mg/kg/dose IV for urine output < 3 mL/kg/hr after CPM. See Section 5.3 for additional details.

Cytarabine: IV over 1-30 minutes or Subcutaneous
75 mg/m^2/dose on Days 1-4, 8-11, 29-32 and 36-39

Mercaptopurine: PO
60 mg/m^2/dose on Days 1-14 and 29-42. Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dose using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix I for details. **Do not escalate or modify dose based on blood counts during this course.**

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 15, 22, 43 and 50

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Pegaspargase: IM (or IV over 1-2 hours)
2500 International units/m^2/dose **x 1 dose** on Days 15 and 43

For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Testicular Radiation Therapy
Patients with T-ALL and persistent testicular disease at end-Induction will receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Within the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (See Section 14.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. T-NHL patients with testicular disease are not eligible for this study.

Cranial Radiation Therapy
Prophylactic cranial radiation therapy (1200 cGy in 8 once-daily fractions) for Intermediate/High Risk T-ALL patients randomized to Arm A (CMTX) should be given during Weeks 3 and 4 of Consolidation (see Section 14.0). Cranial XRT (1800 cGy in 10 once-daily fractions) for CNS3 patients and prophylactic cranial XRT (1200 cGy in 8 once-daily fractions) for Intermediate/High Risk T-ALL patients randomized to Arm C (HDMTX) will be given during DI. Intrathecal therapy is NOT held during the concomitant administration of CRT. Low Risk T-ALL patients (defined in Section 4.1) and all T-NHL patients will NOT receive any CRT.

The therapy delivery map (TDM) for Consolidation is on the next page.

Following completion of Consolidation, the next course (Interim Maintenance, Section 4.5 or 4.6) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.3.1 CONSOLIDATION Arm A (CMTX) and Arm C (HDMTX)

This Consolidation course is for patients randomized or assigned to either treatment arm WITHOUT NELARABINE (Arms A and C).

Patient name or initials _____ DOB _____

*Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later). Patients with T-ALL and persistent testicular disease at end-Induction will receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Within the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (See Section 14.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 8, 15, 22 & 29 **for HR (T-ALL or T-NHL)** Days 1, & 8 **for CNS3 T-ALL** Days 1, 8, 15, & 22 **for all other patients**	**Note age-based dosing** **Please note CNS3 status and risk assignment-based schedule. See Section 4.1.1 for details of risk assignment.**	a. Hx/PE b. Weight (BSA) c. CBC/diff/platelets d. CSF cell count, cytospin e. ALT, creatinine, bilirubin f. BM evaluation† g. PB for MRD (T-ALL only) T-NHL only: h. Chest CT/Chest x-ray i. Abdomen/Pelvis CT j. Bone scan † T-ALL patients are considered off protocol therapy if not M1 at end-Consolidation **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 30 min	1000 mg/m²/dose	Days 1 & 29	See Section 4.3 for admin guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m²/dose	Days 1-4, 8-11, 29-32 & 36-39		
Mercaptopurine (MP)	PO	60 mg/m²/dose	Days 1-14 & 29-42	See Sec 4.3 & Appendix I for admin guidelines	
VinCRIStine (VCR)	IV Push over 1 min+	1.5 mg/m²/dose	Days 15, 22, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Pegaspargase (PEG-ASP)	IM (or IV over 1-2 hours)	2500 International units/m²/dose	Days 15 & 43	For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Therapy Delivery Map **Ht** cm **Wt** kg **BSA** m²

Date Due	Date Given	Day	IT MTX@ mg			CPM mg	ARAC mg	MP mg	VCR mg	PEG-ASP IU	Studies	Comments
			HR (T-ALL & T-NHL)	**CNS3 T-ALL**	**All other patients**							
			Enter calculated dose above and actual dose administered below									
		1		___mg	___mg	___mg	___mg	___mg			a, b, c, d, e	
		2					___mg					
		3					___mg					
		4					___mg					
		8	___mg	___mg	___mg		___mg				c, d	
		9					___mg					
		10					___mg					
		11					___mg					
		12										
		13										
		14										
		15$	___mg		___mg				___mg	___IU	c, d	
		22	___mg		___mg				___mg		c, d	
		29	___mg			___mg	___mg	___mg			c, d, (f, g)&	
		30					___mg					
		31					___mg					
		32					___mg					
		36					___mg				c	
		37					___mg					
		38					___mg					
		39					___mg					
		42										
		43							___mg	___IU	a, c	
		50							___mg		c	
		56									c, f^β, &, g^&, (h, i, j)^γ	
		57	**Start next course (Interim Maintenance, Sec 4.5. or 4.6) on Day 57 or when blood count parameters are met (whichever occurs later).**									

@ Please note the different IT MTX schedules according to risk assignment group and CNS status (see Section 4.1.1 for details).

$ IR/HR T-ALL patients on Arm A are expected to begin prophylactic cranial XRT during Week 3 & High Risk T-ALL pts **ONLY**; see Section 7.1 for details

β Obtain in T-NHL if positive at diagnosis (see Section 7.2 for details) γ T-NHL only (see Section 7.2 for details)

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.4 CONSOLIDATION Arms B (CMTX + Nel) and D (HDMTX + Nel) Weeks 6-16

This Consolidation course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D).

Criteria to begin Consolidation

Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). **Once Consolidation therapy has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 43 only**. Once the Day 1 or Day 43 Nelarabine has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated.

T-ALL patients who are High Risk with MRD > 1% and/or M2 marrow on Day 29 should be randomized and proceed directly to Consolidation without waiting for count recovery.

T-ALL patients who are Induction failures with an M3 marrow at Day 29 should sign consent for post-Induction therapy and start Consolidation therapy [Arm D (HDMTX + Nel)] immediately after Day 29 marrow results are known and should not wait for count recovery to occur.

T-NHL patients who are Induction failures with NR (see Section 11.3) should sign consent for post-Induction therapy and start Consolidation therapy on Arm B (CMTX + Nel) immediately after Day 29 evaluation results are known and should not wait for count recovery to occur.

Nelarabine: IV (over 60 minutes)
650 mg/m^2/dose on Days 1-5 and 43-47

NOTE: the drug manufacturers of Nelarabine have included as part of the agent's risks/side effects that patients receiving intrathecal chemotherapy or craniospinal irradiation with Nelarabine may be at increased risk of neurological adverse events.

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Days 15, 22, 57 and 64 (omit Day 22 if CNS3 T-ALL). The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Cyclophosphamide: IV (over 30 minutes)
1000 mg/m^2/dose on Days 8 and 50. Reduce urine specific gravity to ≤ 1.015 prior to administering. Give IV fluids to maintain urine output. May use Furosemide 0.25 – 0.5 mg/kg/dose IV for urine output < 3 mL/kg/hr after CPM. See Section 5.3 for additional details.

Cytarabine: IV over 1-30 minutes or Subcutaneous
75 mg/m^2/dose on Days 8-11, 15-18, 50-53 and 57-60

Mercaptopurine: PO
60 mg/m^2/dose on Days 8-21 and 50-63. Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dose using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix I for details. **Do not escalate or modify dose based on blood counts during this course.**

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 22, 29, 64 and 71

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Pegaspargase: IM (or IV over 1-2hours)
2500 International units/m^2/dose **x 1 dose** on Days 22 and 64

For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Testicular Radiation Therapy
Patients with T-ALL and persistent testicular disease at end-Induction receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 14.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. T-NHL patients with testicular disease are not eligible for this study.

Cranial Radiation Therapy
Prophylactic cranial radiation therapy (1200 cGy in 8 once-daily fractions) for Intermediate/High Risk T-ALL patients randomized to Arm B (CMTX + Nel) should be given during Weeks 4 and 5 of Consolidation (see Section 14.0). Cranial XRT (1800 cGy in 10 once-daily fractions) for CNS3 T-ALL patients and prophylactic cranial XRT (1200 cGy in 8 once-daily fractions) for Intermediate/High Risk T-ALL patients randomized to Arm D (HDMTX + Nel) will be given during DI. Intrathecal therapy is NOT held during the concomitant administration of CRT. Low Risk T-ALL patients (defined in Section 4.1) and all T-NHL patients WILL NOT receive any cranial XRT.

The therapy delivery maps (TDMs) for Consolidation are on the next two pages.

Following completion of Consolidation, the next course (Interim Maintenance, Section 4.5 or 4.6) starts on Day 78 or when blood count parameters are met (whichever occurs later).

4.4.1a **CONSOLIDATION Arm B (CMTX + Nel) and Arm D (HDMTX + Nel)**
This Consolidation course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D).

Patient name or initials _____ DOB _____

*Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later). Patients with T-ALL and persistent testicular disease at end-Induction receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 14.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. This Course lasts 11 weeks (77 days) and this Therapy Delivery Map is on **two (2)** pages.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Nelarabine (Nel)	IV over 60 min	650 mg/m^2/dose	Days 1-5 & 43-47	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 15, 22*, 57 & 64 * Omit Day 22 for CNS3 T-ALL pts	**Note age-based dosing**
Cyclophosphamide (CPM)	IV over 30 min	1000 mg/m^2/dose	Days 8 & 50	See Section 4.4 for admin guidelines
Cytarabine (ARAC)	IV or SubQ	75 mg/m^2/dose	Days 8-11, 15-18, 50-53 & 57-60	
Mercaptopurine (MP)	PO	60 mg/m^2/dose	Days 8-21 & 50-63	See Section 4.4 & Appendix I for admin guidelines
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 22, 29, 64 & 71	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**
Pegaspargase (PEG-ASP)	IM (or IV over 1-2 hours)	2500 International units/m^2/dose	Days 22 & 64	For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

OBSERVATIONS
a. Hx/PE
b. Weight (BSA)
c. CBC/diff/platelets
d. CSF cell count, cytospin
e. ALT, creatinine, bilirubin
f. BM evaluation†
g. PB for MRD (T-ALL only)

T-NHL only:
h. Chest CT/Chest x-ray
i. Abdomen/Pelvis CT
j. Bone scan

† T-ALL patients are considered off protocol therapy if not M1 at end-Consolidation

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Therapy Delivery Map **Ht** **cm** **Wt** **kg** **BSA** **m^2**

Date Due	Date Given	Day	Nel mg	IT MTX mg	CPM mg	ARAC mg	MP mg	VCR mg	PEG-ASP IU	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		1	___ mg							a, b, c, e	
		2	___ mg								
		3	___ mg								
		4	___ mg								
		5	___ mg								

		8			___ mg	___ mg	___ mg			c	
		9				___ mg					
		10				___ mg					
		11				___ mg					

		15		___ mg		___ mg				c, d	
		16				___ mg					
		17				___ mg					
		18				___ mg					

		21									
		22$		___ mg@				___ mg	___ IU	c, d@	
		23									
		24									
		25									
		26									

		29						___ mg		c	
		30									
		31									
		32									
		33									

		36								c	

@ Not for CNS3 T-ALL pts

$ IR/HR T-ALL pts on Arm B are expected to begin prophylactic cranial XRT during Week 4

4.4.1b **CONSOLIDATION Arm B (CMTX + Nel) and Arm D (HDMTX + Nel)**
This Consolidation course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D).

Patient name or initials _____ DOB _____

*Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL (whichever occurs later). Patients with T-ALL and persistent testicular disease at end-Induction receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 14.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. This Course lasts 11 weeks (77 days) and this Therapy Delivery Map is on **two (2)** pages.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Nelarabine (Nel)	IV over 60 min	650 mg/m^2/dose	Days 1-5 & 43-47		a. Hx/PE b. Weight (BSA) c. CBC/diff/platelets d. CSF cell count, cytospin e. ALT, creatinine, bilirubin f. BM evaluation† g. PB for MRD (T-ALL only) T-NHL only: h. Chest CT/Chest x-ray i. Abdomen/Pelvis CT j. Bone scan † T-ALL patients are considered off protocol therapy if not M1 at end-Consolidation **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 15, 22*, 57 & 64 * Omit Day 22 for CNS3 T-ALL pts	**Note age-based dosing**	
Cyclophosphamide (CPM)	IV over 30 min	1000 mg/m^2/dose	Days 8 & 50	See Section 4.4 for administration guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m^2/dose	Days 8-11, 15-18, 50-53 & 57-60		
Mercaptopurine (MP)	PO	60 mg/m^2/dose	Days 8-21 & 50-63	See Section 4.4 & Appendix I for administration guidelines	
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 22, 29, 64 & 71	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Pegaspargase (PEG-ASP)	IM (or IV over 1-2hours)	2500 International units/m^2/dose	Days 22 & 64	For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Therapy Delivery Map **Ht____cm** **Wt____kg** **BSA____m^2**

Date Due	Date Given	Day	Nel mg	IT MTX mg	CPM mg	ARAC mg	MP mg	VCR mg	PEG-ASP IU	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		43	___mg							a, c, (f, g)**	
		44	___mg								
		45	___mg								
		46	___mg								
		47	___mg								

		50			___mg	___mg	___mg			a, c	
		51				___mg					
		52				___mg					
		53				___mg					

		57		___mg		___mg				c, d	
		58				___mg					
		59				___mg					
		60				___mg					

		63									
		64		___mg				___mg	IU	c, d	

		71						___mg		c	

		77								a, b, c, f$^{\beta}$, **, g**, (h, i, j)$^{\gamma}$	
		78	**Start next course (Interim Maintenance, Sec 4.5. or 4.6) on Day 78 or when blood count parameters are met (whichever occurs later).**								

** HR & IF T-ALL pts only; see Section 7.1 for details
β Obtain in T-NHL if positive at diagnosis (see Section 7.2 for details) γ T-NHL only (see Section 7.2 for details)

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.5 INTERIM MAINTENANCE Arms A (CMTX) and B (CMTX + Nel) Weeks 14-21 (Arm A) & 17-24 (Arm B)

This Interim Maintenance (IM) course is for patients randomized or assigned to either treatment arm with Capizzi methotrexate (Arms A and B).

Criteria to begin Interim Maintenance – Capizzi Methotrexate
Begin IM when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts 10 days after initial dose of methotrexate.

A) If ANC is < 500/µL or platelets < 50,000/µL, hold all chemotherapy and repeat blood counts in 4 days.
   1. If ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previously.
   2. If ANC is still < 500/µL or platelets < 50,000/µL, give VCR, PEG-ASP and IT MTX (if due) and repeat counts in 7 days to begin next dose of MTX if counts are adequate. If counts now adequate, reduce dose of MTX by 20%. Do not make up missed dose of MTX. If counts still too low, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL.
B) If ANC ≥ 500/µL but < 750/µL and platelets ≥ 50,000/µL but < 75,000/µL, give same dose of MTX as previously.
C) If ANC ≥750/µL and platelets ≥ 75,000/µL escalate MTX by 50 mg/m^2/dose
D) If allergic to pegaspargase, give Erwinia L-asparaginase as described in Section 5.1.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1, 11, 21, 31 and 41

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: IV push
Start dose at 100 mg/m^2/dose and **escalate by 50 mg/m^2/dose** (see Section 5.8.2) on Days 1, 11, 21, 31 and 41. Discontinue escalation and resume at 80% of last dose if delay is necessary for myelosuppression and/or Grade 3 mucositis.

Pegaspargase: IM (or IV over 1-2 hours)
2500 International units/m^2/dose on Days 2 and 22.

For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Note: Continue pegaspargase dosing despite ANC and platelet count.

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Days 1 and 31. The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

See Section 5.8 for Dose Modifications based on hepatotoxicity and/or mucositis.

The therapy delivery map (TDM) for Interim Maintenance is on the next page.

Following completion of Interim Maintenance, the next course (Delayed Intensification, Section 4.7 or 4.8) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.5.1 **INTERIM MAINTENANCE Arm A (CMTX) & Arm B (CMTX + Nel)** This IM course is for patients randomized or assigned to either of the treatment arms with Capizzi methotrexate (Arms A and B).	Patient name or initials DOB

Begin IM when peripheral counts recover with an ANC ≥ 750/μL and platelets ≥ 75,000/μL. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts 10 days after initial dose of methotrexate. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on ***one (1)*** *page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE, weight (BSA) b. CBC/diff/platelets* c. CSF cell count, cytospin d. ALT, creatinine, bilirubin * Obtain repeat counts if chemotherapy is held; see Section 4.5 **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV Push	Start dose @ 100 mg/m²/dose then escalate by 50 mg/m²/dose	Days 1, 11, 21, 31 & 41	See Sections 4.5 and 5.8.2 for details	
Pegaspargase (PEG-ASP)	IM (or IV over 1-2 hours)	2500 International units/m²/dose	Days 2 & 22	For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl Note: Continue PEG-ASP dosing despite ANC & plt count	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1 – 1.99 — 8 mg 2 – 2.99 — 10 mg 3 – 8.99 — 12 mg ≥ 9 — 15 mg	Days 1 & 31	**Note age-based dosing**	

Therapy Delivery Map **Ht** **cm** **Wt** **kg** **BSA** **m²**

Date Due	Date Given	Day	VCR ____mg	IV MTX *(escalating dose)*	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg		____mg	a, b, c, d	
		2			____IU			

		11	____mg	____mg			b, d	

		21	____mg	____mg			b, d	
		22			____IU			

		31	____mg	____mg		____mg	b, c, d	

		41	____mg	____mg			b, d	

		56						
		57	**Start next course (Delayed Intensification, Sec 4.7. or 4.8) on Day 57 or when blood count parameters are met (whichever occurs later).**					

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.6 INTERIM MAINTENANCE Arms C (HDMTX) and D (HDMTX + Nel) Weeks 14-21 (Arm C) & 17-24 (Arm D)

This Interim Maintenance (IM) course is only for T-ALL patients randomized to either treatment arm with High-Dose methotrexate (Arms C and D). T-NHL patients DO NOT receive HDMTX and will NOT receive therapy on either of these arms.

Criteria to begin Interim Maintenance – High-Dose Methotrexate
Begin IM when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. All chemotherapy should be held for ANC < 750/µL or platelets < 75,000/µL. If counts fail to recover within 2 weeks notify the Study Chair.

Review of BFM and past COG protocols indicates that excess toxicity is not encountered in patients who are > 2 m^2 and receive more than 10 grams of methotrexate. The methotrexate dose should be dosed on the actual meter-squared basis and not capped.

Hold any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors aspirin-containing medications, or TMP-SMX on the days of the MTX infusion and until the MTX level is less than 0.4 µM. In the presence of delayed clearance, continue to hold TMP-SMX until the MTX level is less than 0.1 µM.

High-Dose Methotrexate: IV
5000 mg/m^2/dose on Days 1, 15, 29 and 43. See Section 4.6.1 and Appendix IV for High-Dose methotrexate infusion and leucovorin rescue guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1, 15, 29 and 43

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Mercaptopurine: PO
25 mg/m^2/dose on Days 1-56. Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dosing using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 175 mg/m^2/week as possible. See Appendix I for details. **Do not escalate or modify dose based on blood counts during this course.**

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Days 1 and 29. The volume of CSF removed should equal at least half the volume delivered. **Deliver within 6 hours of the start of IV MTX (hr -6 to +6).**

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

4.6.1 HD MTX Infusion Guidelines

(Please see Section 5.8.1 for additional information.)

When IT therapy and HDMTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

Hold TMP-SMX on the days of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 µM. In the presence of delayed clearance continue to hold TMP-SMX until MTX level is less than 0.1 µM

Hold any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 µM. In the presence of delayed clearance continue to hold these drugs until MTX level is less than 0.1 µM

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HD MTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 µM.

Hour 0: MTX 500 mg/m^2 IV mixed in a final volume of 65 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L and infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 mixed in a final volume of 2935 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L given by continuous IV infusion over 23.5 hours at 125 mL/m^2/hr. Be certain that the HD MTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Hours 24, (36), 42 and 48: Draw MTX level and serum creatinine; NOTE: 36 hour level is only drawn if needed (see below)

> **For MTX levels that exceed these expected values modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/hr**, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point, assure appropriate urine pH and urine volume as above and draw a 42 hour level. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see Section 5.8.1). For patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m^2/hr). If subsequent course is not associated with delayed clearance, attempt to use standard hydration.
>
> **If the 24 hour level is < 150 µM** draw the next level at hour 42 and refer to table in Section 5.8.1.

If the 24 hour level is ≥ 150 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. While waiting for the result and if the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table in Section 5.8.1.

If the 42 and 48 hour levels are ≤ 1 and 0.4 µM, respectively, give leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin. **If levels exceed these values, see Section 5.8.1.**

See Section 5.8 for Dose Modifications based on hepatotoxicity and/or mucositis.

The therapy delivery map (TDM) for Interim Maintenance is on the next page.

Following completion of Interim Maintenance, the next course (Delayed Intensification, Section 4.7 or 4.8) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.6.2 INTERIM MAINTENANCE Arm C (HDMTX) & Arm D (HDMTX + Nel)

This IM course is only for T-ALL patients randomized to either of the treatment arms with High-Dose methotrexate (Arms C and D).

Patient name or initials _____

DOB _____

Begin IM when peripheral counts recover with an ANC ≥ 750/μL and platelets ≥ 75,000/μL. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. All chemotherapy should be held for ANC < 750/μL or platelets < 75,000/μL. If counts fail to recover within 2 weeks notify the Study Chair. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on ***one (1)*** *page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High-Dose Methotrexate (HD MTX)	IV over 24 hours	5000 mg/m^2/dose	Days 1, 15, 29 & 43	See Section 4.6.1 for administration guidelines	a. Hx/PE, weight (BSA) b. CBC/diff/platelets c. CSF cell count, cytospin d. ALT, creatinine, bilirubin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	IV/PO	15 mg/m^2/dose	42, 48 & 54 hrs post HDMTX	See Section 4.6.1 & Appendix IV for details	
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1, 15, 29 & 43	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Mercaptopurine (MP)	PO	25 mg/m^2/dose	Days 1-56	See Section 4.6 for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 1 & 29	Deliver within 6 hours of the start of IV MTX (hr -6 to +6) **Note age-based dosing**	

Therapy Delivery Map **Ht** ____ **cm** **Wt** ____ **kg** **BSA** ____ **m^2**

Date Due	Date Given	Day	HD MTX ____ mg	LCV ____ mg	VCR ____ mg	MP ____ mg	IT MTX ____ mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	____ mg		____ mg	____ mg	____ mg	a, b, c, d	
		2							
		3		____ mg					
		4		____ mg ____ mg					
		5							

		15	____ mg		____ mg			b, d	
		16							
		17		____ mg					
		18		____ mg ____ mg					
		19							

		29	____ mg		____ mg		____ mg	b, c, d	
		30							
		31		____ mg					
		32		____ mg ____ mg					
		33							
		34							

		43	____ mg		____ mg			b, d	
		44							
		45		____ mg					
		46		____ mg ____ mg					
		47							

		56							
		57	**Start next course (Delayed Intensification, Sec 4.7. or 4.8) on Day 57 or when blood count parameters are met (whichever occurs later).**						

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.7 **DELAYED INTENSIFICATION Arms A (CMTX) and C (HDMTX)** (NO Nelarabine) Weeks 22-30

This Delayed Intensification (DI) course is for patients randomized or assigned to either treatment arm WITHOUT NELARABINE (Arms A and C).

Criteria to begin Delayed Intensification (NO Nelarabine)

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy on Days 1 and 29. **Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY**. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1, 8, 15, 43 and 50

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (may give IV)
All patients, regardless of age, receive discontinuous dexamethasone: 5 mg/m^2/dose BID (i.e., 10 mg/m^2/day, divided BID) on Days 1-7 and 15-21.

DOXOrubicin: IV push
25 mg/m^2/dose on Days 1, 8 and 15

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Pegaspargase: IM (or IV over 1-2 hours)
2500 International units/m^2/dose on Day 4 [**OR** 5 **OR** 6] **AND** Day 43

For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Days 1, 29 and 36. The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg

2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Cyclophosphamide: IV (over 30 minutes)
1000 mg/m^2/dose on Day 29.

Reduce urine specific gravity to ≤ 1.015 prior to administering. Give IV fluids to maintain urine output. May use Furosemide 0.25 – 0.5 mg/kg/dose IV for urine output < 3 mL/kg/hr after CPM. See Section 5.3 for additional details.

Cytarabine: IV over 1-30 minutes or Subcutaneous
75 mg/m^2/dose on Days 29-32 and 36-39

Thioguanine: PO
60 mg/m^2/dose on Days 29-42.

Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dose using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details. **Do not escalate or modify dose based on blood counts during this course. Please note: TG should not be administered to any patient receiving CRT during this stage of therapy (i.e. IR/HR T-ALL patients randomized to Arm C and all CNS3 T-ALL patients).**

Cranial Radiation Therapy
Prophylactic cranial XRT (1200 cGy in 8 once-daily fractions) for Intermediate/High Risk T-ALL patients randomized to Arm C (HDMTX) and cranial XRT (1800cGy in 10 once-daily fractions) for CNS3 T-ALL patients should start on Day 50 of DI. Intermediate and High Risk T-ALL patients randomized to Arm A (CMTX) received CRT in Consolidation and WILL NOT receive prophylactic cranial XRT during this phase of therapy. Low Risk T-ALL patients (defined in Section 4.1) and all T-NHL patients WILL NOT receive any cranial XRT. Please see Section 14.0 for all CRT details.

The therapy delivery maps (TDMs) for Delayed Intensification are on the next two pages.

Following completion of Delayed Intensification, the next course (Maintenance, Section 4.9) starts on Day 64 or when blood count parameters are met (whichever occurs later).

4.7.1a **DELAYED INTENSIFICATION Arm A (CMTX) & Arm C (HDMTX) (NO Nelarabine)**

This Delayed Intensification course is for patients randomized or assigned to either treatment arm WITHOUT NELARABINE.

Patient name or initials

DOB

*Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy on Days 1 and 29. Once Delayed Intensification has begun, it may be interrupted for myelosuppression on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE, weight (BSA) b. CBC/diff/platelets c. CSF cell count, cytospin d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (may give IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 15 min	25 mg/m²/dose	Days 1, 8, & 15	See Section 4.7 for administration guidelines	
Pegaspargase (PEG-ASP)	IM (or IV over 1-2 hours)	2500 International units/m²/dose	Day 4 [**OR** 5 **OR** 6] **AND** Day 43	For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1 – 1.99 — 8 mg 2 – 2.99 — 10 mg 3 – 8.99 — 12 mg ≥ 9 — 15 mg	Days 1, 29 & 36	**Note age-based doing**	
Cyclophosphamide (CPM)	IV over 30 min	1000 mg/m²/dose	Day 29	See Section 4.7 for administration guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42 (omit all TG for IR/HR T-ALL pts receiving CRT on Arm C)	See Section 4.7 & Appendix II for administration guidelines	

Therapy Delivery Map **Ht____cm** **Wt____kg** **BSA____m²**

Date Due	Date Given	Day	VCR mg	DEX mg mg	DOXO mg	PEG-ASP IU	IT MTX mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	mg	mg mg	mg		mg	a, b, c, d	
		2							
		3							
		4							
		5				IU			
		6							
		7							
		8	mg		mg			b	
		9							
		10							
		11							
		12							
		13							
		14							
		15	mg	mg mg	mg			b	
		16							
		17							
		18							
		19							
		20							
		21							
		22						b	
		This therapy delivery map continues on the next page with Day 29.							

4.7.1b **DELAYED INTENSIFICATION Arm A (CMTX) & Arm C (HDMTX) (NO Nelarabine)**

This Delayed Intensification course is for patients randomized or assigned to either treatment arm WITHOUT NELARABINE.

Patient name or initials

DOB

*Patients should have ANC ≥ 750/μL and platelets ≥ 75,000/μL prior to starting therapy on Days 1 and 29. Once Delayed Intensification has begun, it may be interrupted for myelosuppression on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE, weight (BSA) b. CBC/diff/platelets c. CSF cell count, cytospin d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (may give IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 15 min	25 mg/m²/dose	Days 1, 8, & 15	See Section 4.7 for administration guidelines	
Pegaspargase (PEG-ASP)	IM (or IV over 1- 2 hours)	2500 International units/m²/dose	Day 4 [**OR** 5 **OR** 6] **AND** Day 43	For IV: Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1 – 1.99 — 8 mg 2 – 2.99 — 10 mg 3 – 8.99 — 12 mg ≥ 9 — 15 mg	Days 1, 29 & 36	**Note age-based dosing**	
Cyclophosphamide (CPM)	IV over 30 min	1000 mg/m²/dose	Day 29	See Section 4.7 for administration guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42 (omit all TG for IR/HR T-ALL pts receving CRT on Arm C)	See Sec 4.7 & Appendix II for administration guidelines	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	PEG-ASP ____IU	IT MTX ____mg	CPM ____mg	ARAC ____mg	TG$ mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29			____mg	____mg	____mg	____mg$	a, b, c, d	
		30								
		31								
		32								
		33								
		34								
		35								
		36			____mg		____mg		b, c	
		37								
		38								
		39								

		42								
		43	____mg	IU					b	

		50$	____mg						b	

		57							b	

		63								
		64	**Start next course (Maintenance, Sec 4.9) on Day 64 or when blood count parameters are met (whichever occurs later)**							

$ IR/HR T-ALL patients on Arm C and all CNS3 T-ALL patients are expected to begin cranial XRT on Day 50. Hold all thioguanine (Days 29-42) for pts receiving cranial XRT.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.8 DELAYED INTENSIFICATION Arms B (CMTX + Nel) and D (HDMTX + Nel)

Weeks 25-33

This Delayed Intensification (DI) course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D).

Criteria to begin Delayed Intensification

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy on Days 1 and 29. **Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY**. Once the Day 1 therapy or Day 29 Nelarabine has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proved or presumed infection and resumed when the signs of infection have abated.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1, 8, 15 and 50

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (may give IV)
All patients, regardless of age, received discontinuous dexamethasone: 5 mg/m^2/dose BID (i.e., 10 mg/m^2/day, divided BID) on Days 1-7 and 15-21

DOXOrubicin: IV push
25 mg/m^2/dose on Days 1, 8 and 15

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Pegaspargase: IM (or IV over 1-2 hours)
2500 International units/m^2/dose on Day 4 [**OR** 5 **OR** 6] **AND** Day 50

For IV: Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Days 1, 36 and 43. The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Nelarabine: IV (over 60 minutes)
650 mg/m^2/dose on Days 29-33

NOTE: the drug manufacturers of Nelarabine have included as part of the agent's risks/side effects that patients receiving intrathecal chemotherapy or craniospinal irradiation with Nelarabine may be at increased risk of neurological adverse events.

Cyclophosphamide: IV (over 30 minutes)
1000 mg/m^2/dose on Day 36.

Reduce urine specific gravity to ≤ 1.015 prior to administering. Give IV fluids to maintain urine output. May use Furosemide 0.25 – 0.5 mg/kg/dose IV for urine output < 3 mL/kg/hr after CPM. See Section 5.3 for additional details.

Cytarabine: IV over 1-30 minutes or Subcutaneous
75 mg/m^2/dose on Days 36-39 and 43-46

Thioguanine: PO
60 mg/m^2/dose on Days 36-49.

Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dose using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details. **Do not escalate or modify dose based on blood counts during this course. Please note: TG should not be administered to any patient receiving CRT during this stage of therapy (i.e. IR/HR T-ALL patients randomized to Arm D and all Induction Failures/CNS3 T-ALL patients).**

Cranial Radiation Therapy
Prophylactic cranial XRT (1200 cGy in 8 once-daily fractions) for Intermediate/High Risk T-ALL patients randomized to Arm D (HDMTX + Nel) and cranial XRT (1800cGy in 10 once-daily fractions) for CNS3 T-ALL patients should start on Day 50 of DI. Intermediate/High Risk T-ALL patients randomized to Arm B (CMTX + Nel) received CRT in Consolidation and WILL NOT receive prophylactic cranial XRT during this phase of therapy. Low Risk T-ALL patients (defined in Section 4.1) and all T-NHL patients WILL NOT receive any cranial XRT. Please see Section 14.0 for all CRT details.

The therapy delivery maps (TDMs) for Delayed Intensification are on the next two pages.

Following completion of Delayed Intensification, the next course (Maintenance, Sections 4.10 and 4.11) starts on Day 64 or when blood count parameters are met (whichever occurs later).

4.8.1a **DELAYED INTENSIFICATION Arm B (CMTX + Nel) & Arm D (HDMTX + Nel)**
This Delayed Intensification course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D).

Patient name or initials

DOB

*Patients should have ANC ≥ 750/μL and platelets ≥ 75,000/μL prior to starting therapy on Days 1 and 29. Once Delayed Intensification has begun, it may be interrupted for myelosuppression on Day 29 ONLY. Once the Day 1 therapy or Day 29 Nelarabine has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proved or presumed infection and resumed when the signs of infection have abated. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE b. Weight (BSA) c. CBC/diff/platelets d. CSF cell count, cytospin e. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (may give IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 15 min	25 mg/m²/dose	Days 1, 8, & 15	See Section 4.8 for administration guidelines	
Pegaspargase (PEG-ASP)	IM (or IV over 1-2 hours)	2500 International units/m²/dose	Day 4 [**OR** 5 **OR** 6] **AND** Day 50	For IV: Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 36 & 43	**Note age-based dosing**	
Nelarabine (Nel)	IV over 60 min	650 mg/m²/dose	Days 29-33		
Cyclophosphamide (CPM)	IV over 30 min	1000 mg/m²/dose	Day 36	See Section 4.8 for administration guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m²/dose	Days 36-39 & 43-46		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 36-49 (omit all TG for IR/HR T-ALL pts receiving CRT on Arm D)	See Section 4.8 & Appendix II for administration guidelines	

Therapy Delivery Map **Ht cm Wt kg BSA m²**

Date Due	Date Given	Day	VCR mg	DEX mg mg	DOXO mg	PEG-ASP IU	IT MTX mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	mg	mg mg	mg		mg	a, b, c, d, e	
		2							
		3							
		4							
		5				IU			
		6							
		7							
		8	mg		mg			c	
		9							
		10							
		11							
		12							
		13							
		14							
		15	mg	mg mg	mg			c	
		16							
		17							
		18							
		19							
		20							
		21							
		22						c	
		This therapy delivery map continues on the next page with Day 29.							

4.8.1b **DELAYED INTENSIFICATION Arm B (CMTX + Nel) & Arm D (HDMTX + Nel)**
This Delayed Intensification course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D)

Patient name or initials

DOB

Patients should have ANC ≥ 750/μL & plts ≥ 75,000/μL prior to starting therapy on Days 1 and 29. Once Delayed Intensification has begun, it may be interrupted for myelosuppression on Day 29 ONLY. Once the Day 1 therapy or Day 29 Nelarabine has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proved or presumed infection and resumed when the signs of infection have abated. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE b. Weight (BSA) c. CBC/diff/platelets d. CSF cell count, cytospin e. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (may give IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total dose: 10 mg/m²/day, divided BID	
DOXOrubicin (DOXO)	IV push over 15 min	25 mg/m²/dose	Days 1, 8, & 15	See Section 4.8 for administration guidelines	
Pegaspargase (PEG-ASP)	IM (or IV over 1-2 hours)	2500 International units/m²/dose	Day 4 **[OR** 5 **OR** 6**] AND** Day 50	For IV: Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 36 & 43	**Note age-based dosing**	
Nelarabine	IV over 60 min	650 mg/m²/dose	Days 29-33		
Cyclophosphamide (CPM)	IV over 30 min	1000 mg/m²/dose	Day 36	See Section 4.8 for administration guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m²/dose	Days 36-39 & 43-46		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 36-49 (omit all TG for IR/HR T-ALL pts receiving CRT on Arm D)	See Section 4.8 & Appendix II for administration guidelines	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Day	VCR mg	PEG-ASP IU	IT MTX mg	Nel mg	CPM mg	ARAC mg	TG$ mg	Studies
			Enter calculated dose above and actual dose administered below							
		29				____mg ↓				a, b, c, e
		30								
		31								
		32								
		33								

		36			____mg		____mg	____mg ↓	____mg$ ↓	a, c, d
		37								
		38								
		39								
		40								
		41								
		42								
		43			mg			____mg ↓		c, d
		44								
		45								
		46								
		47								
		48								
		49								
		50$	mg	IU						c

		57								c

		63								
		64	**Start next course (Maintenance, Sec 4.10 & 4.11) on Day 64 or when blood count parameters are met (whichever occurs later)**							

$ T-ALL IR/HR pts on Arm D and all T-ALL Induction Failures/CNS3 pts are expected to begin cranial XRT on Day 50. Hold all thioguanine (Days 36-49) for pts receiving cranial XRT.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.9 MAINTENANCE Arms A (CMTX) and C (HDMTX) (NO Nelarabine) Week 30 until End of Therapy

This Maintenance course is for patients randomized or assigned to either treatment arm WITHOUT NELARABINE (Arms A and C).

Maintenance begins when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. Only mercaptopurine and PO methotrexate will be interrupted for myelosuppression as outlined in Section 5.9.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1, 29 and 57

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

PrednISONE: PO
20 mg/m^2/dose BID (i.e., 40 mg/m^2/day, divided BID) x 5 days every 4 weeks on Days 1-5, 29-33 and 57-61

Mercaptopurine: PO
75 mg/m^2/dose on Days 1-84.

Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dose using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.9 for dose escalation during Maintenance.**

Methotrexate: PO
20 mg/m^2/dose weekly on Days 8, 15, 22, 29*****, 36, 43, 50, 57, 64, 71 and 78. **See Section 5.9 for dose escalation during Maintenance.**

***** Omit Day 29 of FIRST 4 CYCLES FOR LOW RISK T-ALL & STANDARD RISK T-NHL PATIENTS ONLY

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Day 1 **(also on Day 29 of the first 4 cycles of Maintenance for Low Risk T-ALL and Standard Risk T-NHL patients ONLY)**. The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

The therapy delivery map (TDM) for Maintenance is on the next page.

Begin subsequent Maintenance cycles regardless of counts. Only mercaptopurine and PO methotrexate will be interrupted for myelosuppression as outlined in Section 5.9.

GIRLS T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **two** years from the start of Interim Maintenance (~ Week 119).
BOYS T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **three** years from the start of Interim Maintenance (~ Week 171).
T-NHL patients (regardless of gender): Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **two** years from the start of Interim Maintenance (~Week 119)
May stop therapy on anniversary date if prednisone is completed for the 5-day prednisone pulse. Anniversary date is defined as the date marking two (2) years (for T-ALL girls and all T-NHL patients, regardless of gender) and three (3) years (for T-ALL boys) from the start of Interim Maintenance.

4.9.1 MAINTENANCE Arm A (CMTX) & Arm C (HDMTX)

This Maintenance course is for patients randomized or assigned to either of the treatment arms WITHOUT NELARABINE (Arms A and C). Maintenance is given in 12-week cycles and is repeated until two (2) years (for T-ALL girls and all T-NHL patients, regardless of gender) and three (3) years (for T-ALL boys) from the start of Interim Maintenance.

Patient name or initials

DOB

Maintenance begins when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. Only Mercaptopurine and PO Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. This Cycle lasts 12 weeks (84 days) and this Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE b. Weight (BSA) c. CBC/diff/platelets d. CSF cell count, cytospin e. ALT, creatinine, bilirubin T-NHL only: f. Chest CT/Chest x-ray g. Abdomen/Pelvis CT h. Bone scan **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
PrednISONE (PRED)	PO	20 mg/m²/dose BID	Days 1-5, 29-33 & 57-61	Total daily dose: 40 mg/m²/day, divided BID	
Mercaptopurine (MP)	PO	75 mg/m²/dose	Days 1-84	See Appendix I for admin guidelines; see Sec 5.9 regarding dose escalation	
Methotrexate (MTX)	PO	20 mg/m²/dose weekly	Days 8, 15, 22, 29@, 36, 43, 50, 57, 64, 71 & 78	See Section 5.9 regarding dose escalation @ Omit Day 29 of first 4 cycles only (for Low Risk T-ALL & Standard Risk T-NHL pts)	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Day 1 Day 29 (Cycles 1-4) **Low Risk T-ALL & Standard Risk T-NHL pts ONLY**	**Note age-based dosing** See Section 2.1 for rationale on omitting Day 29 IT MTX in certain risk groups.	

Enter Cycle # _____ **Ht** _____ **cm** **Wt** _____ **kg** **BSA** _____ **m²**

Date Due	Date Given	Day	VCR ___ mg	PRED ___ mg ___ mg	MP ___ mg	PO MTX ___ mg	IT MTX ___ mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	___mg	___mg ___mg	___mg		___mg	(a, c)^ (b, d, e)#	
		---		↓	↓				
		5							

		8				mg			

		15				mg			

		22				mg			

		29	___mg	___mg ___mg		___mg@	___mg**	(a, c)^, d**	
		---		↓	↓				
		33							

		36				mg			

		43				mg			

		50				___mg			

		57	___mg	___mg ___mg		mg		(a, c)^	
		---		↓	↓				
		61							

		64				___mg			

		71				___mg			

		78				___mg			

		84						(a, c)^ (f, g, h)&	
		85	**Begin next cycle on Day 85 regardless of counts and repeat until two years (for T-ALL girls and all T-NHL pts, regardless of gender) and three years (for T-ALL boys) from the start of Interim Maintenance. Only MP & PO MTX will be interrupted for myelosuppression during subsequent Maintenance cycles as outlined in Section 5.9.**						

Start of each 12-week cycle ^ Every 4 weeks each 12-week cycle ** First 4 cycles only (**Low Risk T-ALL & Standard Risk T-NHL pts ONLY**)
@ Omit in first 4 cycles only for Low Risk T-ALL & Standard Risk T-NHL pts & T-NHL pts only at completion of Maintenance therapy (see Section 7.2)

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.10 **MAINTENANCE Arms B (CMTX + Nel) and D (HDMTX + Nel)** CYCLES 1-3 (Weeks 34 – 69)

This Maintenance course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D).

Maintenance begins when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. Only mercaptopurine and PO methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. **If delays exceed two weeks or interfere with Nelarabine administration, please notify the Study Chair.**

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1 and 57

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

PrednISONE: PO
20 mg/m^2/dose BID (i.e., 40 mg/m^2/day, divided BID) on Days 1-5 and 57-61.

Mercaptopurine: PO
75 mg/m^2/dose on Days 1-28 and 36-84.

Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dose using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.9 for dose escalation during Maintenance.**

Methotrexate: PO
20 mg/m^2/dose weekly on Days 8, 15, 22, 36, 43, 50, 57, 64, 71 & 78. **See Section 5.9 for dose escalation during Maintenance.**

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Day 1. The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Nelarabine: IV (over 60 minutes)

650 mg/m^2/dose on Days 29-33. **DO NOT administer concomitantly with other chemotherapy agents.**

NOTE: the drug manufacturers of Nelarabine have included as part of the agent's risks/side effects that patients receiving intrathecal chemotherapy or craniospinal irradiation with Nelarabine may be at increased risk of neurological adverse events.

Repeat above cycle two (2) times for a total of three (3) cycles with Nelarabine. Then proceed to additional 12-week Maintenance cycles (Section 4.11) until End of Therapy.

The therapy delivery map (TDM) for this block of Maintenance therapy is on the next page.

4.10.1 MAINTENANCE Arm B (CMTX + Nel) & Arm D (HDMTX + Nel) CYCLES 1-3 (Weeks 34-69)

This Maintenance therapy block is for patients randomized or assigned to either of the treatment arms PLUS NELARABINE (Arms B and D). This block of Maintenance therapy is repeated twice for a total of three (3) cycles with Nelarabine.

Patient name or initials

DOB

*Maintenance begins when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL. Only Mercaptopurine and PO Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. **If delays exceed two weeks or interfere with Nelarabine administration, please notify the Study Chair.** This Cycle lasts 12 weeks (84 days) and this Therapy Delivery Map is on **one (1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE b. Weight (BSA) c. CBC/diff/ platelets d. CSF cell count, cytospin e. ALT, creatinine, bilirubin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
PrednISONE (PRED)	PO	20 mg/m²/dose BID	Days 1-5 & 57-61	Total daily dose: 40 mg/m²/day, divided BID	
Mercaptopurine (MP)	PO	75 mg/m²/dose	Days 1-28 & 36-84	See Appendix I for admin guidelines; see Section 5.9 regarding dose escalation	
Methotrexate (MTX)	PO	20 mg/m²/dose weekly	Days 8, 15, 22, 36, 43, 50, 57, 64, 71 & 78	See Section 5.9 regarding dose escalation	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) – Dose 1 – 1.99 – 8 mg 2 – 2.99 – 10 mg 3 – 8.99 – 12 mg ≥ 9 – 15 mg	Day 1 ONLY	**Note age-based dosing**	
Nelarabine (Nel)	IV over 60 min	650 mg/m²/dose	Days 29-33	Note: only three (3) cycles of Nelarabine **DO NOT administer concomitantly with other chemotherapy agents**	

Enter Cycle # **Ht** cm **Wt** kg **BSA** m²

Date Due	Date Given	Day	VCR mg	PRED mg mg	MP mg	PO MTX mg	IT MTX mg	Nel mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		1	mg	mg mg	mg		mg		(a, c)^ (b, d, e)#	
		---		↓	↓					
		5								

		8				mg				

		15				mg				

		22				mg				

		28								
		29						mg	(a, c)^	
		---						↓		
		33								

		36			mg	mg				
		---			↓					
		43				mg				

		50				mg				

		57	mg	mg mg		mg			(a, c)^	
		---		↓						
		61								

		64				mg				

		71				mg				

		78				mg				

		84							(a, c)^	
		85	**Begin next cycle on Day 85 and repeat two times for a total of three (3) cycles with Nelarabine**							

^ Every 4 weeks # Every 12 weeks

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

4.11 MAINTENANCE CONTINUED AFTER CYCLE THREE Arms B (CMTX + Nel) and D (HDMTX + Nel)

This Maintenance course is for patients randomized or assigned to either treatment arm PLUS NELARABINE (Arms B and D).

Maintenance continues when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. Only mercaptopurine and PO methotrexate will be interrupted for myelosuppression as outlined in Section 5.9**.**

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (max dose 2 mg) on Days 1, 29 and 57

Special precautions: FOR INTRAVENOUS USE ONLY
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

PrednISONE: PO
20 mg/m^2/dose BID (i.e., 40 mg/m^2/day, divided BID) x 5 days every 4 weeks on Days 1-5, 29-33 and 57-61.

Mercaptopurine: PO
75 mg/m^2/dose on Days 1-84.

Give at least 1 hour after evening meal. To be taken without milk or citrus products. Adjust dose using half tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix I for details. **See Section 5.9 for dose escalation during Maintenance.**

Methotrexate: PO
20 mg/m^2/dose weekly on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78. **See Section 5.9 for dose escalation during Maintenance.**

Intrathecal Methotrexate: IT
For intrathecal administration, dilute with 5-10 mL preservative-free normal saline or lactated Ringer's solution on Day 1. The volume of CSF removed should equal at least half the volume delivered.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

The therapy delivery map (TDM) for Maintenance continued after Cycle Three is on the next page.

Begin subsequent Maintenance cycles regardless of counts. Only mercaptopurine and PO methotrexate will be interrupted for myelosuppression as outlined in Section 5.9**.**

GIRLS T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **two** years from the start of Interim Maintenance (~ Week 121).
BOYS T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **three** years from the start of Interim Maintenance (~ Week 173).
T-NHL patients (regardless of gender): Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **two** years from the start of Interim Maintenance (~Week 121).
May stop therapy on anniversary date if prednisone is completed for the 5-day prednisone pulse. Anniversary date is defined as the date marking two (2) years (for T-ALL girls and all T-NHL patients, regardless of gender) and three (3) years (for T-ALL boys) from the start of Interim Maintenance.

4.11.1 MAINTENANCE CONTINUED AFTER CYCLE THREE Arm B (CMTX + Nel) & Arm D (HDMTX + Nel)

This Maintenance therapy block is for patients randomized or assigned to either of the treatment arms PLUS NELARABINE (Arms B and D). Maintenance is given in 12-week cycles and is repeated until two (2) years (for T-ALL girls and all T-NHL patients, regardless of gender) and three (3) years (for T-ALL boys) from the start of Interim Maintenance.

Patient name or initials

DOB

*Maintenance continues when peripheral counts recover with ANC ≥ 750/μL and platelets ≥ 75,000/μL. Only Mercaptopurine and PO Methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. This Cycle lasts 12 weeks (84 days) and this Therapy Delivery Map is on **one (1) page**.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE b. Weight (BSA) c. CBC/diff/platelets d. CSF cell count, cytospin e. ALT, creatinine, bilirubin T-NHL only: f. Chest CT/Chest x-ray g. Abdomen/Pelvis CT h. Bone scan **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
PrednISONE (PRED)	PO	20 mg/m²/dose BID	Days 1-5, 29-33 & 57-61	Total daily dose: 40 mg/m²/day, divide BID	
Mercaptopurine (MP)	PO	75 mg/m²/dose	Days 1-84	See Appendix I for admin guidelines; see Section 5.9 regarding dose escalation	
Methotrexate (MTX)	PO	20 mg/m²/dose weekly	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	See Section 5.9 regarding dose escalation	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) – Dose 1 – 1.99 – 8 mg 2 – 2.99 – 10 mg 3 – 8.99 – 12 mg ≥ 9 – 15 mg	Day 1 ONLY	**Note age-based dosing**	

Enter Cycle #_____ Ht ____ cm Wt ____ kg BSA ____ m²

Date Due	Date Given	Day	VCR mg	PRED mg mg	MP mg	PO MTX mg	IT MTX mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	mg	mg mg	mg		mg	(a, c)^ (b, d, e)#	

		5							
		8				mg			

		15				mg			

		22				mg			

		29	mg	mg mg		mg		(a, c)^	

		33							

		36				mg			

		43				mg			

		50				mg			

		57	mg	mg mg		mg		(a, c)^	

		61							

		64				mg			

		71				mg			

		78				mg			

		84						(a, c)^ (f, g, h)&	
		85	**Begin next cycle on Day 85 regardless of counts and repeat until 2 years (for T-ALL girls and all T-NHL pts, regardless of gender) and 3 years (for T-ALL boys) from the start of Interim Maintenance. Only MP & PO MTX will be interrupted for myelosuppression during subsequent cycles of Maintenance as outlined in Sec 5.9.**						

^ Every 4 weeks # Every 12 weeks & T-NHL pts only at completion of Maintenance therapy (see Section 7.2)

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE

5.0 DOSE MODIFICATION FOR TOXICITIES

Notify the Study Chair at the time of removing a patient from protocol therapy for toxicity. The drugs are listed in alphabetical order

5.1 Asparaginase [Pegaspargase (PEG-Asparaginase) or Erwinia]

Allergy

Local Allergic Reactions (inflammation at injection site, swelling): Continue pegaspargase administration in the presence of Grade 1 allergy (transient flushing or rash; drug fever < 38ºC).

Systemic Allergic Reactions: Discontinuation may be considered for severe Grade 2 or higher allergic reactions as defined by CTCAE v4.0.

Note: Pre-medication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged since anti-histamine use may mask the appearance of systemic allergy. Systemic allergy is frequently associated with the presence of asparaginase neutralizing antibodies, which render asparaginase therapy ineffective. In the event of severe systemic or recurrent local allergic reaction, Erwinia asparaginase (now FDA-approved for this indication) should be substituted.

Anaphylaxis: Discontinue pegaspargase if the patient develops Grade 3 anaphylaxis as defined by CTCAE v4.0 (symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, Erwinia asparaginase (now FDA-approved for this indication) should be substituted.

Erwinia asparaginase has a shorter half life and is associated with a shorter duration of asparagine depletion than native *E. coli* asparaginase, with "head-to-head" comparisons of Erwinia and *E. coli* asparaginase, using the same dose and schedule for both preparations, demonstrating a superior outcome, favoring *E. coli* asparaginase[47,48]. Pegaspargase has a longer half-life and is associated with more prolonged asparagine depletion than native *E. coli* asparaginase, but the largest randomized trial comparing weekly native to bi-weekly pegaspargase wasn't powered to detect a difference in outcome[49] Current COG trials have adopted pegaspargase as the preparation of choice, based on the results of CCG 1962. COG AALL07P2 showed that Erwinia asparaginase was well tolerated and achieved nadir serum asparaginase activity at both 48 and 72 hours after dosing that was similar to that achieved with pegaspargase. Based on these and other data, the FDA approved Erwinia asparaginase for use following allergy to pegaspargase, with a dose of Erwinia 25,000 IU/m^2 x 6 doses IM on a Monday/Wednesday/Friday schedule substituted for a single dose of pegaspargase

The dose modification guidelines for ALL trials recommend the substitution for replacement of Erwinia asparaginase for either native or pegaspargase utilizing the following schedule:

Phase(s) of Treatment	Drug(s)	Replacement Schedule for Erwinia asparaginase[#]
Standard Induction, Re-Induction, Interim Maintenance, Delayed Intensification, or phases of therapy in which pegaspargase doses are 13+ days apart	One or more doses of pegaspargase (2,500 IU/m^2)	25,000 IU/m^2/dose IM M/W/F x 6 doses for each dose of pegaspargase

[#]If a patient develops a Grade 3 or higher anaphylaxis to Erwinia, discontinue future asparaginase therapy. Consider discontinuation for severe Grade 2 or higher allergic reactions.

To replace a dose of intravenous pegaspargase that was discontinued during the infusion due to an allergic reaction, the following recommendations may be used to guide patient care.

In the event that a pegaspargase infusion is discontinued for an allergic reaction, regardless of amount received, substitution with Erwinia asparaginase should begin approximately 48 hours after pegaspargase has been discontinued and preferably to coincide with the recommended Monday/Wednesday/Friday administration schedule detailed above in patients who are clinically stable. Up to 6 doses of Erwinia asparaginase may be administered, as tolerated, to replace the incomplete intravenous pegaspargase dose. Of note, Erwinia asparaginase is recommended only for pegaspargase hypersensitivity reactions, and not for pancreatitis, hepatitis, coagulation abnormalities, or other non-hypersensitivity toxicities associated with pegaspargase. To best suit the needs of each individual patient, additional modifications to these recommendations may be made at the discretion of the treating physician.

Coagulopathy: If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

Hyperbilirubinemia: asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity. There are no specific guidelines available.

Hyperglycemia: Do not modify dose. Treat hyperglycemia as medically indicated.

Hyperlipidemia: Do not modify dose.

Ketoacidosis: Hold asparaginase until blood glucose can be regulated with insulin.

Pancreatitis (Grade 3-4): Discontinue asparaginase in the presence of hemorrhagic pancreatitis or severe pancreatitis. In the case of mild pancreatitis, asparaginase should be held until symptoms and signs subside, and amylase levels return to normal and then resumed. Severe pancreatitis is a contraindication to additional asparaginase administration.

Thrombosis: Withhold asparaginase until resolved, and treat with appropriate anti-thrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing LMWH or anti-thrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate. For significant thrombosis, not line related, consider evaluation for inherited predisposition to thrombosis.

CNS Events (bleed, thrombosis or infarction): Hold asparaginase. Treat with FFP, factors or anticoagulation as appropriate. Resume at full dose when all symptoms have resolved (and evidence of recanalization in case of thrombosis by CT/MRI). Consider evaluation for inherited predisposition to thrombosis.

5.2 Nelarabine (Compound 506U78)

If neurologic toxicity develops prior to the completion of 5 days of therapy, Nelarabine should be halted and the study chair should be called immediately. If Grade 4 Nelarabine-related neurotoxicity develops, the patient will be taken off Nelarabine indefinitely.

NOTE: THE DRUG MANUFACTURERS OF NELARABINE HAVE INCLUDED AS PART OF THE AGENT'S RISKS/SIDE EFFECTS THAT PATIENTS RECEIVING INTRATHECAL CHEMOTHERAPY OR CRANIOSPINAL IRRADIATION WITH NELARABINE MAY BE AT INCREASED RISK OF NEUROLOGICAL ADVERSE EVENTS.

Peripheral Neurotoxicity

Investigators are cautioned to monitor patients carefully for the development of signs and symptoms of peripheral neuropathy. In the event that a patient develops initial signs or symptoms of peripheral

neuropathy attributed to the administration of Nelarabine, the agent should be discontinued for the course. Only resume Nelarabine if peripheral neuropathy resolves to less than Grade 2 toxicity. Nelarabine should NOT be continued in patients who develop signs or symptoms suggestive of an ascending polyneuropathy, including a Guillain-Barré-like syndrome, even if these symptoms resolve. It is recommended that patients who develop neurotoxicity in association with Nelarabine undergo a thorough neurologic evaluation to establish a diagnosis and to exclude other potential etiologies (e.g. disease progression, concomitant illness, etc.). If a Guillain-Barré-like syndrome is suspected, therapeutic measures considered appropriate for the individual patients (i.e. intravenous immunoglobulin, plasmapheresis, steroids, and supportive care) should be instituted as soon as possible. It is strongly recommended that you consult with your institution's neurologist.

Central Neurotoxicity

In patients who develop Grade 3 CNS events (e.g., somnolence, mood alteration, irritability, confusion, etc.) that return to < Grade 2 severity prior to the next planned course of Nelarabine, the Nelarabine dose is to be prescribed without treatment interruption.

Nelarabine will not be made up if any doses are missed during a 5-day treatment course. Patients who are unable to receive a 5-day course of Nelarabine because of toxicity should proceed to the next planned course of protocol therapy as soon as recovery allows.

Rhabdomyolysis

If patient(s) develop myalgia or myoglobinuria, they should be evaluated for the potential of having rhabdomyolysis. The patient should receive a workup that includes AST, ALT, creatinine, and creatine kinase (CK)/(CPK) at a minimum. Consideration should be given to consulting a nephrologist. The Study Chair(s) should be notified if the patient develops either of the above symptoms, and the nelarabine should be held. If the patient is stable, other protocol therapy may continue while the patient is undergoing evaluation. Following study chair notification and evaluation for rhabdomyolysis, a decision should be rendered regarding permanently discontinuing the nelarabine.

5.3 **Cyclophosphamide**

Hematuria: Omit in the presence of macroscopic hematuria. If there is a history of previous significant hematuria, hydrate before cyclophosphamide until specific gravity is < 1.010 and hydrate at 125 mL/m^2/hr for 24 hours after dose. Monitor for adequate urine output as per institution guidelines. Give IV mesna at a total dose that is 60% of the cyclophosphamide dose divided to 3 doses (eg, if the cyclophosphamide dose is 1000 mg/m^2, the total mesna dose is 600 mg/m^2 or 200 mg/m^2). Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat 4 and 8 hours after the start of cyclophosphamide. This total daily dose of mesna can also be administered as IV continuous infusion. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion.

5.4 **Cytarabine (ARAC)**

ARAC Syndrome: Do not withhold ARAC for fever if it is likely to have been caused by the ARAC. Obtain blood cultures if a central line is present. For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis.

5.5 **Intrathecal Cytarabine**

Do not withhold dose given on Day 1 of Induction.

5.6 **Daunorubicin and Doxorubicin (Anthracyclines)**

Cardiac Toxicity: Discontinue for clinical or echocardiographic evidence of cardiomyopathy (SF < 27% or EF < 50%) or Grade 3-4 left ventricular systolic dysfunction (LVSD) per CTCAE version 4.0.

Note: use the following updated term to report decreases in the SF or EF: *Cardiac disorders-other.*

Myelosuppression (beyond Induction): If patient has severe infection or severe mucositis (Grade 3-4) and an ANC < 500/μL delay anthracycline during phases other than Induction. During Induction, continue with anthracycline administration. Subsequent doses should be given at full dose.

Hyperbilirubinemia:[50]

Direct bilirubin <1.2 mg/dL	-Full dose
Direct bilirubin 1.2-3.0 mg/dL	-50% dosage decrease.
Direct bilirubin 3.1-5.0 mg/dL	-75% dosage decrease.
Direct bilirubin >5 mg/dL	-Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

Extravasation:
In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines.

5.7 Intrathecal Methotrexate

Systemic toxicity: The dosage for IT chemotherapy will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC < 500/μL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

Dose modifications following an episode of acute neurotoxicity:
Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.[51-53] These toxicities are poorly understood and currently it is impossible to predict who will suffer these complications. In addition, there are no data clearly linking the occurrence of an acute neurotoxic event with an increased risk of long-term neurocognitive dysfunction, nor do changes present on MRI at the time of an acute event clearly correlate with or predict outcome.[53-58] It is clear however, that CNS prophylaxis is a mandatory component of curative therapy for children with ALL. Effective prophylaxis generally takes 2 forms; cranial, or less commonly, craniospinal radiation, with a limited number of doses of IT therapy or prolonged IT therapy with either IT MTX or triple IT therapy (MTX, ARAC and hydrocortisone). Certain protocols, for example BFM 2000[28], include fewer doses of IT MTX, with an acceptably low frequency of CNS relapse, but the backbone of the BFM therapies is not the same as those currently used by the Children's Oncology Group. The exclusive use of IT ARAC has not been studied or described in the context of ALL therapy nor can one demonstrate the safety of omitting multiple doses of IT therapy without concomitant use of cranial irradiation or high dose Methotrexate.

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches or any others. Thus the treating physician must evaluate the patient and, with the family, make the best possible decision with respect to the relative risk and benefit of continued therapy.

Following an acute neurotoxic event, a history and physical exam should guide the differential diagnosis. A neurology consult may be of value and should be considered. Seizures and other transient events may be linked to fever, infection, encephalitis, meningitis, hypertension, electrolyte disturbance, hypoglycemia, trauma, intracranial hemorrhage or thrombosis, narcotic withdrawal, illicit drug use, or other causes in addition to the direct side effects of chemotherapy. Appropriate laboratory studies may include, but are not limited to, blood cultures, a CBC, electrolytes, including glucose, calcium, magnesium and phosphorus, renal and liver function studies and/or an examination of the CSF. Imaging studies may include a CT scan and/or an MRI. The CT is commonly normal, in the absence of stroke, but if calcifications are present, this finding may be indicative of a more severe mineralizing leukoencephalopathy.[59] MRI abnormalities may be pronounced, but transient. Posterior reversible

encephalopathy may be present on MR with extensive diffusion abnormalities, but these do not appear to correlate with subsequent demyelination or gliosis.[60-62] Additional studies, including MR angiography and/or venogram should be considered, if clinically indicated (e.g. focal deficits).

Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration.[63] For patients who return to their "pre-event" status, without residual deficits on physical or neurologic exam, there are few data to support or guide therapeutic interventions. It is reasonable to hold the next dose of IT therapy, or, substitute IT ARAC for 1 dose of IT MTX, or triple IT therapy. It is also reasonable to include leucovorin rescue at a dose of 5 mg/m^2 q 12 hrs x 2 doses beginning 48 hours after the LP. This pattern of rescue was associated with a clear diminution in the incidence of acute neurotoxicity in one case series.[63] There have been questions about potential interference of leucovorin with the efficacy of the IT MTX, but there are little data to support or refute this position. Moreover, the administration 48 hours later would minimize any potential interference. If the event does not recur, resumption of standard therapy should be considered, following one modified or omitted IT dose. In the face of multiply recurrent events, or evidence of progressive encephalopathy, another evaluation is warranted and the treating physician may consider a more prolonged or definitive change in therapy. These decisions are extremely difficult and may hinge on an individuals view of the importance of quality of life versus an increase in the risk of relapse. Since the greatest impact of CNS prophylaxis occurs early in therapy, the timing of these events may also influence clinical decisions. Cranial radiation has been suggested as an alternative to continued IT therapy though much of the literature on long-term neurocognitive dysfunction supports a more deleterious effect from CRT than IT therapy.[64-67] Dramatic deviations from protocol recommended therapy might result in the child being taken off protocol therapy.

The use of dextromethorphan (DM) has been suggested as a neuroprotectant, capable of preventing NMDA mediated neurotoxicity without prohibitive toxicity. Low dose therapy has been recommended, in part, based on data suggesting that DM is concentrated in brain relative to serum. However, the literature on the use of DM supports a tight dose response relationship, with the likelihood of sparing an initially unaffected area, following ischemic damage, linked to dose, in both clinical trials and animal models of CNS ischemia.[68-71] At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander and others[72] have raised concerns about the potential deleterious effects of long-term NMDA receptor blockade on memory because hippocampal long-term potentiation is dependent on the activation of the NMDA receptor. Thus in the absence of a clinical trial there are few data to support the addition of DM.

Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture:
Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by LP. NOTE: Obstruction to CSF flow may be a contraindication to intrathecal and/or intraventricular therapy.

Viral, bacterial, or fungal meningitis: Omit until resolved.

5.8 High-Dose Methotrexate (HD MTX) and Leucovorin Rescue

[*Please note that **HD MTX** refers to* IV *MTX **5 g/m^2 given over 24 hrs***]
Review of methotrexate dosing on BFM-based protocols indicated that excessive methotrexate toxicity has not been encountered in patients larger than 2 m^2 who receive more than 10 grams of methotrexate. The investigator should base the methotrexate on the patient's meter-squared dosing and not cap at 10 grams of methotrexate.

5.8.1 HD MTX Infusion Guidelines

See Appendix IV for a flowchart of the HDMTX/LCV guidelines.

When IT therapy and HDMTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

Hold TMP-SMX on the days of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 µM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Hold any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors, TMP/SMX or aspirin-containing medications on the day of HD MTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 µM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 minutes) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HD MTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 µM.

Hour 0: MTX 500 mg/m^2 IV mixed in a final volume of 65 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L and infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 mixed in a final volume of 2935 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L given by continuous IV infusion over 23.5 hours at 125 mL/m^2/hr. Be certain that the HD MTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Hours 24, (36), 42 and 48: Draw MTX level and serum creatinine; NOTE: 36 hour level is only drawn if needed (see below)

For MTX levels that exceed these expected values modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point, assure appropriate urine pH and urine volume as above and draw a 42 hour level. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see below). For patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m^2/hr). If subsequent course is not associated with delayed clearance, attempt to use standard hydration.

If the 24 hour level is < 150 µM draw the next level at hour 42 and refer to table below.

If the 24 hour level is ≥ 150 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. While waiting for the result and if the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table below.

If the 42 and 48 hour levels are ≤ 1 and 0.4 µM, respectively, give leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin.

(36 hr MTX level)	42 hr MTX level	48 hr MTX level	Leucovorin Rescue++
Only required if 24 hr level is ≥ 150 µM. See below for guidelines**	1.01 to 9.9 µM	0.41 to 5.9 µM	Continue 15 mg/m^2 q 6h until MTX level < 0.1 µM (draw q12-24 h).
	10 to 19.9 µM	6 to 9.9 µM	Increase to 15 mg/m^2 q 3h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	20 to 200 µM	10 to 100 µM	Increase to 100 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	> 200 µM	> 100 µM	Increase to 1000 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.

** **If the 36 hour level exceeds 3 µM**, increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also **consider glucarpidase if 36 hour MTX level exceeds 10 µM** (see below).

++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 µM and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

Nephrotoxicity: Postpone course if pre-treatment (MTX) serum creatinine is > 1.5 x baseline or GFR creatinine clearance < 65 mL/minute/1.73m^2. If renal function does not recover, omit MTX. Do not give HDMTX to a patient with this degree of renal impairment, assuming that prolonged excretion can be managed with glucarpidase. Patients who must omit more than one course of HDMTX will be removed from protocol therapy.

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G_2, Voraxaze™).[73,74] ASD Healthcare is the sole supplier of glucarpidase in the US. To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue will remain on study.

Liver Dysfunction: Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of intravenous MTX. Blood samples for ALT should not be drawn following the start of MTX infusions as MTX causes significant short term elevations in ALT levels.

ALT	IV MTX
< 10 X ULN	Continue with therapy as scheduled
10 – 20 X ULN	Continue with therapy as scheduled for 1 cycle
10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20 X ULN	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20 X ULN for > 2 weeks	Evaluate with AST, Bili, Alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given.

* Please see Section 8.1.2 for TMP/SMX substitutions

Hold IV MTX for direct hyperbilirubinemia of > 2.0 mg/dL.

For patient's allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone (1-2 mg/kg/day, maximum dose 100 mg/day), aerosolized pentamidine (300 mg/q month ≥ 5 years of age), or atovaquone (30 mg/kg/day if 1-3 mo. or > 2 years, 45 mg/kg/day if between 3 mo. & 2 years) may be considered.

Mucositis: For Grade 3-4 mucositis, withhold IV MTX until resolved. Increase leucovorin rescue following the next course from three to five doses on a q6 hr schedule. If subsequent course is not associated with Grade 3-4 mucositis, attempt to decrease the leucovorin. If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25%, increase hydration to 200mL/m^2/hr and continue increased leucovorin as above. Should subsequent courses be well tolerates, use a stepwise approach to resuming a standard approach to drug delivery. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Myelosuppression: All chemotherapy should be held for ANC < 750/µL or platelets < 75,000/µL.

5.8.2 Capizzi Methotrexate Regimens

Liver Dysfunction: Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of intravenous MTX. Blood samples for ALT should not be drawn following the start of MTX infusions as MTX causes significant short term elevation in ALT levels.

ALT	IV MTX
< 10 X ULN	Continue with therapy as scheduled
10 – 20 X ULN	Continue with therapy as scheduled for 1 cycle
10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20 X ULN	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20 X ULN for > 2 weeks	Evaluate with AST, Bili, Alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given.

* Please see Section 8.1.2 for TMP/SMX substitutions

Hold IV MTX for direct hyperbillirubinemia of > 2.0 mg/dL

Mucositis: For Grade 3-4 mucositis, withhold IV MTX until resolved. Discontinue MTX dose escalation and resume at 80% of last dose if therapy is delayed for myelosuppression or Grade 3 or greater mucositis. If mucositis recurs, consider culturing lesions for herpes simplex.

Myelosuppression:

A) If ANC is < 500/µL or platelets < 50,000/µL, hold all chemotherapy and repeat blood counts in 4 days.
   1. If ANC ≥ 500/µL and platelets ≥ 50,000/µL, give same dose of methotrexate as previous cycle.
   2. If ANC is still < 500/µL or platelets < 50,000/µL, give VCR, PEG-ASP and IT MTX (if due) and repeat counts in 7 days to begin next dose of MTX if counts are adequate. If counts now adequate, reduce dose of MTX by 20%. Do not make up missed dose of MTX. If counts still too low, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL.

B) If ANC ≥ 500/µL but < 750µL and platelets ≥50,000/µL but < 75,000/µL, give same dose of MTX as previously.

C) If ANC ≥ 750/µL and platelets ≥ 75,000/µL escalate MTX by 50 mg/m^2/dose.

5.9 PO Methotrexate (MTX) and 6-Mercaptopurine (6-MP)

Interim Maintenance with HD MTX:

If ANC is < 750/µL and/or platelets < 75 000/µL, hold mercaptopurine. Restart mercaptopurine at full dose with next cycle of HD MTX when ANC is ≥ 750/µL and platelets are ≥ 75 000/µL. Do not make up missed doses. Consider a marrow evaluation in the face of persistent or prolonged cytopenias.

If patient develops severe or unexpected myelosuppression, see section below on thiopurine pharmacology testing.

Maintenance:

If neutrophil count falls below 500/µL or if platelet count falls below 50,000/µL during Maintenance, 6-MP and MTX only will be held until recovery above these levels. For the first drop in ANC or platelets, resume chemotherapy (both 6-MP and MTX) at the same dose the patient was taking prior to the episode of myelosuppression. If neutrophil count falls below 500/µL or if platelet count falls below 50,000/µL for a second (or greater) time, discontinue doses of MP and MTX until ANC is ≥ 750/µL and platelets are ≥ 75,000/µL. Restart both 6-MP and MTX at 50% of the dose prescribed at the time the medication was stopped. Then continue to increase to 75% and then 100% of the dose prescribed prior to stopping the medication at 2-4 week intervals provided ANC remains ≥ 750/µL and platelets remain ≥ 75,000/µL. Consider discontinuing TMP/SMX as per supportive care guidelines in Section 8.1.2. If neutrophil count falls below 500/µL or if platelet count falls below 50,000/µL on > 2 occasions during Maintenance, perform thiopurine pharmacology testing as described below. Should therapy be withheld for myelosuppression or elevated transaminase, do not "make up" that week. Resume therapy at the correct point, chronologically.

Dose escalation during Maintenance:

No dose escalations are recommended during the first cycle of Maintenance. Thereafter, for ANC ≥ 1500/µL on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s) alternately increase doses of MTX or MP by 25%. If both MTX and 6-MP are increased once without a fall in ANC, consider noncompliance as a possibility. Noncompliance can be assessed by obtaining a sample for RBC thioguanine nucleotides (TGNs). Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2-4 hours later. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance.

Mucositis Grade 3-4:
MTX should be reduced to 50% if Grade 3 toxicity develops; withhold in the presence of Grade 4 toxicity until there is a resolution, then resume at 50% of original dose with gradual dose escalation. If mucositis persists or recurs, consider culturing for herpes simplex.

Liver Dysfunction:
For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total bilirubin. Monitor SGPT/ALT or SGOT/AST and total bilirubin every 2 weeks during Consolidation and every 4 weeks during Maintenance as long as transaminases remain over 5x ULN.

Continue full dose therapy unless either of the following occurs:

1) Direct bilirubin > 2.0 mg/dL
2) SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) on 2 determinations at least 1 week apart.

If either of these occurs, hold MTX and monitor labs as above, weekly. Restart at full dose therapy when the transaminase is less than 5x ULN, if bilirubin is normal. If liver dysfunction persists, consider a trial period with MTX but without 6-MP, especially if red cell 6-MP methylated derivatives are elevated. If liver function improves in the absence of MP, consider resuming MP dose at 50% and escalating every two weeks as tolerated. Also consider liver biopsy.

Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in SGPT/ALT or SGOT/AST above 5x ULN.

Thiopurine Pharmacology Testing and Dosage Adjustments:
6-MP and 6-TG are methylated directly by thiopurine methyltransferase (TPMT) to an inactive metabolite. TPMT activity varies tremendously among patients, because of a common inherited genetic defect in TPMT. One in 300 patients is completely deficient (homozygous defective) and 10% of the population are moderately deficient in TPMT activity because they have inherited one variant (non-functional) TPMT allele (i.e., heterozygotes).[75-78] Patients with low TPMT form higher concentrations of the thioguanine nucleotides (TGNs) and are more susceptible to acute thiopurine toxicity (primarily myelosuppression, involving neutropenia, thrombocytopenia, and anemia). Patients with the complete deficiency of TPMT tolerate less than 10% of protocol doses of 6MP (10 to 30 mg/m^2/day 3 days per week). About 35% of heterozygotes require a lower dose of 6MP to avoid dose-limiting myelosuppression.[79]

There are now CLIA certified tests for TPMT genotype and phenotype, and for thiopurine metabolites (6-methyl mercaptopurine [6-MMP] and 6-TGN) measurements. Only 3 SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide.[75,80-83] Thus, the genotyping test has a low false negative rate, and may be preferable to TPMT phenotype testing in cases where a history of red cell transfusions would potentially confound assessments of RBC TPMT activity. When the genotyping result is coupled with a phenotyping test for TPMT or with thiopurine metabolite concentrations in erythrocytes, the reliability of the tests will be even greater. Moreover, metabolite levels can provide an index of patient compliance with thiopurine therapy.

Recommendations for Thiopurine Monitoring and Dosage Adjustments:
Since 6-MP is first introduced during Consolidation, concomitantly with myelosuppressive therapy, TPMT genotyping should be considered during Induction, prior to the initiation of 6-MP administration. If TPMT testing has not been performed, consider TPMT testing and/or an assessment of 6-TGN and methlymercaptopurine metabolites when myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy being delivered:

- For patients who have received full dose thiopurine therapy during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status
- TPMT genotyping will be informative in all patients, if at least one mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5%-10% of mutants. NOTE: *Genotyping can be done despite recent transfusions.*

Suggested Dose Adjustments in Patients with Unacceptable Myelosuppression:

- If the patient is *homozygous deficient* for TPMT, the thiopurine dose should be *reduced to* 10-20 mg/m^2/day 3 days per week. If the patient is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30%-50%. Do not increase the dose in response to a high ANC for 4 weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are not often necessary.

- If the patient is homozygous wild-type (high activity) for TPMT, then discontinue TMP/SMX and use pentamidine or dapsone. For modifications of the oral 6-MP and MTX see the beginning of this section (5.9).

5.10 Steroids (Dexamethasone and Prednisone)

Hypertension: Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

Hyperglycemia: Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

Pancreatitis: Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain > 72 hours and ≥ Grade 3 amylase elevation (> 2.0x ULN).

Osteonecrosis (ON): Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) during Induction or Delayed Intensification. Consider omitting Maintenance steroid for osteonecrosis Grade 1 (clinically asymptomatic, radiographic finding only). Omit Maintenance steroid for osteonecrosis Grade 2 or greater, and notify study chair. Consider resuming Maintenance steroid after 6 months if joint symptoms have resolved and if MRI findings have significantly improved or normalized.

Varicella: Steroids should be held during active infection except during Induction. Do not hold during incubation period following exposure.

Inability to use oral doses:
For dexamethasone, substitute the IV preparation mg for mg. For prednisone, substitute IV methylprednisolone at 80% of the oral prednisone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same; prednisone is converted in the liver to prednisolone.

Severe infection: Do not hold or discontinue steroids during Induction without serious consideration, as this is a critical period in the treatment of ALL. Later in therapy, one may consider holding steroid until patient achieves cardiovascular stability, except for "stress doses."

Severe psychosis: Steroid dose may be decreased by 50% for severe psychosis.

5.11 **PO 6-Thioguanine (6-TG)**

Delayed Intensification:
Oral 6-TG will be held for suspected or proven serious infection.

For severe and/or unexpected myelosuppression, evaluate for TPMT activity as described in Section 5.9.

5.12 **Vincristine**

**** PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (SEE APPENDIX V)**

Severe neuropathic pain (Grade 3 or greater): Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. NOTE: neuropathic pain can be not only severe but difficult to treat. However, since vincristine is an important component of curative therapy and the majority of neuropathies are ultimately reversible, vincristine therapy may be given at full dose at investigator discretion. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies. Drugs such as gabapentin may be of value.

Vocal Cord paralysis: Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. See above for comment on CMT.

Foot Drop, paresis: Should be Grade 3 to consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vincristine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. See above for comment on CMT. Physical therapy may be beneficial to maintain range of motion and provide AFO's and other forms of support. Drugs such as gabapentin may be of value.

Jaw pain: Treat with analgesics; do not modify vincristine dose.

Hyperbilirubinemia:[84,85]

Direct bilirubin	Dose reduction
< 3.1 mg/dL	Full dose (maximum dose: 2 mg)
3.1-5.0 mg/dL	50% of calculated dose (maximum dose: 1 mg)
5.1-6.0 mg/dL	75% of calculated dose (maximum dose: 0.5 mg)
> 6 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

Constipation or ileus (> Grade 3) or typhlitis: Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% of calculated dose (maximum dose: 1 mg) and escalate to full dose as tolerated.

Extravasation:
In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines.

5.13 Drug Interactions

Since concurrent use of enzyme inducing anticonvulsants (e.g. phenytoin, phenobarbital, and carbamazepine) with antileukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes [86,87]. Neither Gabapentin nor Levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsant. Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole) and the macrolide group of antibiotics (e.g. erythromycin, clarithromycin, and azithromycin) may have potent inhibitory effects on drug-metabolizing enzymes. Patients receiving some antileukemic drugs (e.g. vincristine, anthracyclines, etoposide) may experience excess toxicity when these agents are given concomitantly; alternate antifungal and antibacterial therapy should be used where possible (see table below).

DRUGS	POTENTIAL INTERACTION	ACTION TO BE TAKEN
Anticonvulsants	Induction of drug metabolizing enzymes Lowered EFS	AVOID phenytoin, Phenobarbital, carbamazepine Consider Gabapentin or Levetiracetam (Keppra) as alternative
Rifampin	Induction of drug metabolizing enzymes	DO NOT USE
Azole Antifungals (fluconazole, itraconazole*, posaconazole, voriconazole, ketoconazole)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS. May need dose reductions of vincristine*, anthracyclines, etoposide, steroids
Macrolide Antibiotics (erythromycin, clarithromycin, azithromycin roxithromycin telithromycin)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS. May need dose reductions of vincristine, anthracyclines, etoposide, steroids

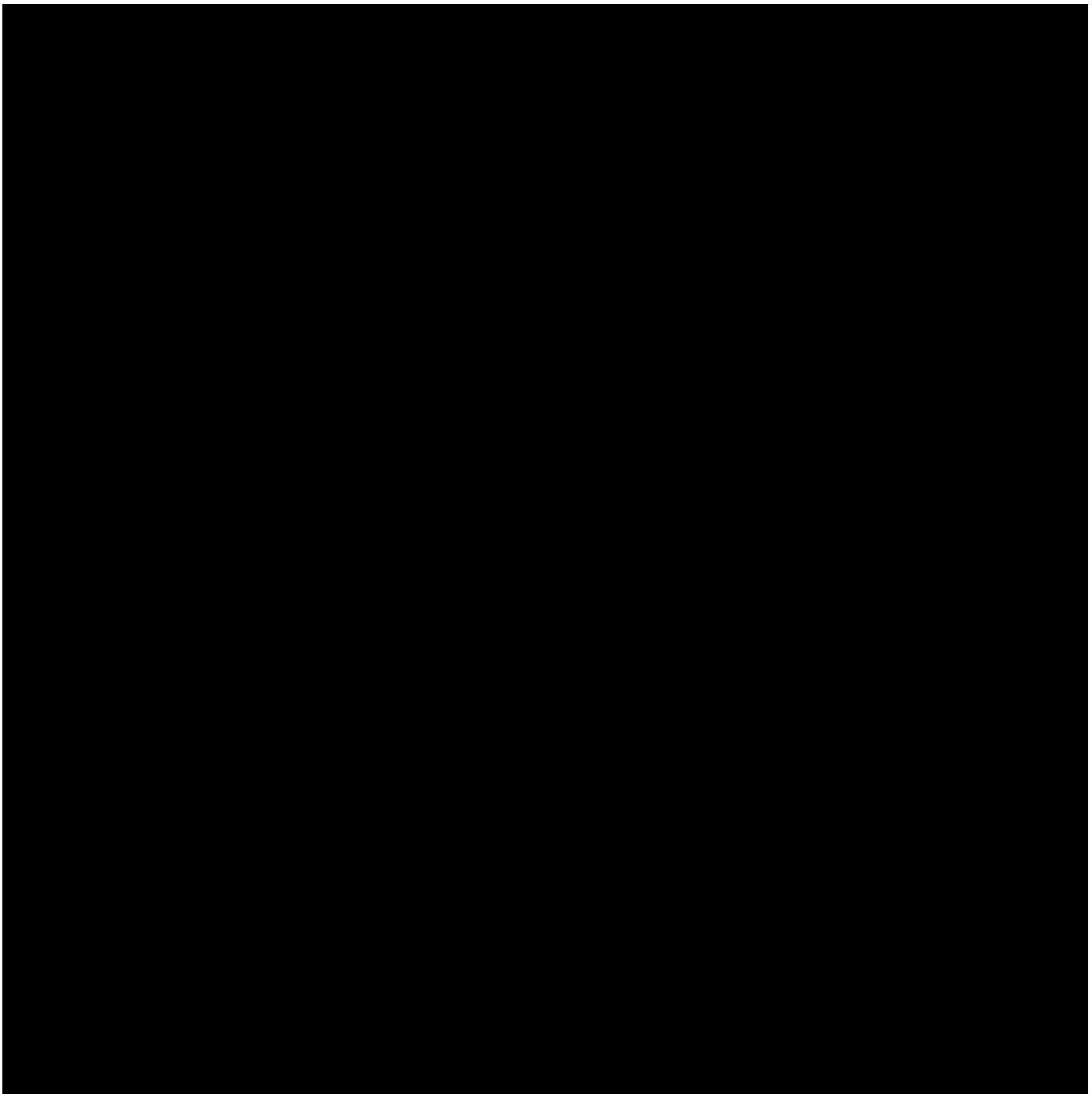
***Itraconazole should NOT be used in patients who are receiving vincristine due to a serious drug-drug interation leading to severe neurotoxicity**.[88,89]

For more complete list of CYP 3A 4/5 Inhibitors and Inducers see Appendix III.

Possible Drug Interactions with Capizzi Methotrexate:
Avoid non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim/sulfamethoxazole (TMP/SMX), penicillins, probenecid, IV contrast media, proton pump inhibitors, phenytoin and fosphenytoin. Urinary acidifiers can cause methotrexate to precipitate in the urinary tract.

Possible Drug Interactions with High Dose Methotrexate:
When IT therapy and high dose methotrexate are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV methotrexate infusion (hour -6 to +6, with 0 being the start of the methotrexate bolus).

Hold non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim/sulfamethoxazole (TMP/SMX), penicillins, probenecid, IV contrast media, proton pump inhibitors, phenytoin and fosphenytoin on the days of high dose methotrexate infusion and for at least 72 hours after the start of the high dose methotrexate infusion and until the methotrexate level is less than 0.4 μM. In the presence of delayed clearance, continue to hold TMP/SMX until methotrexate level is less than 0.1 μM.



7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required & Optional Clinical, Laboratory and Disease Evaluations for T-ALL

STUDIES**	Induction	Consolidation[3] **Arms A and C**	Consolidation[3] **Arms B and D**	Interim Maintenance*	Delayed Intensification	Maintenance
Hx/PE	Weekly	As shown	As shown	As shown	As shown	Every 4 weeks
BSA	Start of Course	Start of Course	Start of Course	Start of Course	Day 1, 29	Every 12 weeks
CBC/diff/plts	Weekly	Weekly	Weekly	Prior to each MTX dose	Weekly	Every 4 weeks
MTX Levels				Arm C (HDMTX) & Arm D (HDMTX + Nel) ONLY[4]		
Peripheral Blood for Host Polymorphisms	Day 29[5]					
Bone Marrow Cytomorphology	Baseline and Days 8, 15[1], 29	**Day 29 & End of Course** for HR patients	**Day 43 & End of Course** for HR & IF patients			
Bone Marrow MRD Assessment	Day 15[1,2] & 29[2]	**Day 29**[2] **& End of Course**[2] for HR patients	**Day 43**[2] **& End of Course**[2] for HR & IF patients			
Peripheral Blood MRD Assessment#	Day 8[2] & 29[2]	**Day 29**[2] **& End of Course**[2] for HR patients	**Day 43**[2] **& End of Course**[2] for HR & IF patients			
CSF cell count & cytospin	With each IT	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, ALT, creatinine, BUN	Baseline	Start of Course	Start of Course	Prior to each MTX dose	Day 1, 29	Prior to each 12 wk cycle
TPMT testing	Baseline (see Section 5.9)					
Varicella titer	Baseline					

[1] If Day 8 BMA was M2 or M3 obtain additional bone marrow for morphology & MRD on Day 15.
[2] Send Induction Day 15 BM and Day 8 PB samples to ALL Flow Cytometry Reference Lab ONLY for MRD; send Induction Day 29 BM/PB, Consolidation Day 29 BM/PB (Arms A/C) or Day 43 BM/PB (Arms B/D) and End of Course samples to ALL Flow Cytometry Reference Lab for MRD (see AALL08B1 for shipping requirements and addresses) for patients that are High Risk or Induction Failures.
[3] During Consolidation obtain BM for morphology at Day 29 (Arms A/C) or Day 43 (Arms B/D) and End of Course for patients that are High Risk or Induction Failures. Patients not in remission at end-Consolidation are off protocol therapy.
[4] See HD MTX Infusion Guidelines Section 4.6.1.
[5] Obtain if patient consented on AALL08B1: send to ALL Molecular Reference Lab for host polymorphisms (see AALL08B1 for shipping requirements)
* See Section 5.8.1 regarding MTX levels for HD MTX (Arms C and D only)
# Send to ALL Flow Cytometry Reference Lab ONLY for MRD
****If patient(s) develop myalgia or myoglobinuria, they should be evaluated for the potential of having rhabdomyolysis, as described in Section 5.2.**

7.2 Required & Optional Clinical, Laboratory and Disease Evaluations for T-NHL

STUDIES**	Induction	Consolidation[3] **Arm A**	Consolidation[3] **Arm B**	Interim Maintenance	Delayed Intensification	Maintenance	Relapse
Hx/PE	Weekly	As shown	As shown	As shown	As shown	Every 4 weeks	
BSA	Start of Course	Start of Course	Start of Course	Start of Course	Day 1, 29	Every 12 weeks	
CBC/diff/plts	Weekly	Weekly	Weekly	Prior to each MTX dose	Weekly	Every 4 weeks	
Bone Marrow Cytomorphology	Baseline & Day 29[1]	End of Course if positive at diagnosis	End of Course if positive at diagnosis				At relapse
Bone Marrow MRD Assessment	Baseline[2]						
CSF cell count & cytospin	With each IT	With each IT	With each IT	With each IT	With each IT	With each IT	
Bilirubin, ALT creatinine, BUN	Baseline	Start of Course	Start of Course	Prior to each MTX dose	Day 1, 29	Prior to each 12-week cycle	
TPMT testing	Baseline (see Section 5.9)						
Varicella titer	Baseline						
Chest CT/Chest x-ray[3]	Baseline[3] & end-Induction[3]	End of Course[3]	End of Course[3]			Completion of Therapy[3]	
Abdomen/Pelvis CT	Baseline & end-Induction[4]	End of Course[4]	End of Course[4]			Completion of Therapy[4]	
Bone scan[5]	Baseline & end-Induction	End of Course	End of Course			Completion of Therapy	
Diagnostic Biopsy/Cytology[6]	Baseline[7]						At relapse[7]
Optional Banking/Biology[6]	Baseline[7]						At relapse[7]

[1] Obtain in T-NHL beyond Day 1 only if morphologically positive at diagnosis.

[2] Send baseline BM sample to ALL Flow Cytometry Reference Lab ONLY for MRD; see Section 16 for shipping requirements and address.

[3] Obtain chest CT for all patients at Baseline and at end-Induction. The baseline chest CT may be delayed until the patient is stable. If patient has CR at end-Induction, no subsequent chest CT is required but a chest x-ray will be performed at end-Consolidation and end of therapy. If patient does not have CR at end-Induction, a chest CT will be performed at end-Consolidation. If patient has CR at end-Consolidation, a chest x-ray will be performed at end of therapy. If patient does not have CR at end-Consolidation, a chest CT will be performed at end of therapy. **Note:** Patients who have NR and have not achieved at least a PR at end-Consolidation are off protocol therapy.

[4] Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at Baseline are negative, no repeat scans are required.

[5] Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease.

[6] See Sections 15 and 16 for guidelines regarding tissue acquisition, processing and shipping. NOTE: This study includes retrospective central pathology review.

[7] Obtain extra tissue samples in patients who consent to specimen banking; see Sections 15 & 16.

****If patient(s) develop myalgia or myoglobinuria, they should be evaluated for the potential of having rhabdomyolysis, as described in Section 5.2.**

7.3 Targeted Toxicities

Neurological adverse events for Nelarabine are: ataxia (incoordination), confusion, depressed level of consciousness, dizziness/lightheadedness, memory loss, mood alternation/anxiety, agitation, encephalopathy, disequilibrium, Guillain-Barré-like syndrome, neuropathy motor/sensory, seizures, speech impairment (slurred speech), tremor or vertigo and visual disturbances.

Non-neurological toxicities also described to occur with Nelarabine include the following (by system): cardiovascular, constitutional, gastroenterological, hemorrhage, metabolic (pancreatitis), ocular/visual and pain. Any Grade 3-5 non-hematologic toxicities affecting these systems would also require reporting.

Collection of data for targeted toxicities may include additional information to that obtained through the usual CTCAE information that will be routinely collected (see Section 12.0). Expedited reporting rules apply to patients experiencing any Grade 3, Grade 4 or Grade 5 neurological toxicities after receiving Nelarabine.

If patient(s) develop myalgia or myoglobinuria, they should be evaluated for rhabdomyolysis, as described in Section 5.2.

7.4 Studies to be Obtained After Stopping Therapy

Note: Refer to COG's Long term follow-up Guidelines for monitoring cardiac function. Found at: http://www.survivorshipguidelines.org/

1st year	PE, CBC/diff/plts q month, ALT q 2 months until normal BMA, CSF, as clinically indicated
2nd year	PE, CBC/diff/plts q 2 months
3rd year	PE, CBC/diff/plts q 3 months
4th year	PE, CBC/diff/plts q 6 months
5th year	PE, CBC/diff/plts q 6-12 months.

7.5 At Relapse

T-ALL patients who relapse should have samples of blood and bone marrow sent to the appropriate Molecular Reference Laboratory (see AALL08B1 for details).
T-NHL patients: see Section 7.2 for instructions.

8.0 SUPPORTIVE CARE GUIDELINES

Aggressive supportive care improves outcome, particularly in High Risk patient populations receiving very intensive therapy as incorporated in this trial. The following guidelines are intended to give general direction for optimal patient care and to encourage uniformity in the treatment of this study population. Investigators are requested to report unexpected or unusually severe complications to Study Chair. Please also see the supportive care manual developed by CCG/POG (Supportive Care of Children with Cancer, A Altman ed, 3rd ed).

8.1 General Guidelines

Patients are recommended to have central venous access with either a totally implantable devide (port-a-cath) or a tunneled catheter (Broviac, Groshong or Hickman). The risks and benefits associated with these devices should be discussed with the patient by members of the oncology and surgical care teams. The

goal is to select a venous access catheter that will have the least likelihood of developing catheter-related complications for each individual patient.

8.1.1 Blood Components

Blood products should be irradiated following current FDA guidelines found at:
http://www.fda.gov/cber/gdlns/gamma.htm

Investigators in Canadian institutions need to follow the CSA standards for Blood and Blood Components CAN/CSA-Z902-04 issued in March 2004 and available at: http://www.shopcsa.ca.

Red blood cells (RBCs)
Transfusion with RBCs is indicated to correct severe or symptomatic anemia or acute blood loss. In the setting of extreme hyperleukocytosis investigators should be mindful that PRBC's may contribute to hyperviscosity.

Platelets
Transfusion with platelets is indicated to correct bleeding manifestations and may be indicated for severe thrombocytopenia without bleeding particularly in the setting of an invasive procedure.

8.1.2 Infection Prophylaxis

Pneumocystis carinii
All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 5 mg/kg/day divided bid three sequential days per week. For patient's allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone (1-2 mg/kg/day, maximum dose 100 mg/day), aerosolized pentamidine (300 mg/q month ≥ 5 years of age), or atovaquone (30 mg/kg/day if < 3 mo. or > 2 years, 45 mg/kg/day if between 3 mo. & 2 years) may be considered.

Varicella Vaccine
May be given to the siblings of patients in remission and stable at the physician's discretion. Administration to the non-immune patients is not recommended.

Gamma globulin
If clinically indicated, IgG levels may be monitored throughout treatment. If the IgG level falls below age-determined normal levels, IVIG at 400 mg/kg may be administered at the discretion of the investigator. Note of IVIG administration should be made on data form.

Antifungals
Azole antifungal agents (i.e. fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Investigator caution is advised if azole antifungals are used.

8.1.3 Treatment of Established or Presumed Infections

Fever with Neutropenia
For patients with ANC < 500/µL and temperature between 38.0°C and 38.5°C twice in 12 hours, or ≥ 38.5°C, empiric parenteral broad spectrum antibiotics should be instituted after obtaining appropriate cultures. The risk of sepsis is higher during Induction and while the peripheral neutrophil count is falling rather than rising. The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on each of your institution's experience regarding the type of infecting organisms and their antibiotioc sensitivity patterns. Duration of therapy should be determined by site of infection (if

identified), culture results, and response to treatment. If fever and neutropenia persist, systemic antifungal therapy with amphotericin B should be initiated after 3-5 days. When severe mucositis or a sepsis syndrome is present in patients with their initial febrile neutropenia, or a patient has a history of prior alpha hemolytic sepsis, consider inclusion of Vancomycin in the empiric antibiotic regimen.

Primary Varicella Infection (Chickenpox)
Patients should be treated promptly with acyclovir 1500 mg/m²/day intravenously divided q 8 hours, and monitored closely for the development of invasive systemic disease.

Empiric Management of Pulmonary Infiltrates
Pulmonary infiltrates should be evaluated in the context of the patients clinical and laboratory profile. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a mold infection (Aspergillus, mucor), consider using broad spectrum antibiotics. If the patient develops progressively worsening clinical or laboratory features then more aggressive diagnostic measures should be undertaken. Pulmonary infiltrates should then be evaluated with bronchoscopy and biopsy, lavage or open lung biopsy. If a procedure cannot be tolerated, begin empiric treatment with amphotericin B given[89] the high likelihood of fungal disease during Induction. It is advisable to seek an infectious disease consult under these circumstances. Empiric coverage should include treatment for gram-negative and positive bacteria, Legionella (erythromycin), Pneumocystis (TMP/SMX), and fungi (amphotericin/ambesome) pending culture results. If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis and brain are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician. **Azole antifungal agents (i.e. fluconazole, itraconazole, voriconazole) given concurrently with vincristine may INCREASE the risk of neurotoxicity and myelosuppression.[88,89] Investigator caution is advised if azole antifungals are used.**

Management of Mucositis/Perirectal Cellulitis
Mucositis should be managed with IV hydration and hyperalimentation if indicated, effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy and empiric antiviral and antifungal therapy as indicated. Management of perirectal cellulitis should include broad-spectrum antibiotic therapy with dual gram-negative coverage as well as anaerobic coverage (i.e. ceftazidime + aminoglycoside + metronidazole; or piperacillin-tazobactam + aminoglycoside), Sitz baths, a strong barrier technique and effective analgesia.

8.1.4 Antiemetic Protection
Antiemetics should be given as needed. The routine use of steroids is discouraged, including dexamethasone, but may be appropriate in select patients with demonstrated intolerance to higher-dose chemotherapeutic agents.

8.1.5 Use of Filgrastim
The routine use of filgrastim is not generally recommended, but may be used at the discretion of the investigator in situations of serious infection with neutropenia.

8.2 Guidelines for Induction

8.2.1 Acute Tumor Lysis Syndrome
The risk for serious acute tumor lysis syndrome (TLS) is usually restricted to the first 72 hrs after initiation of therapy; however, it may spontaneously occur prior to treatment. To manage the metabolic derangements caused by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, the following steps should be intiated:

1. Begin allopurinol at a dose of 300 mg/m²/day in 3 divided doses and continue until peripheral blasts and extramedullary disease are reduced. In some situations it may be appropriate to use Rasburicase.
2. Hydrate at 2400-3000 mL/m²/day to maintain urine output > 100 mL/m²/hour until peripheral blasts and extramedullary disease are reduced.
3. Alkalinize urine with $NaHCO_3$ 20-40 mEq/L IV fluid to maintain urine pH between 6.5 and 7.5. Alkalinization is not recommended when treating with Rasburicase.
4. If the patient has oliguria or severe renal dysfunction, consider the use of Rasburicase at 0.15 to 0.2 mg/kg/dose and obtaining a nephrology consult.
5. While patients are on steroid therapy they should receive an H2 blocker.

Refer also to the discussion of TLS in the Supportive Care Manual (Supportive Care of Children with Cancer, ed A Altman, 3rd edition, 2004)

8.2.2 Induction – Infectious Complications

Since steroid-containing 4 drug ALL inductions may be associated with higher rates of toxicity, investigators are cautioned to pay close attention to a number of factors during the early phases of treatment. Patients may experience profound myelosuppression and immune suppression during this time. Since prednisone may mask fever, as well as other components of the inflammatory response sepsis during Induction, the warning signs of septic shock may be associated with very mild and subtle symptoms. Caregivers must also be made aware that patients may experience very rapid clinical deterioration. This suggests the need for a supportive care network that can recognize and respond to sudden changes in a patient's condition. In addition it should be noted that several serious toxic events have had an intestinal component. Patients with subtle GI symptoms should be monitored very closely.

In this population with High Risk ALL, rapidly assess patients clinically and by appropriate laboratory parameters for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Patients at greatest risk will be those with WBC > 100,000/μL and extramedullary disease. Suggested initial studies to be obtained prior to initiating antileukemia therapy include complete blood count (CBC), prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes, including creatinine, BUN, uric acid, phosphorous, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

9.1 Criteria for Removal From Protocol Therapy

a) T-ALL patients found to meet criteria for the AALL0622 Ph+ ALL study (or successor)
b) T-NHL patients found to meet criteria for Ph+ T-NHL
c) Recurrent leukemia following complete remission.
d) For T-NHL: Progressive lymphoma
e) For T-ALL: Induction failure patients may be removed from therapy following Consolidation at investigator discretion
f) For T-NHL: NR at end of Consolidation therapy (see Section 11.3)
g) Refusal of further protocol therapy by patient/parent/guardian.
h) Completion of planned therapy.
i) Physician determines it is in patient's best interest.
j) Development of a second malignancy.
k) Adverse Event/Side Effects/Complications

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

9.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of the date the patient was enrolled on this study.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Design (Amendment #5)

The anticipated number of newly diagnosed T-lineage ALL patients is estimated to be 230/year (~19/month). About 25% and 75% of T-lineage patients would be in the age/WBC defined NCI criteria for standard risk (age 1-9 and WBC < 50,000/µL) and high risk (age 10+ or WBC > 50,000/µL) groups, respectively.

The long term EFS result in the overall T-lineage group in recent COG studies is approximately 80%, with the vast majority of EFS events occurring in the first three years. Unlike the pattern of outcome seen for B-precursor ALL, it is rare to see events occur beyond 4 years among patients with T-ALL. This outcome can be modeled reasonably well by a linear decreasing hazard rate with no appreciable risk of failure after completion of year 4.

For this study, definitions of T-lineage risk groups have been chosen to conduct the study in a manner that provides appropriate treatment strategies for these different groups. The Low Risk subset of T-lineage is defined for this study as those who are age 1-9.99 with WBC ≤ 50,000/µL (i.e., NCI standard risk), but who in addition have CNS1 status at diagnosis and have no testicular leukemia at diagnosis, who have a morphologic M1 marrow by Day 14, and who have MRD < 0.1% at end of Induction. We estimate that this will result in approximately 18% of the overall T-lineage group being in the "Low Risk" group for this study. The "High Risk" subset for this study will be those patients with either M2 morphologic marrow status or MRD > 1% at the end of Induction. This group is estimated to be approximately 20% of the overall T-lineage group, leaving 62% in the "Intermediate Risk" subset.

European data from the BFM group have suggested a poor outcome for T-lineage patients with MRD levels > 1%. Data from COG studies on MRD status suggest that about 15%-20% of T-lineage patients will have MRD > 1% at end of Induction. However, insufficient follow-up is currently available to determine their ultimate EFS outcome. Data from COG studies suggest that most traditional prognostic factors in B-precursor ALL have minimal effect on outcome for T-lineage ALL. Patients in recent COG studies with M2 marrow status at the end of Induction had a 4 year EFS of 56%. It is expected there will be substantial overlap in the two criteria for High Risk (HR) status with many patients who are in both the MRD > 1% and end Induction marrow status of M2. We estimate that approximately 20% of patients will be High Risk by these combined criteria. We will assume that the 4 year EFS outcome for the High Risk subset is 56%. We also assume that the 4 year EFS for the Low Risk (LR) and Intermediate Risk (IR) subsets will be 92% and 84%, respectively. These assumptions would give an EFS of 80% for the overall T-lineage population which is reasonably consistent with the observed results in recent COG studies. Since randomization in this study will occur after successful completion of Induction (about 2.5% are estimated to have either Induction death or M3 non-response), the EFS post-randomization will be a bit

higher. The assumed EFS post-randomization for the 3 risk groups are 93%, 86% and 60% - resulting in an overall post-randomization 4 year EFS of approximately 82%.

The basic therapy backbone for all the patients in this study will use the ABFM regimen. The initial design at the start of this study (safety phase) will involve a randomization at the completion of Induction for all patients achieving remission to two regimens that will differ only in the dose and schedule of MTX delivery: either HDMTX or CMTX. Children who are in the LR subset will be excluded from CNS irradiation and will be non-randomly assigned to regimens without Nelarabine throughout all stages of this study. IR patients will receive prophylactic CNS irradiation, but they will not receive Nelarabine during the safety phase of the study. During the safety phase, HR risk patients will be randomized to receive Nelarabine or no Nelarabine in addition to randomization to receive HDMTX or CMTX. Once sufficient accrual and follow-up is available (described in following section), an assessment of the toxicity profile for Nelarabine will be performed. If Nelarabine is found to be safe in the context of this treatment backbone and the MTX regimens, the initial study randomization to HDMTX vs. CMTX would be modified to a larger 2x2 randomization in an expanded efficacy phase which includes the IR risk patients.

		Safety Phase			Efficacy Phase		
T-ALL Risk	ABFM	MTX question	Nelarabine question	CNS XRT	MTX question	Nelarabine question	CNS XRT
Low Risk	yes	Yes	No	No	yes	no	no
Intermediate Risk	yes	Yes	No	Yes	yes	yes	yes
High Risk	yes	Yes	Yes	Yes	yes	yes	yes

T-cell Lymphoblastic Lymphoma Patients

The T-NHL patients will be stratified separately on this study, and will also be analyzed separately without impacting the analyses for the T-ALL patients. The number of T-NHL patients to be accrued during the Efficacy Phase of AALL0434 is projected to be around 68/year. Adjusting for loss to randomization, about 35 patients/year will be classified as High Risk at the end of Induction and will be randomized to CMTX ± Nelarabine. Those classified as Standard Risk (17 patients/year) will be assigned to Arm A (CMTX, no Nelarabine). About 2 patients/year will be classified as Induction failures (no PR, CR or CR_u by Day 29 of Induction) and will be assigned to Arm B (CMTX + Nelarabine). Over a 4-year accrual period, approximately 140 High Risk patients will be accrued. There will be insufficient power for any formal comparison of outcomes between randomized regimens for these patients, but informal comparisons will be made. Outcome analyses for the 68 Standard Risk and 8 Induction Failure patients will essentially be descriptive due to small numbers.

10.1.1 **Study Re-design - (Amendment #9)**

Overall accrual rate (as of 09/30/2011) for the T-ALL patients has been around 256 per year over the past year compared to the projected 230/year in the protocol; and the actual loss to post-Induction randomization/assignment is around 20% instead of the estimated 10%. In addition, the distribution of post-Induction risk assignments - Low risk (LR), Intermediate risk (IR), and High risk (HR) is currently 9%, 71%, and 20% respectively, differing from what was projected above (18%, 62%, and 20% respectively). Due to this, the annual accrual rate to the MTX and nelarabine randomizations are currently the same – around 175 patients/year (compared to the prior estimates of 201 and 165 patients, respectively).

Per the current design in the protocol, the MTX question is to accrue 1206 patients to ensure that we get the required 615 patients for the nelarabine randomization during that accrual duration. This results in the MTX randomization being well over-powered at 91.6% power. This amendment modifies the statistical

considerations for the 2 randomizations as detailed below in Section 10.3, in order to cater to the change in distribution of risk groups. The baseline event free survival (EFS) rates and detectable improvement in EFS remain the same as was originally specified. Both randomizations will have the same efficacy and futility monitoring procedures as was previously specified, using the updated expected total events for each.

The annual accrual rate for T-NHL patients has also been higher than expected and is around 68 patients per year. With the increased accrual rates for T-ALL and T-NHL, the target accrual on this study will be 1707, in order accrual of the required eligible, evaluable patients for study objectives.

10.1.1.1 Study re-design (Amendment #11)

On April 17th 2015, following review of a planned protocol specified interim monitoring, the Data Safety Monitoring Committee released the results of the randomized comparison of Capizzi *versus* High Dose Methotrexate (HDM) regimens on study. Per protocol specified interim monitoring 4-year disease-free survival rates (DFS) are 92.5% (SE 1.8%) for the CM regimen vs. 86.1% (SE 2.4%) for the HDM regimen ($p = 0.0173$). Although the efficacy monitoring boundary (was not crossed (the p-value is equal to the boundary), the conditional probability of proving HDMTX is superior to CMTX given the current data (12/31/2015 data freeze), was very small (<0.0001). The baseline outcomes for patients on this study are higher than projected. Hence the expected total number of events for both the MTX randomization and the Nelarabine randomization are lower than projected in the original study design. This amendment is to update the study design to reflect the lower expected event horizon for the Nelarabine randomization (which would impact the interim monitoring for outcomes. The details of the redesign done by an independent statistician who does not have knowledge of the interim results for the nelarabine randomization and was provided with the updated event rate for the control arm, are provided in section 10.3.2 below.

10.1.2 Amended study accrual (Amendment #10)

The total target accrual for the study has been increased from 1707 to 1900 patients. This increase is necessary in order to get the required eligible, evaluable patients (as given in Section 10.3.1 below) for the Methotrexate and Nelarabine post-induction randomizations. The reasons for this increase in projected total accrual, are: a) The projected accrual rates for T-ALL and T-NHL on study were 256 and 68 patients per year, respectively while the actual rates (as of 9/9/2013) are 247 and 86 patients per year. The T-NHL patients do not participate in the two randomized study questions, but their increased accrual rate has taken up accrual slots that would have been taken otherwise by T-ALL patients who would likely get randomized. b) The loss at the end of induction to the post-induction randomizations was higher (24%) than that projected (20%). c) The actual accrual rates for each of the randomizations are both around 145 patients/year as opposed to the projected rates (175 pts/year). Based on data as of 9/9/2013, an additional 115 patients are needed for EACH of the post-induction randomizations. This translates to about 270 (200 T-ALLs, 70 T-NHLs) enrollments to the overall study (adjusting for losses end of induction and for the 30 patients currently on induction therapy yet to be risk assigned). As of 9/9/2013, 77 accrual slots were still available before current target accrual of 1707 is met. Hence the required increase in target accrual is by 193 (270-77), to give a new target accrual of 1900. The study is projected to meet the new accrual target by September 2014. No changes are required to any of the statistical analyses plans and power calculations given in the following sections.

10.2 Nelarabine Toxicity Assessment and Duration of Safety and Efficacy Phases

The initial assessment of Nelarabine toxicity will occur for the first 20 HR patients receiving Nelarabine with 10 in both the HDMTX and CMTX regimens. An adequate period of follow-up in these patients is necessary to judge the toxicity. The delivery of Nelarabine starts in the first week of the Consolidation phase (at 6 weeks from study entry) and the last dose will be given at week 60, which is early in

Maintenance. During the evaluation period for the Safety Phase, HR patients will continue to randomize to all four treatment arms. This approach will allow us to gain further experience with Nelarabine in HR patients. We will evaluate the HR patients in the Safety Phase of the study at approximately 8 weeks following the week 36 dose of Nelarabine (through week 43 in the Maintenance phase). The rationale for choosing this time-point is that it will allow patients to have resolved radiation-induced somnolence syndrome and other potentially confounding neurotoxicities. It has been our experience on AALL00P2 that Nelarabine toxicities occurred acutely after exposure and we do not anticipate significant additional Nelarabine toxicities occurring after the Week 43 observational time point. In addition, this will shorten the time interval for follow-up required before proceeding to the Efficacy Phase. Based on the anticipated annual accrual rate, we estimate that it will take about 12 months to obtain this initial cohort of 20 HR patients randomized to Nelarabine. Then an additional 10 months after the last of this group is entered will be needed to reach the time in Maintenance with adequate follow-up for toxicity assessment. The HR patients receiving Nelarabine will be compared directly to their randomized HR controls who are not receiving Nelarabine with the comparison further stratified by the methotrexate regimen received. These toxicity analyses and any recommendations from the ALL Steering Committee regarding the opening of the Nelarabine randomization to the IR subset will be provided to the COG DSMC for their review and approval before any decision to open the randomization further. If results at this first toxicity comparison require additional patient entries for further assessment, the original randomization to Nelarabine will continue in just the HR patients. If this second stage of toxicity assessment is needed, it will take place at approximately one year after the initial assessment, at which time a decision to either open or not open the Nelarabine randomization to include the IR patients will occur. The total planned length of the safety phase HR randomization is intended to not exceed 3 years. HR T-ALL patients will continue to be randomized for the Nelarabine question throughout the safety phase.

10.3 Primary Treatment Comparisons and Statistical Power (Amendment #9)

The primary endpoint for the study analyses and the endpoint used for the subsequent power calculations is event-free survival (EFS) following initial remission since randomization occurs after Induction. EFS events include any type of relapse, death in remission or second malignant neoplasm. Since CNS relapse has been an important event in many studies of T-lineage patients, that outcome will be a secondary endpoint which will be examined for various treatment regimen comparisons, and in the subset of patients who will not receive XRT CNS prophylaxis. "Intent-to-treat" analyses (i.e. based on the regimen to which patients are initially randomized) will be the primary approach used to assess treatment efficacy.

The following calculations allow for a 2.5% failure rate in Induction (the combined M3 non-response rate and Induction death rate) and a 10% rate of randomization refusal. This provides 201 patients per year (approximately 36 LR, 125 IR and 40 HR) who will be available for the MTX randomization after allowing for the attrition due to Induction failure and those who refuse randomization. The planned study accrual duration will be approximately 6 years providing a total of 1206 patients who will be randomized to HDMTX versus CMTX. The power calculation for this comparison is based on a 2-sided log rank test (alpha = 0.05) with the first analysis occurring when approximately 20% of the expected events from the projected EFS event horizon have occurred. Four subsequent analyses will occur at approximately 40%, 60%, 80% and 100% of the expected event total. A t^2 spending function for the stopping boundary (with truncation at 3 standard deviations) will be used to allocate greater importance to the later analyses. For the MTX comparison, the long term EFS baseline outcome in these patients is expected to be 82% at 4 years. In this study, a clinically important difference is assumed to be an improvement to 89% EFS which represents a relative EFS event reduction of approximately 41% for the better regimen (viz., relative hazard rate, RHR = 0.587). The event horizon is calculated using the previous EFS outcome assumptions and assuming an accrual of 6 years with a follow-up of 3 years after the last patient is randomized. For this situation, one would expect a total of 174 EFS events which results in a cumulative power to detect a difference by the last analysis of 91.6%. The z-value upper and lower monitoring boundaries for the 5

looks at the data are ± 3, 2.744, 2.477, 2.281, and 2.115. If a slightly smaller improvement to 88% EFS occurs (RHR = 0.644), the cumulative power to detect a difference by the last analysis would be 80.4%.

Upon completion of the study, smaller differences in EFS outcome than those described above might occur. In that case, it would still be useful to identify which of the 2 methotrexate treatment approaches might be selected for use in future T-ALL studies. Part of this selection process would involve the overall comparison of toxicity and complications data for HDMTX and CMTX, but another part of the evaluation would relate to the final EFS results for the regimens. If the final EFS efficacy comparison described above does not achieve the conventional significance level used (overall alpha = 0.05), the regimens would also be compared using a more liberal significance criterion ($p \leq 0.20$) to choose which regimen is better. With this criterion and the sample size for the methotrexate randomization, true EFS differences in the neighborhood of 4% would permit identification of the better regimen with high probability. For example, if one of the methotrexate regimens has an EFS of 82% and the other has an EFS of 86%, the probability that the better regimen is selected would be .852 and the probability that the poorer regimen would be selected is only 0.003 (with a .145 probability that no regimen would be selected based on the criterion being used). The table below (Table 1) shows that the selection rates remain reasonably stable for this 4% EFS difference if the baseline outcome departs somewhat from the assumed 82%. If a slightly smaller EFS difference of 3% occurs (with one regimen at 82% and the other at 85%), the selection probabilities are still in a reasonable range with the probability that the better regimen is selected being 0.737 and the probability that the poorer regimen would be selected is 0.001. Of course, this type of comparison would need to be considered in conjunction with the toxicity and complications analysis in order to decide which regimen is preferable to the other for choice in a future study.

Table 1: Regimen Selection Probabilities with a True 4% Difference in EFS Outcome:

Poorer Regimen True EFS	Better Regimen True EFS	Probability of Selecting Better Regimen	Probability of Selecting Poorer Regimen	Probability of No Selection
82%	86%	0.852	0.003	0.145
80%	84%	0.832	0.004	0.164
84%	88%	0.875	0.002	0.123

The power calculation for the randomized Nelarabine versus no Nelarabine comparison is based on a 1-sided log rank test (alpha = 0.05) since we wish to see if the addition of Nelarabine improves the outcome of T-lineage patients. The Nelarabine comparison will also have 5 planned analyses of the data and utilize the same type of t^2 spending function. The following calculations assume a 3 year period of randomization to the Nelarabine question for the HR subset before the randomization is expanded to include the IR group. If the study duration is approximately 6 years, this would eventually result in about 615 patients randomized to this comparison (240 HR patients over 6 years, 375 IR patients over 3 years). Since the more favorable LR subset of T-lineage patients will be excluded from this randomization (i.e., those who are aged 1-10 years and CNS1 and no testicular disease and RER and MRD- are excluded), the assumed long term EFS outcome in this group of patients is assumed to be 76% at 4 years (resulting from the above mixture of the IR and HR groups). A clinically important difference is an improvement to 85% EFS, representing a relative EFS event reduction of approximately 41% for the better regimen (viz., RHR = 0.592). The number of expected EFS events with 3 years of follow-up after the last randomized patient is enrolled would be 119 events. In this situation, the cumulative power to detect a difference by the last analysis is 85.9%. The 1-sided z-value monitoring boundaries for the 5 looks at the data are 2.878, 2.470, 2.200, 1.982 and 1.790. If the IR patients can be enrolled sooner than 3 years into the study because the Nelarabine safety is established before that time, this would increase the statistical power figures given above.

With the planned study duration, there should also be reasonable statistical power to examine some of the treatment differences within the risk group subsets. This would be of particular interest for the Nelarabine randomization. In the HR subset, the cumulative power to detect a change in EFS outcome from 60% to 75% (RHR = 0.563) would be 77.2%. For the IR subset the power to detect a change in EFS outcome will be less since those patients would only begin enrollment after the safety phase is completed. For example, in the IR subset the power to detect a change in EFS outcome from 86% to 93% (RHR = 0.481) for the Nelarabine regimen comparison would be 68.4%.

Secondary comparisons of the incidence of CNS relapse will be examined. This will be performed for the comparison of the 2 MTX regimens and also for comparing Nelarabine versus no Nelarabine. Comparison of overall survival (OS) will also be a secondary endpoint for the regimen comparisons.

Based on the treatment regimens chosen for this design and experience with factorial designs in numerous other COG ALL studies, the occurrence of an important statistical interaction effect on EFS for the 2 main treatment factors is thought to be unlikely. Hence, the preceding power calculations are based on the assumption that the stratified analysis of either factor across levels of the other factor will allow the "pooled" analysis to be valid. However, analyses will be performed regularly to assess the possibility of an interaction effect (using a Cox regression likelihood ratio test) which will assess the four individual treatment regimens in the 2 x 2 design to see if a non-proportional hazards effect occurs for the combinations of the two main effect factors. If strong evidence exists for the presence of a statistical interaction of the MTX and Nelarabine regimens, then separate analyses of a regimen effect would need to be done within each level of the other treatment factor. This would result in substantial attenuation of the statistical power and might necessitate extension of the study duration to achieve better power to detect treatment differences.

Since the comparison of the methotrexate regimens utilizes a selection type analysis, no futility testing will be used for that comparison. However, futility testing boundaries will be used for the comparison of "Nelarabine" versus "No Nelarabine" to decide if stopping should occur for similarity of outcome. This will be tested with a Pampallona-Tsiatis type lower monitoring boundary when approximately 20%, 40%, 60% and 80% of the EFS event information is available. This boundary has the property that the probability of rejecting H_A (i.e. relative hazard of 0.5237 favoring Nelarabine) when H_A is true is 5%. The z-values corresponding to stopping for futility at the four interim analyses are -1.595, -0.656, +0.021 and +0.584, respectively.

The proportional hazards assumption underlying the log rank test appears to have been reasonably valid for the treatments studied in many previous COG trials in ALL. However, that assumption for this trial will be regularly examined at the times the treatment regimens are compared. Should it not appear valid, other statistics will be used for comparing treatment outcome (e.g., cure model statistics and/or 4-year EFS comparisons).

If during the conduct of the trial, results emerge which establish the superiority of one of the regimens for a particular comparison in the factorial design (i.e., either for the methotrexate regimen comparison or for the Nelarabine comparison), the entire study would not be stopped. In this case, the study will continue the randomization for the remaining comparison with all additional patients assigned to the better regimen for the part of the randomization which was terminated.

10.3.1 **Study Re-design Power Calculations (Amendment #9)**

The distribution of post-Induction risk assignments - Low risk (LR), Intermediate risk (IR), and High risk (HR) is currently 9%, 71%, and 20% respectively, differing from what was projected above (18%, 62%, and 20% respectively). Due to this, the annual accrual rate to the MTX and nelarabine randomizations are currently the same – around 175 patients/year (compared to the prior estimates of 201 and 165 patients,

respectively). The updated power calculations reflecting this, and interim monitoring rules are given below.

MTX randomization: Using a 2-sided alpha of 5%, there is power of 85.3%, to detect an improvement in 4-year EFS from 82% to 89%. A total of 980 patients will be accrued (total expected events: 142) with minimum followup of 3 years. As of 09/30/2011 a total of 580 patients have already been accrued to this randomization. Hence the remaining 400 patients can be accrued to this post-Induction randomization over 2.3 years (projected study closure date of 02/01/2014 instead of the currently projected date of 04/15/2015). Overall, a total of 605 patients will be enrolled at study entry during this time period, to give 590 eligible, evaluable patients for the post-Induction randomizations/treatment assignments. Interim analyses will be done as specified earlier in Section 10.3, with the first analysis occurring when approximately 20% of the expected events from the projected EFS event horizon have occurred. Four subsequent analyses will occur at approximately 40%, 60%, 80% and 100% of the expected event total. A t^2 spending function for the stopping boundary (with truncation at 3 standard deviations) will be used to allocate greater importance to the later analyses. Since the comparison of the methotrexate regimens utilizes a selection type analysis, no futility testing will be used for that comparison.

Nelarabine randomization: With a 1-sided alpha of 5%, there is 85.9% power, to detect an improvement in 4-year EFS from 76% to 85%. The total number of patients required is the same as currently specified in Section 10.3 (615 patients) (total expected events: 119) with minimum followup of 3 years. As of 09/30/2011 a total of 215 patients have been accrued to this randomization. Hence the remaining 400 patients can also be accrued over 2.3 years as specified for the MTX randomization. The Nelarabine comparison will also have 5 planned interim analyses of the data for efficacy (at 20%, 40%, 60%, and 100% information) and utilize the same type of t^2 spending function as for the MTX randomization.

Futility testing boundaries will be used for the comparison of "Nelarabine" versus "No Nelarabine" to decide if stopping should occur for similarity of outcome. This will be tested with a Pampallona-Tsiatis type lower monitoring boundary when approximately 20%, 40%, 60% and 80% of the EFS event information is available. This boundary has the property that the probability of rejecting H_A (i.e. relative hazard of 0.5237 favoring Nelarabine) when H_A is true is 5%. The z-values corresponding to stopping for futility at the 4 interim analyses are -1.595, -0.656, +0.021 and +0.584, respectively.

10.3.2 **Study Re-design Power Calculations for Nelarabine randomization (Amendment #11)**

The study closed to accrual on 07/25/2014. Total expected accrual for the study was determined based on estimating losses during/at the end of induction and the required sample sizes for the two randomized study questions. Due to a lower rate of loss than projected, a higher number of (n= 659) patients than the projected 615 were randomized to +/- nelarabine. A total of 336 and 323 patients were randomized to no nelarabine vs. nelarabine regimens.

It is assumed that the 336 and 323 patients randomized to the two arms were accrued uniformly during the 3.83 years (from 9/22/2010 to 7/25/2014) when the efficacy phase of the nelarabine randomization was open, with a minimum follow up of 3 years. Assuming a cure rate model for each arm that has exponential distribution for the first four years and reaches a plateau at 4 years; accounting for 5 interim analyses (using an alpha t^2 spending function) at approximate 20%, 40%, 60%, 80% and 100%, there is 80% power to detect improvement in 4-year EFS from 82% to 89% (93 events) with a one sided significance level of 0.05. Given the additional expected toxicities due to the addition of nelarabine, 7% is considered to be a clinically meaningful improvement in outcome to plan for. Three interim analyses for efficacy have already occurred thus far. The next planned interim analysis for efficacy and futility will be conducted at 80% information (74 events). Final analysis will be conducted when the specified event horizon (93 events) is reached or when the last patient randomized to +/- nelarabine has 3 years of follow-up, whichever comes first.

10.4 Toxicity Assessment and Monitoring

Neurological toxicities are of special concern with Nelarabine. The toxicities for the Nelarabine patients will be examined in two primary ways: First, they will be compared directly to their randomized control not receiving Nelarabine with additional examination of the comparison within the separate methotrexate regimen subsets. These comparisons will focus on Grade 3 or higher non-hematologic toxicities. Next, the overall incidence of selected neurologic toxicities will also be monitored since these represent an important target category for Nelarabine toxicity (see Section 7.3).

For toxicity monitoring rules related to Nelarabine, any death clearly attributable to Nelarabine will lead to closure of the Nelarabine randomization with subsequent review and consideration given to re-opening the randomization at a lower dose and/or restricting patient entry to only those with High Risk disease. A second monitoring rule will look for 10% Grade 4 or 20% Grade 3 peripheral neuropathies that fail to resolve within one week, attributable to Nelarabine and not matched by a similar neurologic toxicity rate on the regimens without Nelarabine. Should this occur, it will lead to a temporary closure of the randomization with consideration to be given to re-opening the randomization at a lower dose and/or restricting patient entry to only those with High Risk disease.

Patients with CNS disease at diagnosis (CNS3) might be at higher risk of neurologic problems with Nelarabine. Thus, specific toxicity comparisons of this small group will be examined for the randomized Nelarabine and no Nelarabine regimens, and those analyses will be provided together with the regular overall study toxicity assessments.

Detailed toxicity data as described above will be regularly provided to the COG DSMC at each of their twice yearly meetings and an *ad hoc* basis as required for judging the safety of Nelarabine.

10.4.1 Amended monitoring for toxic deaths (Amendment # 10)

A formal statistical monitoring rule for toxic deaths attributed to Nelarabine, during post Induction therapy is given below. Based on the rule given in Section 10.4 above, on 09/05/2012, accrual to the study and randomization to Nelarabine was suspended following a death during consolidation of a patient assigned to the Nelarabine + HDMTX arm. The AALL0434 study committee reviewed the data on Nelarabine related toxicities. Although there was one death related to Nelarabine, there were only two other nervous system toxicities (1 Grade 3 seizure and 1 Grade 3 somnolence) for which attribution to Nelarabine was scored as *possible*, and none that were scored as *probable* or *definite* among over 180 patients randomized /assigned to receive Nelarabine on study. The rate of neurological toxicities is well below the level defined as concerning in Section 10.4. The COG DSMC reviewed the data and approved re-opening randomization/assignment of patients on study to Nelarabine containing arms as in the original study design. The DSMC also recommended at the time that with the next amendment a more formal monitoring rule for deaths related to Nelarabine be added to the statistical consideration. Of note, no additional deaths attributed to Nelarabine have occurred after the sole death that occurred in September 2012.

The death rate related to Nelarabine during post-Induction therapy will be closely monitored. About 335 patients will be randomized or assigned to Nelarabine containing regimens for post Induction therapy on this study. If four remission deaths attributed to Nelarabine occur, then the Nelarabine randomization will be temporarily closed to accrual. The deaths will be reviewed by the study committee and the COG data safety monitoring committee, and a decision made with respect to possible therapy modifications and reopening the randomization or permanent closure of the Nelarabine randomization. With this rule, the probability of stopping is 9% if the true toxic death rate is 0.5%. The probability of stopping is 90% if the true toxic death rate due to Nelarabine is 2%.

10.5 Analysis and Monitoring of Special Patient Subsets

There are various patient subsets in this study that will be examined regularly. These subsets were selected either because the AALL0434 treatment is very different than in previous studies for the subset, or the subset is of interest for other reasons.

Patients in the LR subset:
The outcome of the Low Risk patients who do not receive prophylactic CNS irradiation will be contrasted to the historical control experience from recent studies of T-lineage ALL that provided such treatment (POG 9404).

SER patients:
Since SER patients in this study will not receive a second DI phase and previously treated SER T-lineage patients in the CCG-1961 study received 2 DI phases, a comparison of outcome for this subset will be made with that historical control.

Induction failure patients:
In this study, patients failing Induction with an M3 marrow continue to stay on the study and they will receive Nelarabine+HDMTX in a Consolidation phase which might be followed thereafter by BMT. This subset is expected to be a very small group based on the M3 rate at end of Induction for the CCG-1961 T-ALL patients receiving the ABFM chemotherapy (1.2%). Only very limited data is available from previous COG studies about these patients such as the survival outcome following Induction failure. Thus, examination of outcome for this group will be primarily descriptive, but their toxicity experience will be examined separately and their survival outcome will be compared to a similar group of patients treated on previous studies.

10.6 Analyses of Gender and Ethnicity

Using national incidence data (SEER, 1986-1990) one can calculate the sex ratio incidence for male: female cases in childhood ALL to be approximately 1.24 for ages 0-14 or 1.31 for ages 0-19.[91] Data from recent COG trials (CCG-1950/60s) show that the ratio of male to female patients entered on ALL trials is 1.31:1, so the ALL population registered by COG institutions is in excellent agreement with national data for the relative incidence of ALL by sex group. In the subset of patients to be treated in this T-lineage ALL study the estimated sex ratio is 2.32:1 since the male: female sex ratio is much higher in T-lineage ALL which is known to have a male predominance. National data for the ethnicity distribution of the overall US population (1986-1990) suggests that 84.3% of the overall US population are white, 12.2% are black, and 3.5% are non-white, non-black.[91] The relative ethnicity distribution in T-lineage childhood ALL (from the CCG-1950/60s series of studies) was 77.4% whites, 6.0% blacks, 11.0% Hispanics, 3.3% Asians, and 2.3% "other". Using the SEER classification of race, probably most of the Hispanics in the COG racial category classification would be classified as "whites". These data suggest that the racial composition of patients entered in COG ALL trials is similar to what would be expected from national incidence data. One would expect this to be the case since some reports have suggested that 80%-90% of children in the US diagnosed with ALL are enrolled on COG trials.

As has been done in previous COG ALL trials, analyses of effects of sex group and ethnicity on outcome will be examined for this study. Extensive data exists in the literature showing that for all children with ALL, females generally have a better prognosis than males.[92-94] However, it is less clear that this effect also occurs in T-lineage ALL (viz., for the CCG-1950/60s series it was a non-significant difference, $p = 0.42$, relative event rate for males 1.18 times that for females). Numerous reports also exist suggesting certain types of outcome differences by racial category for childhood ALL. The most consistent theme in these reports is a somewhat poorer outcome for black patients as compared to whites.[95,96] The size of this difference is in the neighborhood of 10%-15% lower EFS at late periods of follow-up. Again it is not clear that this is the case in T-lineage ALL (viz., for the CCG-1950/60s blacks had a non-significant

difference in EFS compared to whites with a relative event rate for blacks of only 1.19 times that in whites). With a sex ratio of male: female patients in T-lineage patients of approximately 2.32, the overall size of the AALL0434 study (N = 1900 patients) will provide adequate statistical power in this study to examine any overall prognostic difference in outcome by sex. Examination of prognostic differences in ethnicity categories will be more of a problem because of the relatively small proportions for some ethnicity groups, resulting in adequate statistical power only for larger differences in outcome for certain comparisons. However, analyses will be performed for both gender and ethnicity outcome differences recognizing the above statistical analysis caveats. No a priori evidence exists suggesting that the therapies to be used in this study will have differing effects on either gender groups or ethnicity categories. Nevertheless, examination of different prognostic patterns for sex group or racial category outcome according to treatment regimen will be examined and statistical tests for interaction effects will be used. However, the small subsets that will result for some comparisons and the multiple comparison nature of this type of analysis will require cautious interpretation of any findings.

Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	**106**	+	**102**	=	**208**
Not Hispanic or Latino	**465**	+	**1227**	=	**1692**
Ethnic Category: Total of all subjects	**571** (A1)	+	**1329** (B1)	=	**1900** (C1)
Racial Category					
American Indian or Alaskan Native	**2**	+	**9**	=	**11**
Asian	**23**	+	**40**	=	**63**
Black or African American	**43**	+	**72**	=	**115**
Native Hawaiian or other Pacific Islander	**0**	+	**0**	=	**0**
White	**503**	+	**1208**	=	**1711**
Racial Category: Total of all subjects	**571** (A2)	+	**1329** (B2)	=	**1900** (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Data derived from T-lineage population in CCG-1950/60s studies

11.0 EVALUATION CRITERIA

11.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. The descriptions and grading scales found in the revised CTCAE version 4.0 will be utilized for AE reporting beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 which can be downloaded from the CTEP web site (http://ctep.cancer.gov). Additionally, toxicities are to be reported on the appropriate data collection forms.

11.2 Response Criteria for T-ALL

See definitions in Section 3.3.

11.3 Response Criteria for T-NHL

11.3.1 Complete Response (CR)

Defined as disappearance of all evidence of disease from all sites for at least 4 weeks. This will be determined by physical exam and appropriate imaging studies. Bone marrow aspirate/biopsy must be morphologically normal and any macroscopic nodules in any organs detectable on CT should no longer be present.

11.3.2 Complete Response Unconfirmed (CR_u)

A residual lymph node mass > 1.5 cm in greatest transverse diameter that has regressed by > 75% in sum of the products of the greatest perpendicular diameters (SPD), or any residual lesions in organs that have decreased by > 75%.

11.3.3 Partial Response (PR)

Partial response > 50% decrease in the SPD of the lesions for at least 4 weeks. No new lesions.

11.3.4 No Response (NR)

Failure to qualify for a PR. No new lesions.

11.3.5 Progressive Disease

Greater than 25% increase in the size of any lesions or appearance of new lesion(s).

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

12.2 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.

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

Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via AdEERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

12.3 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 Terminology Criteria (CTCAE)* ***[use version 4.0 beginning 07/01/11]***.

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

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

Step 3: *Determine the attribution of adverse event in relation to the protocol therapy.* Attribution categories are: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.*

Expected **events for a CTEP IND agent are defined as those listed in the ASAEL** (Agent Specific Adverse Event List), a subset of the CAEPR (Comprehensive Adverse Event and Potential Risks). For investigational agents that are not commercially available and are being studied under a company's IND, expected AEs are usually based on the Investigator's Brochure.

***Unexpected* events for a CTEP IND agent are defined as those NOT listed in the ASAEL.**

Guidance on expectedness of the agent is provided in the Drug Information Section of this protocol.

Step 5: *Review Tables A and/or B in this section to determine if:*

- *there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or*
- *there are any protocol-specific exceptions to the reporting requirements.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent, a commercial agent, or a combination of investigational and commercial agents.*

Note: If the patient received at least one dose of investigational agent, follow the guidelines in Table A. If no investigational agent was administered, follow the guidelines in Table B.

12.4 Reporting methods

- Use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at: http://ctep.cancer.gov/protocolDevelopment/default.htm

  An AdEERS report must be submitted by the following method:

  Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers.htm

- Fax supporting documentation **for AEs related to investigational agents** to:
  - The NCI for agents supplied under a CTEP IND **only** (fax # 301-230-0159)
  - and to COG for **all** studies (fax# 626-303-1768; email: COGAdEERS@childrensoncologygroup.org; Attention: COG AdEERS Coordinator).

- **DO NOT send the supporting documentation for AEs related to commercial agents to the NCI.** Fax or email this material to COG (fax # 626-303-1768; email: COGAdEERS@childrensoncologygroup.org; Attention: COG AdEERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**

- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

12.5 When to report an event in an expedited manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web based application **and/or by telephone call to the Study Chair.**

  In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497. In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in

must be entered into the electronic AdEERS system by the original submitter of the report at the site.

- Submit the report **within 5 calendar days** of learning of the event.

12.6 Other recipients of adverse event reports

COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

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

12.7 **Reporting of Adverse Events for investigational agents – AdEERS 24-hour notifications, and complete report requirements**.

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table A. The investigational agent used in this study is **Nelarabine (Compound 506U78; IND # 52611); the IND holder is the NCI.**

Table A

Phase 2 and 3 Trials and COG Group-wide Pilot Studies utilizing an Agent under a CTEP IND or a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3[3]		Grade 3[3]		Grades 4 & 5[2]	Grades 4[3] & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	**24-Hour**; 5 Calendar Days	5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:**

AdEERS 24-hour notification (via AdEERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in Non-CTEP IND studies) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization (see exceptions below
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

[3] Please see exceptions below under section entitled "Additional Instructions or Exceptions."

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Note: All deaths on study require timely reporting to COG via RDE regardless of causality. Attribution to treatment or other cause must be provided.

- **Expedited AE reporting timelines defined:**
  - "24 hours; 5 calendar days" – The investigator must initially report the AE (via AdEERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in non-CTEP IND studies) within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete AdEERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

- Protocol specific reporting of AEs, in addition to the AdEERS requirements, are to be entered in the COG remote data entry system.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via AdEERS for an agent under a CTEP IND [and via AdEERS for non-CTEP IND agent] per the timelines outlined in the table above.

- **Grades 1-4 myelosuppression do not require expedited reporting unless unexpected.**

12.8 Additional Reporting Guidelines and Protocol Specific Requirements

The adverse events listed below do **not** require expedited reporting via AdEERS:

Grade 4 myelosuppression
Grade 3 hemoglobinemia (ie, anemia), leukopenia, neutropenia or thrombocytopenia with hospitalization
Grade 3 infection with hospitalization
Grade 3 mucositis with hospitalization
Grade 3 fever/neutropenia with hospitalization
Grade 3 transfusion with hospitalization
Grade 3 nausea and/or vomiting with hospitalization
Grade 3 diarrhea or gastritis with hospitalization
Grade 4 fever/neutropenia ± hospitalization
Grade 4 hemoglobinemia (ie, anemia), leukopenia, neutropenia or thrombocytopenia ± hospitalization

Neurological toxicities are of special concern with Nelarabine. The Study Chair should also be notified immediately of patients experiencing any Grade 3 or Grade 4 neurological toxicity after receiving Nelarabine.

Rhabdomyolysis has been rarely reported with the use of nelarabine. Routine reporting will include any Grade 3 or higher hepatobiliary enzyme elevation associated with highly elevated creatinine phosphokinase elevation. The CTCAE 4.0 Terms to list are: 1) Liver dysfunction (AST, ALT, CK elevations); 2) Muscle pain/weakness; AND 3) Musculoskeletal other: rhabdomyolysis.

12.9 Toxicities and other adverse events that must be reported for all patients via COG remote data entry

The following toxicities and adverse events must be reported for all patients on study, whether or not they have received any doses of an investigational agent on this study.

Report all Grade 3 and 4 non-hematologic toxicities.

Report all Grade 3 and 4 hematologic toxicities that result in hospitalization or a delay in therapy of > 1 week.

Report all CNS toxicities, Grade 1 and greater.

Report all grades of peripheral neuropathy (neurological toxicities are of special concern with nelarabine. The Study Chair should also be notified immediately of patients experiencing any Grade 3 or Grade 4 neurological toxicity after receiving nelarabine).

Report all Grade 3 and higher infection toxicities.

Report all osteonecrosis (avascular necrosis) Grade 1 and greater that has been confirmed by imaging. If a new site of osteonecrosis (avascular necrosis) is diagnosed during a subsequent reporting period please report each occurrence of toxicity on the AE form and the Osteonecrosis (Avascular Necrosis) Data Form again for the reporting period during which the new site of toxicity was identified. Likewise, during subsequent reporting periods submit these forms if toxicity grade increases, and also if an orthopedic surgical procedure is performed.

If the patient is off protocol therapy and has a newly diagnosed osteonecrosis (avascular necrosis) or develops a new site of osteonecrosis (avascular necrosis) the Osteonecrosis (Avascular Necrosis) CRF should be completed.

12.10 Reporting of Adverse Events for commercial agents – AdEERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.
Commercial reporting requirements are provided in Table B.

COG requires the AdEERS report to be submitted **within 5 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS

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

13.0 RECORDS AND REPORTING

13.1 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Pathology Narrative Reports and Surgical Reports. These forms are submitted through the Imaging Document System in the eRDES.

2. Reference Labs' required reports and QARC data: These data accompany submissions to these centers, which forward their review data electronically to the COG Statistics and Data Center.

3. Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet posted on the COG web site, which includes submission schedule.

13.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

13.3 CTA/CRADA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator(s) confidential/ proprietary information.

14.0 RADIATION THERAPY GUIDELINES

Radiation Therapy for patients on COG protocols can only be delivered at approved COG RT facilities (per COG administrative policy 3.9)

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

All Intermediate and High Risk T-ALL patients randomized to Arms C (HD MTX) and D (HD MTX + Nel) will receive prophylactic cranial radiation therapy (CRT) (1200 cGy) starting on Day 50 of **Delayed Intensification (DI)**. All Intermediate and High Risk T-ALL patients randomized to Arms A (CMTX) and B (CMTX + Nel) will receive prophylactic cranial radiation therapy (CRT) (1200 cGy) during Weeks 3 and 4 (Arm A) and Weeks 4 and 5 (Arm B) of **Consolidation**. All T-ALL patients who were CNS 3 at diagnosis will receive CRT (1800 cGy) starting on Day 50 of DI. T-ALL patients with testicular disease at diagnosis that has not resolved by end Induction (biopsy is required if there is any uncertainty regarding clinical response) will receive testicular irradiation (2400 cGy) during Consolidation. T-ALL patients with testicular disease at diagnosis that resolves by end-Induction will not receive testicular irradiation. No patients with Low Risk T-ALL or T-NHL disease will receive radiation therapy.

14.1 Cranial Irradiation

14.1.1 Equipment and Calibration

14.1.1.1 Modality

X-ray beams with a nominal energy between 4 and 6 MV. The use of IMRT is not permitted in this study.

14.1.1.2 Calibration

Calibrations of therapy units used in this protocol will be verified by the Radiological Physics Center (RPC).

14.1.2 Target Volume

Target volume consists of entire brain and meninges, including frontal lobe as well as posterior halves of globes of eyes, with optic disk and nerve, extending superior to vertex and posterior to occiput. Caudal border will be below skull base at C2 vertebral level.

The target volume shall be defined by means of a CT simulator or conventional simulator. Care must be taken to avoid shielding the posterior orbit and cribriform plate. In case of conventional simulation, radio-opaque markers should be placed on the surface of the fleshy canthus to aid in localizing this point.

14.1.3 Target Dose

14.1.3.1 Prescription Point

The prescription point in the cranial volume is at or near the center. For multi-convergent beams, the prescription point is usually at intersection of the beam axis. Note: Regardless of the location of central axis, dose should be prescribed at the center of the cranial volume (midway between the maximum separation).

14.1.3.2 Dose Definition
Absorbed dose is specified in centigrays (cGy)-to-muscle.

14.1.3.3 Tissue Heterogeneity
No corrections for bone attenuation will be made.

14.1.3.4 Prescribed Dose and Fractionation

14.1.3.4.1 Intermediate and High Risk Patients
These patients will receive prophylactic cranial radiation, consisting of a total dose of 1200 cGy given in 8 daily fractions of 150 cGy per fraction, administered Monday through Friday.

14.1.3.4.2 CNS 3 Patients
All patients who present with CNS 3 leukemia at diagnosis will receive cranial radiation consisting of a total dose of 1800 cGy given in 10 daily fractions of 180 cGy per fraction, administered Monday through Friday.

14.1.4 Dose Uniformity
Dose variations in target volume will be within +7%, -5% of prescription-point dose. (From ICRU Report 50: small high-dose volumes can be excluded from evaluation of dose uniformity but not small low-dose volumes.)

14.1.5 Treatment Interruptions
No corrections will be made for treatment interruptions less than 7 days. For interruptions greater than 7 days, contact the Study Radiation Oncology Coordinator.

14.1.6 Treatment Technique

14.1.6.1 Patient Position
It is recommended that the patient be treated in supine with immobilization appropriate for the child such as a face mask.

14.1.6.2 Beam Configuration
Cranial volume is treated with two lateral, equally weighted photon beams. Fields will extend at least 1 cm beyond periphery of scalp.

14.1.6.3 Field Shaping
Field-shaping will be done with blocks which are at least 5 HVL thick. Multi-leaf collimators are acceptable.

14.1.6.4 Eye Protection
A simple method to minimize lens irradiation, while treating posterior halves of eyes, is to let central axes of horizontal cranial beams go through both orbits. Anterior edges of beams are defined by external block or by independently controlled collimator and meet at a point 1 cm anterior to frontal lobe meninges. Shielding blocks cover anterior halves of eyes and protect nose and mouth. Essentially the same geometry can be achieved with central axes through center of head by angling lateral fields so rays through the eyes lie in the same horizontal plane. It is acceptable to use parallel-opposed beam-pair, without such angling, with shielding blocks that cover anterior half of proximal eye. (Dose to contralateral lens will then increase.)

14.2 **Testicular Radiation**

Only patients with **persistent testicular disease at end-Induction** (based on clinical and/or biopsy findings) will receive testicular irradiation.

14.2.1 Equipment and Calibration

14.2.1.1 Modality

High-energy photon or electron beams. Selection of energy is determined by dose uniformity criterion, and with electrons, lowest possible energy should be used to spare tissues outside target volume. IMRT is not permitted.

14.2.1.2 Calibration

Calibrations of therapy machines used in this protocol will be verified by the Radiological Physics Center.

14.2.2 Target Volume

Planning target volume consists of testes in scrotal sac. (N.B. Cremasteric reflex may move testes high up in inguinal canal.) The field may be reduced as the palpably enlarged mass decreases in size during treatment.

14.2.3 Target Dose

14.2.3.1 Prescription point is at or near center of planning target volume.

14.2.3.2 Dose Definition

Absorbed dose is specified as centigrays (cGy)-to-muscle.

14.2.3.3 Prescribed Dose and Fractionation

Total dose to prescription point will be 2400 cGy in 12 fractions. Patient will be treated with one daily fraction per day of 200 cGy for five days a week.

14.2.4 Dose Uniformity

Variations of dose within planning target volume will be within +7%, -5% of dose to prescription point Uniformity requirement can be met with electron beam of appropriate energy provided bolus is used, which is simplest technique. Bolus may also be needed for photon beams to fulfill dose uniformity requirement. (From ICRU Report 50: small high-dose volumes can be excluded from evaluation of dose uniformity, but not small low-dose volumes.)

14.2.5 Treatment Interruptions

No corrections will be made for treatment interruptions less than 7 days. For interruptions greater than 7 days, contact the Study Radiation Oncology Coordinator.

14.2.6 Treatment Technique

14.2.6.1 Patient Position

Patient will be treated in supine position.

14.2.6.2 Field Shaping

Field shaping can be done with blocks of at least 5 HVL thick. Multi-leaf collimators are acceptable.

14.2.6.3 Normal Tissue Sparing
Testes will be supported posteriorly and, if possible, extended caudally in order to minimize perineal irradiation. Field will not be angled towards perineum. The penis will be excluded from field by fixing it to skin over the symphysis pubis.

14.3 Quality Assurance Documentation

14.3.1 QARC Post Treatment Review
Patients receiving RT on this study will have a simple review of the treatment delivered. There is no on-treatment review in this study. There is no film review required. Within one week of the completion of radiotherapy, the following data will be submitted:

- "RT-2 Radiotherapy Total Dose Record" form.
- Copy of patient's radiation therapy chart, including prescription, and daily and cumulative doses.

14.3.2 Data must be sent to:

Quality Assurance Review Center
Building A, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

14.3.3 Questions regarding the dose calculations or documentation should be directed to:

COG Protocol Dosimetrist
Building A, Suite 201
Quality Assurance Review Center
640 George Washington Highway
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

14.3.4 Questions regarding the XRT section of this protocol should be directed to the Study Radiation Oncology Coordinator:

Natia Esiashvili, MD
Emory Radiation Oncology Department
1365 Clifton road, NE
Atlanta, GA, 30322
Phone: (404) 778-5782
Fax: (404) 778-3643
E-mail: natia@radonc.emory.org

14.4 Definitions of Deviation in Protocol Performance

14.4.1 Minor Deviation
Dose to prescription point differs from that in protocol between 6% and 10%.

14.4.2 Major Deviation

Dose to the prescription point differs from that in the protocol by more than 10%.

15.0 PATHOLOGY GUIDELINES FOR T-NHL

15.1 Pathology Goals

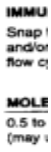
1. Provide quality control by central pathologic review with accurate diagnosis and classification of pediatric non-Hodgkin lymphoma. This is to be based on both morphologic and immunophenotypic criteria. **This study is limited to T-cell lymphoblastic lymphoma**. Patients with B-lineage lymphoblastic lymphoma are not eligible for this study.
2. Employ the recently described World Health Organization (WHO) Lymphoma Classification[97] to facilitate concordance in diagnosis.
3. Correlate morphologic, immunophenotypic and cytogenetic data for the lymphomas included in this treatment protocol.

15.2 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions

15.2.1 Tissue Specimens

Tissue should preferentially, whenever possible, be obtained fresh and delivered immediately to the Pathology Laboratory for optimal handling and distribution (fixation, snap freezing, cytogenetics, etc.). Refer to diagram entitled 'Lymph Node Processing For Institutional Diagnosis And Research Studies In Children's Oncology Group' (Figure 15.1). Submit representative tissue sections for fixation including at least one block with 10% buffered formalin.

Figure 15.1



15.2.2 Cytology Specimens

Cytology or body fluid specimens (i.e. pleural fluid) should be delivered promptly to the pathology laboratory, and handled per primary institutional procedures. Sufficient material should be utilized for morphologic evaluation by cytocentrifuge preparations stained with a Romanowsky stain (i.e. Giemsa or Wright's stains). Provided enough specimen is available, at least one cell block should be prepared with specification of the fixative utilized and the time in fixative.

15.3 Immunophenotyping Recommendations for Primary Institutions

For eligibility in this study, the methodology and criteria for immunophenotypic analysis defined by the submitting institution will be accepted. Recognized methods include: paraffin section immunohistochemistry, frozen section immunohistochemistry, cytocentrifuge (cytospin) immunocytochemistry, and flow cytometry.

For eligibility in this study, an extensive panel of antibodies should be employed for immunophenotypic evaluation. This can be done on snap frozen tissue by immunohistochemistry, and body fluid/cytology specimens by flow cytometry or cytocentrifuge (cytospin) immunocytochemistry. This panel of antibodies is listed as follows:

T-Cell: CD1, CD2, CD3, CD4, CD5, CD7, CD8.
B-Cell: CD19, CD20, Kappa, Lambda.
Myeloid: CD13, CD14, CD33.
Other: CD10, CD25, CD34, CD45, TdT.

The method of TdT evaluation should be specified (i.e. flow cytometry, immunofluorescence, immunohistochemistry).

For cases in which no paraffin embedded tissue has been prepared, and only stained cytospin slides remain available, these cases will be acceptable for protocol submission and pathology review when adequate immunophenotypic data is available from the primary institution. This situation may occur with cases evaluated by cytospin immunocytochemistry or flow cytometry immunophenotyping.

If specimen is limited, preventing a complete immunophenotypic evaluation, a recommended minimum panel of antibodies should include: CD3, CD5, CD19, CD79a and TdT. If specimen is limited to paraffin embedded tissue only, a preferred panel of antibodies should include at least: CD45RO (UCHL-1), CD79a, and TdT. If additional antibodies that may be utilized in paraffin embedded tissue are available at the primary institution, the panel may include: CD3 (polyclonal), CD43 (Leu22), CD22, PAX5[98,99], and CD45RA (4KB5). If immunophenotyping studies are not available locally, the case may be sent as a consultation case for evaluation including immunophenotyping studies to Dr. Sherrie Perkins (see address in Section 15.5.6).

15.4 Pathology Staging Criteria

Cerebrospinal Fluid: Leukocyte count greater than or equal to 5/μL, with presence of blasts. TdT evaluation is strongly recommended.

Bone Marrow: The presence of greater than 5% and less than 25% blasts in a bone marrow aspirate, or focal infiltration in a bone marrow biopsy, represents involvement of the marrow by lymphoblastic lymphoma.

15.5 Retrospective Central Pathology Review

15.5.1 Required Materials

Materials to be submitted for retrospective pathology review to the COG Biopathology Center include the following:

1. Initial diagnostic material prior to therapy
2. Specimens demonstrating relapse of lymphoma at any time
3. Specimens from residual masses demonstrating residual lymphoma or complete response to therapy
4. A copy of all final pathology reports (see details in Section 15.5.1.4)
5. Pathology Data Collection Form
6. Transmittal Form

Please label all materials with the patient's COG patient identification number and the institutional pathology number and block number found on the corresponding pathology report. The materials to be submitted are described below and listed in Table 15-1.

15.5.1.1 Paraffin Blocks
If possible, it is preferred that paraffin blocks be submitted to the COG Biopathology Center. For surgical biopsy specimens, this should include a paraffin block of tissue prepared in 10% Buffered Formalin (as described in Section 15.2.1). For cytology specimens, a paraffin block may be available as a cell block preparation (see Section 15.2.2). If paraffin blocks cannot be submitted, then submit twenty (20) unstained sections (4 microns thick) of unbaked slides air-dried at room temperature and two (2) H&E stained slides from each block. These sections should be place on sialinized slides (i.e. Fisher Superfrost Plus).

15.5.1.2 Cytology Slides
When paraffin blocks have not been prepared, a cytologic preparation of one stained, air-dried cytospin slide (i.e. Romanowsky stain such as Giemsa or Wright's stain) and 10 unstained slides should be submitted.

15.5.1.3 Biopsies of Residual Masses
For these biopsy specimens, send a recut slide (hematoxylin and eosin stain) from all of the paraffin blocks for review. The corresponding pathology report should accompany the slides for review.

15.5.1.4 Pathology Reports
A copy of all pathology reports on each case should be submitted. This should include:

1. Final reports of diagnostic biopsy and bone marrow specimens (even if negative)
2. All immunophenotyping reports of diagnostic biopsy and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available)
3. Results of any genotypic studies (i.e. gene rearrangement studies)
4. Results of any cytogenetic (karyotypic) analysis

15.5.1.5 Pathology Data Collection Forms/COG Pathology Center
A separate pathology data collection form (Institutional Pathology Form) should be completed and submitted along with the above materials. Also, indicate the primary institution pathology diagnosis utilizing the WHO Lymphoma Classification[97] on the data collection form.

15.5.2 Transmittal Form
A specimen transmittal form must be submitted along with the pathology review materials.

15.5.3 Biopathology Center Address
All material submitted for central pathology review should be sent via regular mail or using your institutional courier account to:

COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA 1340*****
Columbus, OH 43205
Phone: (614) 722-2894
Fax: (614) 722-2897

***** The room number is required. Packages not listing the room number could be denied and returned to sender.

15.5.4 Paraffin Blocks and Cytologic Slides-Storage/Return

Paraffin blocks and cytologic slides will be retained at the COG Biopathology Center indefinitely, unless the institution requests their return.

15.5.5 Lymphoma Classification

Morphologic evaluation and classification of the study cases will utilize the criteria described in the WHO Lymphoma Classification.[97] Eligible pediatric lymphomas will be classified as precursor T-cell lymphoblastic lymphoma.

15.5.6 Review Pathologists

For any questions regarding the pathology protocol, please contact:

Sherrie Perkins, MD, PhD
University of Utah and ARUP Laboratories
Department of Hematology
500 Chipeta Way
Salt Lake City, UT 84108
Phone: (801) 581-5854
Fax: (801) 585-3831

TABLE 15-1: MATERIALS TO SEND FOR CENTRAL PATHOLOGY REVIEW

1. Paraffin Blocks
   Send one of the following:
   a. Surgical biopsy specimen: One paraffin block (formalin preferred).
   b. Cytology cell block: One paraffin block (specify fixative).
   c. If blocks cannot be sent, submit twenty unstained and unbaked sections (4 μm) and two H&E stained sections from each block on sialinized slides.

2. Cytology Slides
   Send one stained slide (Romanowsky stain) and 10 unstained slides

3. Biopsies of Residual Masses
   a. Send a recut slide (hematoxylin and eosin stain) from all of the paraffin blocks from each of these types of biopsy specimens.
   b. Send corresponding pathology report.

4. Pathology Reports
   Send all of the following:
   a. Final reports of diagnostic biopsy and bone marrow specimens (even if negative).
   b. All immunophenotyping reports of diagnostic biopsy, and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available).
   c. Results of any genotypic studies (i.e. gene rearrangement studies).
   d. Results of any cytogenetic (karyotypic) analysis.

5. Pathology Data Collection Form

6. Transmittal Form

16.0 BIOLOGY METHODS AND SPECIMEN SUBMISSION FOR T-NHL

16.1 Required Minimal Residual Disease (MRD) Biology Studies

16.1.1 Sample Collection

A single bone marrow specimen will be obtained at diagnosis to assess disease involvement in the bone marrow for subsequent risk stratification. This sample will be shipped to the COG ALL Reference Flow Cytometry Lab using the same shipping and handling requirements as T-ALL patients enrolled on this study.

Samples are to be shipped to Dr. Brent Wood at the University of Washington, Flow Cytometry Laboratory. The Specimen Transmittal Form is to be submitted with each sample submitted to the COG Reference Laboratory. The specimen transmittal form information should always include the name and telephone number of a person designated by the PI to receive calls from the Reference Laboratory directors. The PI's FAX number must also be noted on each sample inclusion form. Because clinical recommendations will be made on these samples, **always** include the patient's initials and COG number on any sample submitted. This is a CLIA requirement. COG ALL Reference Laboratories may be unable to analyze specimens if adequate patient identifiers are not provided.

T-NHL samples for the Reference Laboratories are to be collected in special 15 mL conical tubes (SM) containing EDTA/RPMI as the anticoagulant and media diluent. These tubes will be prepared in the Reference Laboratories and mailed in batches to each participating institution, where they can be stored frozen at -20°C until use. Tubes are stable for 3 months if refrigerated and stable for 1 year if frozen.

To request prepared and pre-packaged sample shipping tubes, click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application. Please select the protocol 'AALL08B1' to order the shipping tubes required for MRD samples. Even though T-NHL patients are not enrolled on AALL08B1, the supplies are still ordered through that protocol.

Bone Marrow Collection Procedures for Reference Laboratories for T-NHL:

a. Collect BM into a syringe and transfer the specimen immediately into the 15 mL shipping media conical tube with RPMI/EDTA.
b. Mix well. Up to 5 mL of BM can be placed in one 15 mL tube with RPMI/EDTA. If you don't have shipping media tubes, you can place the BM into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is greatly enhanced in the shipping media tubes.
c. 5 mL of BM will be sufficient for MRD analysis at diagnosis.

16.1.2 Sample Shipping

T-NHL bone marrow samples for MRD studies will be shipped to one place:

Western Flow Cytometry Reference Laboratory
Brent Wood, MD, PhD
SCCA
Hematopathology Laboratory
Room G7-800
825 Eastlake Ave. E.
Seattle, WA 98109-1028
Phone: 206-288-7060
FAX: 206-288-7127

SAMPLES THAT ARE EXPECTED TO BE DELAYED FOR MORE THAN 48 HOURS—PLACE A COLD PACK (NOT ICE PACK) IN SHIPMENT. ALL TUBES SHOULD BE LABELED WITH AT LEAST TWO PATIENT IDENTIFIERS, INCLUDING THE NAME AND THE COG NUMBER/BIOPATHOLOGY NUMBER. IN ADDITION, A SPECIMEN TRANSMITTAL FORM AVAILABLE ON THE RDE SHOULD ALWAYS BE SUBMITTED WITH EACH SAMPLE.

Call Reference Laboratories only when shipping a sample to be delivered on Saturday.

Samples for the Flow Cytometry Reference Laboratory should be mailed by FEDERAL EXPRESS PRIORITY (DELIVERY BEFORE 10 AM) using the COG Federal Express account number available at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

16.2 Optional Tissue Banking and Subsequent Biologic Studies

Specimens to characterize the biologic nature of the disease will focus on four major areas: 1) immunophenotyping; 2) cytogenetic characterization by FISH; 3) NOTCH mutation analysis; and 4) CGH and gene expression profiling. Tissue collection is requested prior to treatment initiation and also at the time of relapse. It is anticipated that there will be variability in the type and amount of tissue submitted based upon the accessibility of the tumor tissue and the feasibility of obtaining it (i.e. patients with large mediastinal masses who are sedation risks will be expected to have limited tissue available). Minimum requirements for study entry will include sufficient tissue to confirm the diagnosis. Fresh tissue will be obtained whenever possible. All available biologic specimens will be sent to the COG Biopathology Center, which will serve as the central repository for this component of the study. The study committee will assess the state and quantity of material for subsequent studies with allocation to designated laboratories, placing priority in the studies in the rank order listed below. The collection, processing, shipping and analysis of the tissue have been incorporated into the AALL0434 protocol in order to prevent any modification or amendment of the ALL Classification Study (AALL08B1). Specific details of the biologic studies include:

1. *Immunophenotyping*: Immunophenotyping will focus on the characterization of the thymic developmental stage of a particular patient's disease to determine whether this has prognostic significance. Emphasis will be placed on those surface markers that can be obtained from paraffin embedded tissue that should be available from all patients enrolled. This will include $CD4^{-}CD8^{-}$ $sCD3^{-}CD1a$ to establish the developmental stage of the disease for each patient. Data from recently completed A5971 suggests that a phenotype expressing CD1, CD5, and CD8 may correlate with a poor outcome.[100] This observation will be examined in this proposal to determine its validity.
2. *Cytogenetic Analysis*: Limited cytogenetic analysis (via FISH) will be obtained in all specimens with sufficient tissue given the great paucity of data available characterizing the nature of cytogenetic abnormalities in LL. Conventional cytogenetic analysis on fresh tissue will not be attempted as prior studies have failed to yield sufficient specimens to warrant a commitment of resources to this endeavor. This combined with CGH studies below will allow a more detailed characterization of the cytogenetic abnormalities in LL.
3. *NOTCH Mutation Analysis*: Specimens will be collected to characterize both the incidence and prognostic value of the presence of NOTCH mutations and NOTCH expression in patients with LL. Data collected from these studies will be correlated to disease outcome and gene expression analysis to gain further insight on the relevance of NOTCH mutations and the biologic and clinical behavior of the disease.
4. *Comparative Genomic Hybridization (CGH) and Gene Expression Profiling*: The recently completed A5971 study piloted the feasibility of comparative genomic analysis to characterize genetic alterations in a small number of LLs to assess whether this technique can identify

important genetic alternations, which have been difficult to assess due to the limited availability of tissue typically available for cytogenetic analysis. A recent COG analysis comparing T-cell ALL to LL utilizing gene expression profiling demonstrated that there may be several non overlapping genes expressed, distinguishing these two diseases.[101] Based upon the findings of A5971, and the availability of resources, a targeted approach will be expanded to gain more extensive characterization of the incidence of genetic aberrations in LL and their correlation to clinical outcome. This may potentially lead to insight of the important genetic features of high risk disease and possibly reveal potential targets for new therapies.

For cases with a limited amount of tissue available for analysis, the AALL0434 and NHL Biology Committee will prioritize specimens for studies.

16.3 Preparation of Tissue Banking Samples at Time of Diagnosis or Relapse

At diagnosis, at least one square centimeter of snap frozen tumor is requested in addition to the material required for central review (described in Section 15.5). If more than 1 gram is available, cut tissue into 1 gram aliquots. Wrap tissue in foil and snap freeze in liquid nitrogen or cold isopentane. Place tissue in zip-loc bag and, using a waterproof marker, label the bag with the patient's BPC number, specimen type and date obtained. Store specimens at -70°C or colder until shipped. Include a transmittal form with each shipment of specimens.

If tumor tissue is obtained at the time of relapse for clinical purposes, additional material (as described above for diagnosis) is requested for banking and subsequent biologic studies.

The Biopathology Center (BPC) will bank the tissue for future distribution and use including the studies listed above.

16.3.1 Specimen Shipping Instructions

Specimen procurement kits for shipping frozen tumor tissue to the BPC are provided upon request. To request a Specimen Procurement Kit, click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application. Select 'AALL0434' to order kits for the submission of frozen tumor tissue. Specimen procurement kits must be shipped to the BPC, Monday through Thursday for delivery Tuesday through Friday.

1. Before the frozen tissue is placed into the Specimen Procurement Kit, it must first be placed in three separate layers of packaging :
   a. Place the tissue in a zip-loc bag.
   b. Place the zip-loc bag in the plastic watertight biohazard diagnostic envelope and seal the envelope securely.
   c. Place the clear plastic biohazard diagnostic envelope inside the pressure-proof Tyvek diagnostic envelope and seal securely.

2. Place the tissue inside the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.

3. Place the transmittal form inside the compartment.

4. Place the stryofoam lid on top to secure specimns during shipment.

5. Close the outer lid of the Specimen Procurement Kit and tape with filament or other durable sealing tape.

6. Access the BPC Kit Management application to print a Federal Express shipping label. A blank adhesive label is provided in the Specimen Procurement Kit to use when printing the shipping label. Attach the shipping label to the top of the kit. Complete the dry ice label (UN 1845). Stick the dry ice and Exempt Human Specimen labels to the side of the kit.. Arrange for Federal Express pick-up per your usual institutional procedure or by calling 1-800-238-5355.

Ship specimens to:
COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, Room WA1340*****
Columbus, OH 43205
Phone: (614) 722-2865

***** The room number is required. Packages not listing the room number could be denied and returned to sender.

APPENDIX I: MERCAPTOPURINE DOSING GUIDELINES

MERCAPTOPURINE 25 mg/m^2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.49	½ tab / d x 3	75 mg/wk
0.50 - 0.64	½ tab / d x 4	100 mg/wk
0.65 - 0.78	½ tab / d x 5	125 mg/wk
0.79 - 0.92	½ tab / d x 6	150 mg/wk
0.93 – 1.07	½ tab / d x 7	175 mg/wk
1.08 – 1.21	1 tab / d x 1; ½ tab / d x 6	200 mg/wk
1.22 – 1.35	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
1.36 – 1.49	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
1.50 – 1.64	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
1.65 – 1.78	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
1.79 – 1.92	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
1.93 – 2.07	1 tab / d x 7	350 mg/wk
2.08 – 2.21	1½ tab / d x 1; 1 tab / d x 6	375 mg/wk
2.22 - 2.35	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
2.36 – 2.49	1½ tab / d x 3; 1 tab / d x 4	425 mg/wk
2.50 – 2.64	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
2.65 – 2.78	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
2.79 – 2.92	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
2.93 – 3.00*	1½ tab / d x 7	525 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

MERCAPTOPURINE 60 mg/m²

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.33 - 0.38	½ tab / d x 6	150 mg/wk
0.39 - 0.44	½ tab / d x 7	175 mg/wk
0.45 - 0.50	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.51 - 0.56	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.57 - 0.62	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.63 - 0.68	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.69 - 0.74	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.75 - 0.80	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.81 - 0.86	1 tab / d x 7	350 mg/wk
0.87 - 0.92	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.93 - 0.98	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.99 - 1.04	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
1.05 - 1.10	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.11 - 1.16	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.17 - 1.22	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.23 - 1.27	1½ tab / d x 7	525 mg/wk
1.28 - 1.33	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.34 - 1.39	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.40 - 1.45	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.46 - 1.51	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.52 - 1.57	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.58 - 1.63	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.64 - 1.69	2 tab / d x 7	700 mg/wk
1.70 - 1.75	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.76 - 1.81	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk

1.82 - 1.87	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.88 - 1.93	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.94 - 1.99	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
2.00 - 2.05	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
2.06 - 2.11	2½ tab/ d x 7	875 mg/wk
2.12 - 2.17	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
2.18 - 2.23	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
2.24 - 2.29	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
2.30 - 2.35	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
2.36 - 2.41	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
2.42 - 2.47	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
2.48 - 2.52	3 tab/ d x 7	1050 mg/wk
2.53 - 2.58	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.59 - 2.64	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.65 - 2.70	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.71 - 2.76	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.77 - 2.82	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.83 - 2.88	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.89 - 2.94	3½ tab/ d x 7	1225 mg/wk
2.95 - 3.00	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

MERCAPTOPURINE 75 mg/m^2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk
2.41 – 2.45	3½ tab/ d x 5; 4 tab / d x 2	1275 mg/wk
2.46 – 2.49	3½ tab/ d x 4; 4 tab / d x 3	1300 mg/wk

2.50 – 2.54	4 tab/ d x 4; 3½ tab / d x 3	1325 mg/wk
2.55 – 2.59	4 tab/ d x 5; 3½ tab / d x 2	1350 mg/wk
2.60 – 2.64	4 tab/ d x 6; 3½ tab / d x 1	1375 mg/wk
2.65 – 2.69	4 tab/ d x 7	1400 mg/wk
2.70 – 2.73	4 tab/ d x 6; 4½ tab / d x 1	1425 mg/wk
2.74 – 2.78	4 tab/ d x 5; 4½ tab / d x 2	1450 mg/wk
2.79 – 2.83	4 tab/ d x 4; 4½ tab / d x 3	1475 mg/wk
2.84 – 2.88	4½ tab/ d x 4; 4 tab / d x 3	1500 mg/wk
2.89 – 2.92	4½ tab/ d x 5; 4 tab / d x 2	1525 mg/wk
2.93 – 2.97	4½ tab/ d x 6; 4 tab / d x 1	1550 mg/wk
2.98 – 3.00	4½ tab/ d x 7	1575 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

APPENDIX II: THIOGUANINE DOSING GUIDELINES

THIOGUANINE 60 mg/m²

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 40 mg)	Cumulative Weekly Dose
0.31 - 0.35	½ tab / d x 7	140 mg/wk
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.60 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.79 - 0.83	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
0.98 - 1.02	1½ tab /day	420 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.31 - 1.35	2 tab / day	560 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
1.46 - 1.49	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.50 - 1.54	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.55 - 1.59	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.65 - 1.69	2½ tab / d	700 mg/wk
1.70 - 1.73	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.74 - 1.78	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.79 - 1.83	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.84 - 1.88	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.89 - 1.92	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
1.93 - 1.97	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk
1.98 - 2.02	3 tab / d x 7	840 mg/wk
2.03 - 2.07	3 tab / d x 6; 3½ tab / d x 1	860 mg/wk
2.08 - 2.11	3 tab / d x 5; 3½ tab / d x 2	880 mg/wk
2.12 - 2.16	3 tab / d x 4; 3½ tab / d x 3	900 mg/wk
2.17 - 2.21	3½ tab / d x 4; 3 tab / d x 3	920 mg/wk
2.22 - 2.26	3½ tab / d x 5; 3 tab / d x 2	940 mg/wk

2.27 – 2.30	3½ tab / d x 6; 3 tab / d x 1	960 mg/wk
2.31 – 2.35	3½ tab / d x 7	980 mg/wk
2.36 – 2.40	3½ tab / d x 6; 4 tab / d x 1	1000 mg/wk
2.41 – 2.45	3½ tab / d x 5; 4 tab / d x 2	1020 mg/wk
2.46 – 2.49	3½ tab / d x 4; 4 tab / d x 3	1040 mg/wk
2.50 – 2.54	4 tab / d x 4; 3½ tab / d x 3	1060 mg/wk
2.55 – 2.59	4 tab / d x 5; 3½ tab / d x 2	1080 mg/wk
2.60 – 2.64	4 tab / d x 6; 3½ tab / d x 1	1100 mg/wk
2.65 – 2.69	4 tab / d x 7	1120 mg/wk
2.70 – 2.73	4 tab / d x 6; 4½ tab / d x 1	1140 mg/wk
2.74 – 2.78	4 tab / d x 5; 4½ tab / d x 2	1160 mg/wk
2.79 – 2.83	4 tab / d x 4; 4½ tab / d x 3	1180 mg/wk
2.84 – 2.88	4½ tab / d x 4; 4 tab / d x 3	1200 mg/wk
2.89 – 2.92	4½ tab / d x 5; 4 tab / d x 2	1220 mg/wk
2.93 – 2.97	4½ tab / d x 6; 4 tab / d x 1	1240 mg/wk
2.98 – 3.00	4½ tab / d x 7	1260 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their TG doses calculated on actual BSA with no maximum dose.*

APPENDIX III: CYP3A4/5 INHIBITORS AND INDUCERS

Adapted from Cytochrome P-450 Enzymes and Drug Metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th edition. Hudson, OH; LexiComp Inc. 2000: 1364-1371.

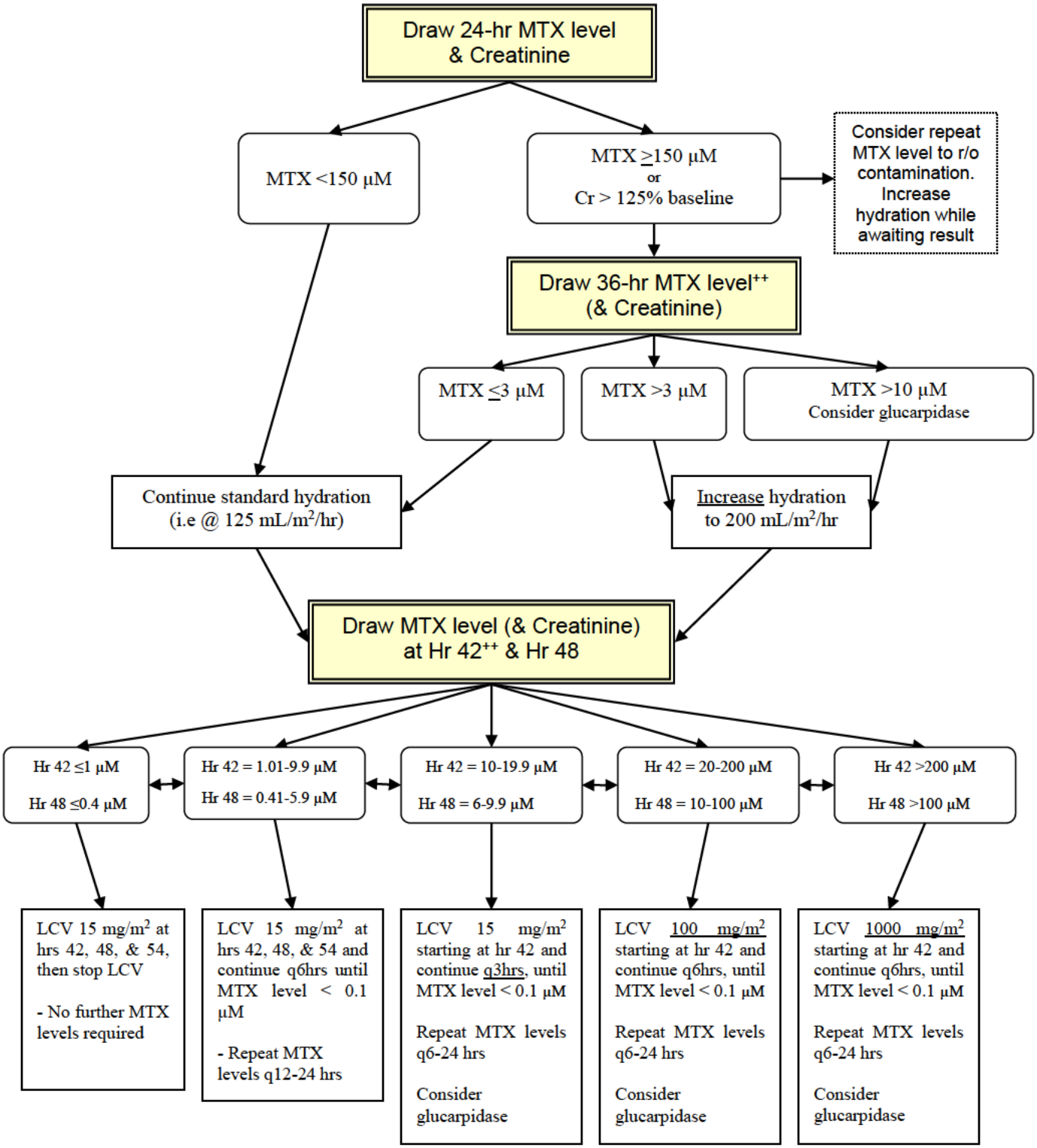
CYP3A4/5 Inhibitors:		CYP3A4/5 Inducers:
Amiodarone	Ritonavir	Carbamazepine
Anastrozole	Roxithromycin	Dexamethasone
Azithromycin	Saquinavir	Ethosuximide
Cannabinoids	Sertindole	Glucocorticoids
Cimetidine	Sertraline	Griseofulvin
Clarithromycin	Telithromycin	Modafinil
Clotrimazole	Troleandomycin	Nafcillin
Cyclosporine	Valproic acid (weak)	Nelfinavir
Danazol	Verapamil	Nevirapine
Delaviridine	Voriconazole	Oxcarbazepine
Dexamethasone	Zafirlukast	Phenobarbital
Diethyldithiocarbamate	Zileuton	Phenylbutazone
Diltiazem		Phenytoin
Dirithromycin		Primidone
Disulfiram		Progesterone
Entacapone (high dose)		Rifabutin
Erythromycin		Rifapentine
Ethinyl estradiol		Rifampin
Fluconazole (weak)		Rofecoxib (mild)
Fluoxetine		St. John's Wort
Fluvoxamine		Sulfadimidine
Gestodene		Sulfinpyrazone
Grapefruit juice		Troglitazone
Indinavir		
Isoniazid		
Itraconazole		
Ketoconazole		
Metronidazole		
Mibefradil		
Miconazole (moderate)		
Nefazodone		
Nelfinavir		
Nevirapine		
Norfloxacin		
Norfluoxetine		
Omeprazole (weak)		
Oxiconazole		
Paroxetine (weak)		
Posaconazole		
Propoxyphene		
Quinidine		
Quinine		
Quinupristin and dalfopristin		
Ranitidine		

This list may not be comprehensive due to new agents coming to market. Below is a link to a list of drugs that are metabolized by cytochrome P450 isoform. Drug names are hyperlinks to specific literature references, most of which include a link to the abstract of the article in the NLM's PubMed database.

http://medicine.iupui.edu/flockhart/

APPENDIX IV: HIGH-DOSE METHOTREXATE FLOW CHART

(Please refer to Section 5.8 for complete details; all levels are timed from the start of the HDMTX infusion)



++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤1 and/or ≤0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

APPENDIX V: MODIFIED ("BALIS") PEDIATRIC SCALE OF PERIPHERAL NEUROPATHIES

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.

- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.

- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.

- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.

- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.

- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).

- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

APPENDIX VI: YOUTH INFORMATION SHEETS FOR PATIENTS WITH T-CELL ALL

INFORMATION SHEET REGARDING RESEARCH STUDY AALL0434
(for children from 7 through 12 years of age)

Intensified Methotrexate, Nelarabine and Augmented Therapy for Children and Young Adults with T-cell Acute Lymphoblastic Leukemia (ALL) or T-cell Lymphoblastic Lymphoma

1. We have been talking with you about a type of cancer called T-cell acute lymphoblastic leukemia or T-ALL. T-ALL is a type of cancer that only affects T-cells (a special kind of cell of your immune system). T-cell ALL grows in the bone marrow. The bone marrow is inside your bones. It is where your blood is made. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-ALL. We will do this by comparing 4 ways to treat T-ALL. Some of the children in this study will get the usual treatment for T-ALL. Some of the children will get extra chemotherapy. We don't know which way is better. That is why we are doing this study.

3. Children who are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. Sometimes X-ray treatments are also given to patients to help kill cancer that is in the brain and/or testicles (if you are a male) or to keep the cancer from moving into the brain. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called 'benefits'. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called 'risks'. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. Steroid drugs, such as the dexamethasone (and less frequently prednisone), are known causes of a disease called "osteonecrosis" (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. If the bones near a joint breakdown it can cause the joint to collapse. The exact reason why corticosteroids cause ON is not known. For patients receiving extra chemotherapy, there is also the risk of side effects involving the nerves, such as numbness and tingling and weakness. Most of the time these side effects are mild and go away within a few days. In rare cases the nerve side effects may be very severe, and then may last for a long time and may not completely go away. It is also possible that your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer for as long as possible.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY AALL0434
(for teens from 13 through 17 years of age)

Intensified Methotrexate, Nelarabine and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia (ALL) or T-cell Lymphoblastic Lymphoma

1. We have been talking with you about a type of cancer called T-cell acute lymphoblastic leukemia or T-ALL. T-ALL is a type of cancer that only affects T-cells (a special kind of cell of your immune system). T-cell ALL grows in the bone marrow. The bone marrow is inside your bones. It is where your blood is made. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-ALL. We will do this by comparing 4 ways to treat T-ALL:
    - Standard chemotherapy for T-ALL
    - Standard chemotherapy for T-ALL, plus an experimental drug called Nelarabine
    - Augmented chemotherapy for T-ALL, which is standard chemotherapy with high-dose methotrexate substituted for methotrexate
    - Augmented chemotherapy for T-ALL, plus Nelarabine

    Some of the children and teens in this study will get the usual treatment for T-ALL. Some of the children and teens will get extra chemotherapy. We don't know which way is better. That is why we are doing this study.

3. Children and teens who are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. Sometimes X-ray treatments are also given to patients to help kill cancer that is in the brain and/or testicles (if you are a male) or to keep the cancer from moving into the brain. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called 'benefits'. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called 'risks'. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints.

    Steroid drugs, such as the dexamethasone (and less frequently prednisone), are known causes of a disease called "osteonecrosis" (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. If the bones near a joint breakdown it can cause the joint to collapse. The exact reason why corticosteroids cause ON is not known.

    For patients receiving Nelarabine, there is also the risk of side effects involving the nerves, such as numbness and tingling and weakness. Most of the time these side effects are mild and go away within

a few days. In rare cases the nerve side effects may be very severe, and then may last for a long time and may not completely go away. It is also possible that adding Nelarabine and/or high-dose methotrexate to your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer for as long as possible. Adding Nelarabine and/or high-dose methotrexate to your treatment plan could also reduce how well your treatment works.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

APPENDIX VII: YOUTH INFORMATION SHEETS FOR PATIENTS WITH T-CELL NHL

INFORMATION SHEET REGARDING RESEARCH STUDY AALL0434
(for children from 7 through 12 years of age)

Intensified Methotrexate, Nelarabine and Augmented Therapy for Children and Young Adults with T-cell Acute Lymphoblastic Leukemia (ALL) or T-cell Lymphoblastic Lymphoma

1. We have been talking with you about a type of cancer called T-cell lymphoblastic lymphoma or T-NHL. T-NHL is a type of cancer that occurs in the lymph system, which is made up of the lymph nodes and other lymph tissue throughout the body. Lymph tissue makes and stores infection-fighting white blood cells called lymphocytes. These cells become cancerous when a subject has lymphoma. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-NHL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-NHL. We will do this by comparing 2 ways to treat T-NHL. Some of the children in this study will get the usual treatment for T-NHL. Some of the children will get extra chemotherapy. We don't know which way is better. That is why we are doing this study.

3. Children who are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. You will also have scans performed to make sure the T-NHL is responding to treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called 'benefits'. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called 'risks'. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. Steroid drugs, such as the dexamethasone (and less frequently prednisone), are known causes of a disease called "osteonecrosis" (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. If the bones near a joint breakdown it can cause the joint to collapse. The exact reason why corticosteroids cause ON is not known. For patients receiving extra chemotherapy, there is also the risk of side effects involving the nerves, such as numbness and tingling and weakness. Most of the time these side effects are mild and go away within a few days. In rare cases the nerve side effects may be very severe, and then may last for a long time and may not completely go away. It is also possible that your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer for as long as possible.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY AALL0434
(for teens from 13 through 17 years of age)

Intensified Methotrexate, Nelarabine and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia (ALL) or T-cell Lymphoblastic Lymphoma

1. We have been talking with you about a type of cancer called T-cell lymphoblastic lymphoma or T-NHL. T-NHL is a type of cancer that occurs in the lymph system, which is made up of the lymph nodes and other lymph tissue throughout the body. Lymph tissue makes and stores infection-fighting white blood cells called lymphocytes. These cells become cancerous when a subject has lymphoma. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-NHL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-NHL. We will do this by comparing 2 ways to treat T-NHL:
    - Standard chemotherapy for T-NHL
    - Standard chemotherapy for T-NHL, plus an experimental drug called Nelarabine

    Some of the children and teens in this study will get the usual treatment for T-NHL. Some of the children and teens will get extra chemotherapy. We don't know which way is better. That is why we are doing this study.

3. Children and teens who are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. You will also have scans performed to make sure the T-NHL is responding to treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called 'benefits'. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called 'risks'. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints.

    Steroid drugs, such as the dexamethasone (and less frequently prednisone), are known causes of a disease called "osteonecrosis" (ON). Osteonecrosis results from the temporary or permanent loss of the blood supply to the bones. Without blood, the bone tissue dies and causes the bone to breakdown. ON is most commonly seen in the hip joint. If the bones near a joint breakdown it can cause the joint to collapse. The exact reason why corticosteroids cause ON is not known.

    For patients receiving Nelarabine, there is also the risk of side effects involving the nerves, such as numbness and tingling and weakness. Most of the time these side effects are mild and go away within a few days. In rare cases the nerve side effects may be very severe, and then may last for a long time and may not completely go away. It is also possible that adding Nelarabine to your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer

for as long as possible. Adding Nelarabine to your treatment plan could also reduce how well your treatment works.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

APPENDIX VIII: STAGING CLASSIFICATION OF CHILDHOOD NON-HODGKIN LYMPHOMA

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APPENDIX IX: AGGREGATE ANALYSIS OF PATIENTS WHO EXPERIENCED RHABDOMYOLYSIS IN TRIALS USING NELARABINE

AE #1147179 (Protocol AALL0434):
A 4-year-old male with precursor T-cell acute lymphoblastic leukemia (T-cell ALL) experienced elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), bilateral lower limb muscle weakness, and rhabdomyolysis while on the consolidation arm of a phase 2/3 study using the investigational agent nelarabine in combination with methotrexate, cyclophosphamide, cytarabine, mercaptopurine, vincristine, pegaspargase, and radiation therapy.

The patient received nelarabine as scheduled from April 19, 2011 to April 23, 2011, and tolerated the treatment well while in the hospital. On April 23, 2011 (Cycle 2, Day 5), laboratory results showed elevated AST and ALT levels immediately following his last dose of nelarabine. On April 26, 2011, the patient presented with abdominal pain associated with dark urine, nonspecific pain in his upper neck, and bilateral leg pain causing difficulty with walking. The neck and leg pain had been present since he left the hospital. His urinalysis showed a protein of 30 mg/dL (reference range: 0-8 mg/dL) and was positive for hemoglobin. His creatine kinase (CK) was 56,846 IU/L (reference range: 60-294 IU/L), his ALT was 770 IU/L (reference range: 1-52 IU/L), and his AST was 1880 IU/L (reference range: 1-51 IU/L). He was admitted to the hospital and started on aggressive hydration, along with alkalinization of his urine. Chemotherapy and his prophylactic Bactrim® were held. It was felt that the patient was experiencing acute rhabdomyolysis due to the nelarabine. On May 1, 2011 (Cycle 2, Day 8 with dose delay), the patient restarted his chemotherapy receiving cyclophosphamide and cytarabine, which he tolerated. By May 2, 2011, the patient's condition had improved; his CK was 1,559 IU/L and his ALT and AST were 321 IU/L and 76 IU/L, respectively, and he was discharged. On May 10, 2011, his ALT and AST were 68 IU/L and 47 IU/L, respectively. Treatment with nelarabine was permanently discontinued. Per the site, as of July 12, 2011, the patient has had no residual side effects from the event.

AE #1668452 (Protocol AALL0434):
A 16-year-old male with Non-Hodgkin's Lymphoma experienced elevated ALT, elevated AST, elevated creatine phosphokinase (CPK), and myalgia while on the consolidation arm of a phase 2/3 study using the investigational agent nelarabine in combination with methotrexate, cyclophosphamide, cytarabine, mercaptopurine, vincristine, pegaspargase, and radiation therapy.

The patient completed Cycle 2, Day 47 of consolidation, which included a 5-day course of nelarabine, on April 26, 2011. He had experienced diffuse but mainly abdominal and chest muscle pain which improved by April 29, 2011 (Cycle 2, Day 50). The patient's symptoms were thought to initially be an episode of myositis associated with nelarabine. Evaluation revealed an elevated CPK of 56,760 IU/L (ULN = 400 IU/L), AST of 1178 IU/L (ULN = 41 IU/L), ALT of 246 IU/L (reference range not provided), and lactate dehydrogenase (LDH) of 1298, consistent with rhabdomyolysis. A previous urinalysis had shown blood without RBCs on microscopic examination; a current urinalysis was unremarkable. He was given IV fluids and increased oral fluids. On May 4, 2011, the patient's CPK was 1086 IU/L. By May 6, 2011, his CPK was 342 IU/L and the rhabdomyolysis was deemed resolved. The patient had no further muscle pain. Nelarabine was permanently discontinued. The patient relapsed with bony metastatic disease in June of 2011.

AE # 1720816 (Protocol E04-5299):
A 12-year-old male with pre-cursor T-cell acute lymphocytic leukemia (ALL) developed motor neuropathy, psychosis, seizure, and rhabdomyolysis before dying of adult respiratory distress syndrome (ARDS) while on a special exception trial using the investigational agent nelarabine.

The patient, who received 4 of the 5 planned doses of nelarabine, tolerated the treatment well until September 17, 2004 (Cycle 1, Day 3), when he experienced a single episode of hallucinations and developed leg weakness. By Cycle 1, Day 5, the patient was experiencing increased leg pain and weakness and was unable to move his legs. The last day of study drug was held. He experienced further hallucinations as well as confusion, then seizure. On September 20, 2004, his creatinine increased to 3.7 mg/dL (reference range: 0.8-1.2 mg/dL), his myoglobin was 4,258.8 ng/mL (reference range: 0-110 ng/mL), and his CPK was 1,653 U/L (reference range: 55-370 U/L), consistent with rhabdomyolysis. Myoglobin decreased to 191.9 ng/mL on September 24, 2004. The patient went into respiratory failure and gradually deteriorated until he expired on October 12, 2004.

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Amendment #6

CHILDREN'S ONCOLOGY GROUP

AALL1231

A Phase III Randomized Trial Investigating Bortezomib (NSC# 681239; IND# 58443) on a Modified Augmented BFM (ABFM) Backbone in Newly Diagnosed T- Lymphoblastic Leukemia (T-ALL) and T- Lymphoblastic Lymphoma (T-LLy)

A Groupwide Phase III Study

NCI Supplied Agent: Bortezomib (NSC# 681239; IND# 58443)

Sponsor: CTEP, NCI, DCTD
Protocol IND: 58443

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ABSTRACT

AALL1231 is a COG group-wide Phase III study for patients between 1-30 years of age with newly diagnosed T- lymphoblastic leukemia (T-ALL) or T-Lymphoblastic Lymphoma (T-LLy) that will assess whether the addition of bortezomib (PS-341) to a modified augmented BFM backbone will decrease relapse risk and improve event-free survival (EFS) and overall survival (OS). Although EFS and OS continue to increase for children and young adults with T-ALL and T-LLy, patients who relapse have a dismal prognosis. These patients are extremely difficult to salvage as they tend to relapse early and with chemotherapy-refractory disease. There is strong biological rationale for introducing bortezomib early in treatment to prevent relapse. Bortezomib has been shown to have a favorable synergistic interaction with backbone chemotherapy drugs and the potential to reverse both innate and acquired steroid resistance. In addition, early phase clinical trials suggest bortezomib is a therapeutically active agent in T-ALL and T-LLy.

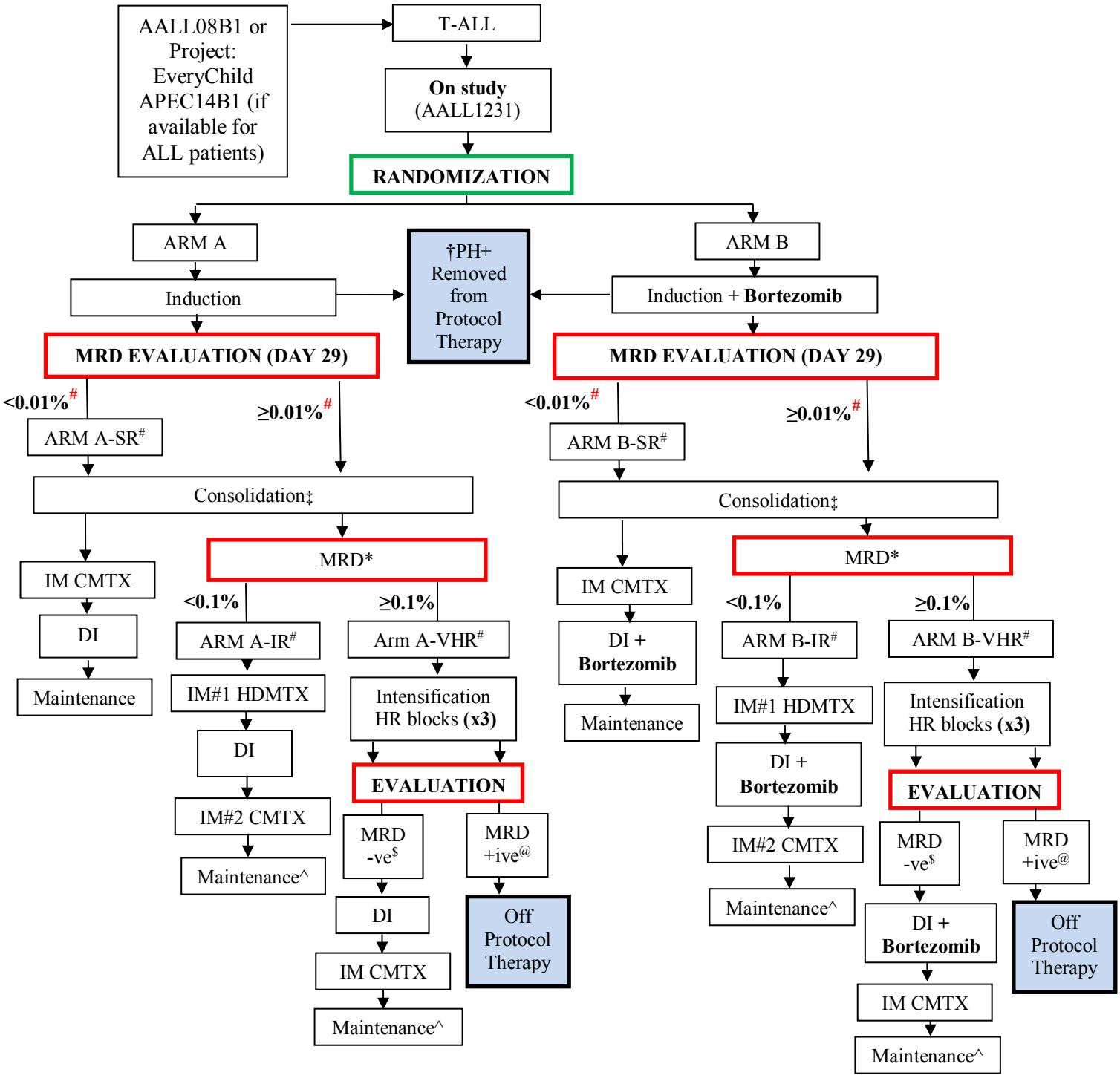
Patients will be randomized to receive backbone therapy with or without bortezomib during Induction and Delayed Intensification. T-ALL patients will be stratified into standard risk (SR), intermediate risk (IR), or very high risk (VHR) groups based on assessments minimal residual disease (MRD) at Day 29 and End of Consolidation (EOC). T-LLy patients will be risk stratified into the same groups, based on percentage disease in marrow at diagnosis and radiographic disease response at end of Induction.

The augmented BFM backbone will be modified in this trial to include dexamethasone as the sole corticosteroid throughout therapy and to increase the exposure to pegaspargase, based on the success of this approach in the recently completed UKALL 2003 trial. This trial also aims to establish whether prophylactic cranial radiation therapy (CRT) can be safely eliminated from the treatment in the vast majority (~90%) of children with T-ALL and to determine if intensification of chemotherapy in VHR T-ALL and T-LLy patients will prevent relapse. Finally, this trial aims to determine whether a response assessment after Intensification therapy in VHR patients (T-ALL and T-LLy) can identify patients who are chemotherapy refractory and who may potentially benefit from novel agents and/or stem cell transplant.

Amendment 3 includes the correction to an error in the date of administration of PEG-Aspargase during Delayed Intensification, and emphasizes supportive care guidelines to remind clinicians of the potential and expected risk of Invasive Fungal Infections, especially during Induction and periods of prolonged neutropenia.

Amendment 4 revises the eligibility criteria for T-cell Lymphoblastic Lymphoma (T-LLy) patients, and clarifies classification study enrollment for T-cell Acute Lymphoblastic Leukemia (T-ALL) patients.

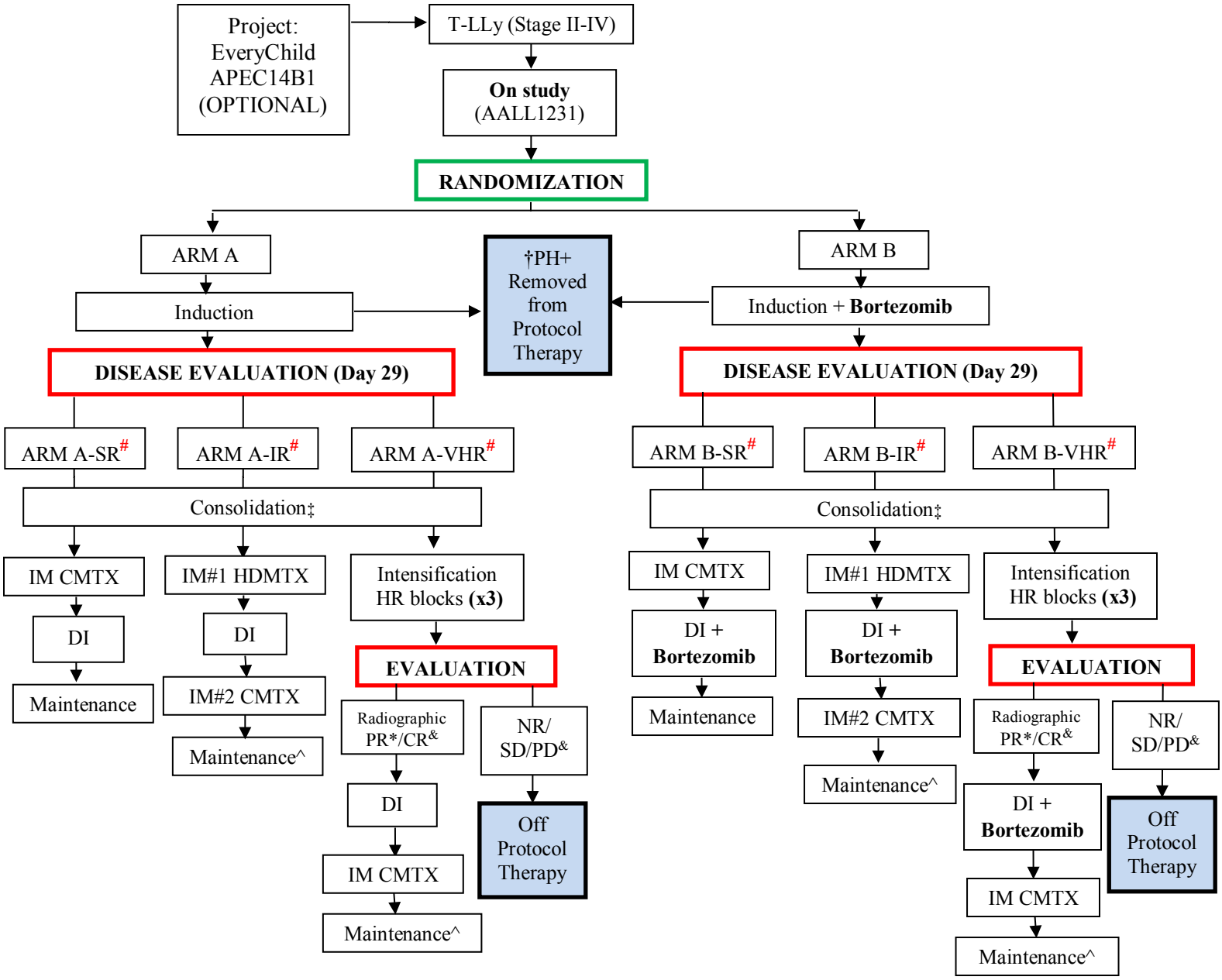
EXPERIMENTAL DESIGN SCHEMA: T-ALL



T-ALL: T-Lymphoblastic Leukemia **MRD:** Minimal Residual Disease
HR: High Risk **SR:** Standard Risk **IR:** Intermediate Risk **VHR:** Very High Risk
IM: Interim Maintenance **DI:** Delayed Intensification **CMTX:** Capizzi Methotrexate
HDMTX: High Dose Methotrexate $Undetectable MRD @Detectible MRD

#See Section 3.4 for definitions. **OF NOTE**, subjects who are CNS2, CNS3, or have testicular disease, or were steroid pre-treated CANNOT be SR.
†See Section 3.5 for details ^ T-ALL: all VHR subjects regardless of CNS status, and IR subjects with CNS3 disease will receive cranial radiation therapy (CRT). See Section 16.1 for details.
‡ Patients with persistent testicular disease at end-Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. See Section 16.2 for details.
*Induction failures are treated as VHR regardless of MRD status

EXPERIMENTAL DESIGN SCHEMA: T-LLy (Stages II-IV)



T-LLy: T-Lymphoblastic Lymphoma **MRD:** Minimal Residual Disease
HR: High Risk **SR:** Standard Risk **IR:** Intermediate Risk **VHR:** Very High Risk
IM: Interim Maintenance **DI:** Delayed Intensification
CMTX: Capizzi Methotrexate **HDMTX:** High Dose Methotrexate
CR: complete response **PR:** Partial Response

#See Section 3.4 for definitions. **OF NOTE**, subjects who are CNS2, CNS3, have testicular disease, or were steroid pre-treated, CANNOT be SR.
†See Section 3.5 for details
^ T-LLy subjects with CNS3 disease receive cranial radiation therapy (CRT). See Section 16.1 for details
*Patients who are in a radiographic PR at the end of the 3 Intensification HR blocks should be re-biopsied. If the biopsy finds residual disease, the patient comes off protocol therapy. If the biopsy does not demonstrate active disease, the patient continues on therapy at DI
‡ Patients with persistent testicular disease at end-Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. See Section 16.2 for details. &See Section 10.4 for details

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To compare EFS in patients with newly diagnosed T-ALL and T-LLy who are randomized to a modified ABFM backbone versus bortezomib plus the modified ABFM backbone.

1.2 Secondary Aims

1.2.1 To determine the safety and feasibility of modifying standard therapy for T-ALL and T-LLy based on the results of UKALL 2003, which includes a dexamethasone-based Induction, additional doses of pegaspargase (PEG-ASP) during Induction and Delayed Intensification (DI), and dexamethasone pulses during Maintenance therapy

1.2.2 To determine if prophylactic (presymptomatic) cranial radiation therapy (CRT) can be safely and effectively eliminated in the 85-90% of T-ALL patients classified as standard or intermediate risk.

1.2.3 To determine the proportion of EOC MRD $\geq$ 0.1% T-ALL patients who become MRD negative (undetectable by flow cytometry) after intensification of chemotherapy, using three high risk (HR) BFM blocks, and to compare EFS between the patients who become MRD negative after the three HR BFM blocks and continue on chemotherapy with those who continue to have detectable MRD and are eligible for other treatment strategies, including hematopoietic stem cell transplant (HSCT). Similarly, to compare the EFS between very high risk (Induction failure) T-LLy patients treated with HR BFM intensification blocks who have partial or complete response (PR or CR) with those who do not respond (NR).

1.3 Correlative Aims

1.3.1 To investigate the prognostic significance of Day 29 BM MRD in T-LLy patients.

1.3.2 To determine if protein expression patterns can predict bortezomib response and drug resistance in T-ALL

1.3.3 To analyze and target relevant signaling pathways in T-ALL blasts, focusing on Early T cell Precursor (ETP) ALL

[redacted]

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility, Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix XIII for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirement s for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study

enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be submitted via the online portal via www.ctsu.org in the member's section, under the Regulatory Submission Portal submitted via the online portal via www.ctsu.org in the member's section, under the Regulatory Submission Portal where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com

3.1.4 Timing

a. **T-ALL PATIENTS MUST BE ENROLLED ON AALL08B1 OR PROJECT:EVERYCHILD (APEC14B1, IF OPEN FOR CLASSIFICATION OF NEWLY DIAGNOSED ALL PATIENTS) BEFORE ENROLLING ON AALL1231**.

T-LLY: PATIENTS WITH T-LLY ARE INELIGIBLE FOR AALL08B1.

EVERY EFFORT SHOULD BE MADE TO ACQUIRE AS MUCH TISSUE AS POSSIBLE. SPECIFIC INSTRUCTIONS REGARDING TISSUE SUBMISSION ARE OUTLINED IN SECTION 13.6. OF NOTE, T-LLY SPECIMENS, INCLUDING DIAGNOSTIC MRD, ARE SUBMITTED AS PER THE INSTRUCTIONS IN AALL1231 AS OUTLINED IN SECTIONS 13 AND 14.

b. Informed consent: Except for administration of intrathecal cytarabine or allowable steroid pretreatment (defined below), *informed consent/parental permission* MUST be signed before protocol therapy begins.

c. Study enrollment: Patients are randomized to receive or not receive bortezomib before protocol therapy begins. Accordingly**, Patients must be enrolled on AALL1231 before protocol therapy begins.** The only exceptions are the first dose of intrathecal chemotherapy may be given before enrollment when administered as part of the initial diagnostic lumber puncture, and in select circumstances, corticosteroids or emergent radiation may be given before enrollment as defined in Section 3.2.2 and Section 3.3.

The date protocol therapy is projected to start must be no later than ***five (5)*** calendar days after the date of study enrollment.

d. Eligibility studies: Patients must meet all eligibility criteria prior to enrollment. Unless otherwise indicated in the eligibility section below, all clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment.

e. Initiation of systemic protocol therapy: Systemic Induction therapy, with the exception of steroid pretreatment as outlined below (Section 3.2.2), must begin within 72 hours of the first dose of intrathecal chemotherapy.

3.1.5 Inclusion of Women and Minorities
Both men and women of all races and ethnic groups are eligible for this study.

3.1.6 Randomization
Randomization will take place at the time a patient is enrolled via OPEN. Randomization will occur prior to Induction therapy for all patients (T-ALL and T-LLy).

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

3.2.1 INCLUSION CRITERIA

a. Classification Study:
- T-ALL: T-ALL patients must be enrolled on AALL08B1 or Project:EveryChild (APEC14B1, if open for the classification of ALL patients) prior to treatment and enrollment on AALL1231.

b. Age at Diagnosis: All patients must be > 1 and < 31 years of age.

c. Diagnosis: Patients must have newly diagnosed T-Lymphoblastic Leukemia (T-ALL) or T-Lymphoblastic Lymphoma (T-LLy) Stages II-IV (see Appendix VIII).

Note: A diagnosis of T-ALL is established when leukemic blasts lack myeloperoxidase or evidence of B-lineage derivation (CD19/CD22/CD20), and express either surface or cytoplasmic CD3 or two or more of the antigens CD8, CD7, CD5, CD4, CD2 or CD1a, and are present either in peripheral blood or >25% in the bone marrow. If surface CD3 is expressed on all leukemic cells, additional markers of immaturity, including TdT, CD34 or CD99 will be assessed for expression. Cases with uncertain expression will receive additional review within the appropriate COG reference laboratory.

For T-LLy patients with tissue available for flow cytometry, the criterion for diagnosis should be analogous to T-ALL. For tissue processed by other means (i.e. paraffin blocks), the methodology and criteria for immunophenotypic analysis to establish the diagnosis of T-LLy defined by the submitting institution will be accepted. See pathologic diagnosis recommendation in Section 13.4 and required studies in Table 7.2, including diagnostic bone marrow MRD.

d. Informed consent: All patients and/or their parents or legal guardians must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

3.2.2 EXCLUSION CRITERIA

a. Prior Therapy: Patients must not have received any cytotoxic chemotherapy for either the current diagnosis of T-ALL, T-LLy or for any cancer diagnosis prior to the initiation of protocol therapy on AALL1231, with the exception of:
   - Steroid pretreatment: Prednisone or methylprednisolone for ≤ 120 hours (5 days) in the 7 days prior to initiating Induction chemotherapy or for ≤ 336 hours (14 days) in the 28 days prior to initiating Induction chemotherapy. Prior exposure to ANY steroids that occurred > 28 days before the initiation of protocol therapy does not affect eligibility. The dose of prednisone or methylprednisolone does not affect eligibility.
   - Intrathecal cytarabine (The CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in Section 3.3) Systemic chemotherapy must begin within 72 hours of this IT therapy; or
   - Pretreatment with hydroxyurea; or
   - 600 cGy of chest irradiation, if medically necessary.

   Pre-treatment with dexamethasone in the 28 days prior to initiation of protocol therapy is not allowed with the exception of a single dose of dexamethasone used during sedation to prevent or treat airway edema. Inhalation steroids and topical steroids are not considered pretreatment.

b. Peripheral neurotoxicity: Pre-existing ≥ grade 2 sensory or motor peripheral neurotoxicity.

c. Seizures disorder: Uncontrolled seizure disorder

d. Diagnosis of Down syndrome (Trisomy 21)

e. Patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.

f. Lactating females who plan to breastfeed.

g. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

h Patient has hypersensitivity to bortezomib, boron, or mannitol.

i Serious medical or psychiatric illness likely to interfere with participation in this clinical study.

j Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and within 30 days of any dose of bortezomib.

3.2.3 Regulatory Requirement

a. All institutional, FDA, and NCI requirements for human studies must be met.

3.3 DEFINITIONS

3.3.1 INITIAL WBC

The first WBC at the treating COG institution. If prior therapy (i.e. steroids) or IV hydration has been administered then the initial WBC prior to therapy and/or hydration should be used.

3.3.2 CNS STAGING AT DIAGNOSIS (for both T-ALL and T-LLy patients)

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of white blood cells (WBCs).

CNS 2: In CSF, presence of < 5/ µL WBCs and cytospin positive for blasts or ≥ 5/µL WBCs with negative Steinherz Bleyer algorithm (see below).

CNS 2a: < 10/ µL RBCs; < 5/ µL WBCs and cytospin positive for blasts;
CNS 2b: ≥ 10/ µL RBCs; < 5/ µL WBCs and cytospin positive for blasts; and
CNS 2c: ≥ 10/ µL RBCs; ≥ 5/ µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).

CNS3: In CSF, presence of ≥ 5/ µL WBCs and cytospin positive for blasts and/or clinical signs of CNS Leukemia.

CNS 3a: < 10/ µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts;
CNS 3b: ≥ 10/µL RBCs, ≥ 5/µL WBCs and positive by Steinherz/Bleyer algorithm (see below); and
CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

3.3.3 TESTICULAR INVOLVEMENT AT DIAGNOSIS

Unilateral or bilateral testicular disease based on clinical exam or imaging. Biopsy is required if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass.

3.3.4 BONE MARROW STATUS for T-ALL

M1: < 5% lymphoblasts
M2: 5 - 25% lymphoblasts
M3: > 25% lymphoblasts.

3.3.5 BONE MARROW STATUS FOR T-LLy PATIENTS

The MRD status of T-LLy patients is required at diagnosis in the MRD central reference laboratory and patients will be risk-stratified as described below. Marrow must have <25% morphologic blasts to be classified as T-LLy.

3.3.6 METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/μL and blasts, the following Steinherz/Bleyer algorithm should be used to distinguished between CNS2 and CNS3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/μL blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = 60/μL; CSF RBC = 1500/μL; blood WBC = 46000/μL; blood RBC = 3.0 X 10^6/μL:

$$\frac{60}{1500} = 0.04 > 2X \frac{46000}{3.0 \times 10^6} = 0.015$$

3.4 RISK STRATIFICATION

Criteria for risk stratification as Standard Risk (SR), Intermediate Risk (IR) or Very High Risk (VHR) for patients with T-ALL or T-LLy enrolled on this trial are outlined in the table below.

Note: Chemotherapy should not be delayed awaiting formal risk stratification by the study team in iMEDIDATA Rave. Please contact the study chair if there are questions regarding risk stratification

		T-ALL				T-LLy[%]		
	SR[#]	**IR**	**IR**	**VHR**	**SR**	**IR**	**IR**	**VHR**
Bone Marrow Results								
MRD at diagnosis*					<1%	<1%	≥1%	Any
Day 29 Status	M1	M1	M1 or M2	M3^				
MRD at Day 29	<0.01%	<0.01%	≥0.01%	Any				
MRD at EOC[+]			<0.1%	≥0.1%^				
CNS Status**	CNS1	Any	Any	Any	CNS1	Any	Any	Any
LP prior to steroids	Yes	Yes or No	Yes or No	Yes or No	Yes	Yes or No	Yes or No	Yes or No
Other Considerations								
Testicular Involvement[$]	None	Any	Any	Any	None	Any	Any	Any
Steroid Pretreatment[@]	None	Any	Any	Any	None	Any	Any	Any
End Induction Response					PR or CR	PR or CR	PR or CR	SD or NR

*MRD result from central reference lab ^M3 at day 29 or MRD≥0.1% at EOC = VHR

[#]SR=standard risk; IR=intermediate risk; VHR=very high risk

**CNS status: Any patient who is CNS2 or CNS3 cannot be Standard Risk and will be assigned to IR or VHR based on MRD response (T-ALL) or end Induction radiographic response (T-LLy)

[$]Testicular disease: Any patient who has testicular involvement at diagnosis cannot be Standard Risk and will be assigned to IR or VHR based on MRD response (T-ALL) or end Induction radiographic response (T-LLy)

[@]Any patient receiving corticosteroids within 4 weeks prior to the diagnostic lumbar puncture cannot be standard risk and will be assigned to IR or VHR based on MRD response.

% T-LLy: See Section 10.4 for additional information regarding the type of imaging and subsequent evaluations used to determine response. See also, evaluation tables in Sections 7.2, 7.3, and 7.4.
+ Patients with Day 29 MRD <0.01% do not need EOC MRD, regardless of features used in risk stratification, including steroid pretreatment, CNS or testicular disease status

3.4.1 CORTICOSTEROID PRETREATMENT AND RISK STRATIFICATION

It is recognized that T-ALL and T-LLy patients often present with hyperleukocytosis and/or mediastinal mass that requires emergent therapy. In addition, many patients present, having already recently received corticosteroids prior to the diagnosis of T-ALL or T-LLy. Corticosteroid exposures that may affect eligibility for the trial are listed in Section 3.2.2. Note: Inhalation steroids and topical steroids are not considered pre-treatment.

Patients with T-ALL receiving steroids within one month (Day -28 to Day -1) prior to the diagnostic lumbar puncture can not be SR and will be assigned to IR or VHR category depending on MRD response

Patients with T-LLy receiving steroids within one month (Day -28 to Day -1) prior to the diagnostic lumbar puncture or bone marrow can not be SR and will be assigned to the IR or VHR category depending on end Induction response

Patients with T-ALL or T-LLy who received steroids > 28 days preceding diagnosis but did not receive corticosteroids within the 28 days (Day -28 to Day -1) preceding diagnosis will not have risk allocation changed and can be SR.

Pre-treatment with prednisone or equivalent does not change the classification of CNS status, e.g. if a patient is pre-treated with corticosteroids and diagnostic LP demonstrates CNS 1 or CNS2, then that patient is NOT treated as CNS3 because of the prior steroid exposure.

Pre-treatment with dexamethasone in the 28 days prior to initiation of protocol therapy is not allowed with the exception of a single dose of dexamethasone used during sedation to prevent or treat airway edema. Patients who receive a single dose of dexamethasone to prevent or treat airway edema in the 28 days preceding diagnosis as described in section 3.2.2 are eligible for study; however, if this dose was given prior to the diagnostic lumbar puncture they can not be SR and will be assigned IR or VHR category based on MRD response. Pre-treatment with a single dose of dexamethasone does not change the classification of CNS status.

3.5 PHILADELPHIA CHROMOSOME POSITIVE (Ph+)

BCR-ABL1 (formerly known as BCR-ABL) fusion determined by FISH or RT-PCR

T-ALL patients entered onto AALL1231 who are later found to meet eligibility criteria for the AALL1122 Ph+ ALL study (or successor) are not eligible for post-Induction therapy on AALL1231 and should be taken off protocol therapy prior to Day 15 of Induction therapy.

T-LLy patients entered onto AALL1231 who are later found to meet the criteria for Ph+ T-LLy are not eligible for post-Induction therapy on AALL1231 and should be removed from protocol therapy prior to or at the end of Induction.

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

See Experimental Design Schema T-ALL and Experimental Design Schema:T-LLy

4.1.1 Randomization

All T-ALL and T-LLy patients will be randomized upon enrollment to receive Induction treatment ± bortezomib. **Arm A is treatment without bortezomib and Arm B is treatment with bortezomib**. After Induction, all patients will receive the same 8 weeks of Consolidation therapy. Subsequent therapy will be dependent on risk assignment, as detailed below.

4.1.2 Treatment based on Risk Assignment

(see also Experimental Design Schema T-ALL and Experimental Design Schema: T-LLy)

a. Standard Risk T-ALL and T-LLy patients will be assigned to backbone therapy with one Interim Maintenance (IM) phase with Capizzi Methotrexate (CMTX) ± bortezomib. (See Section 3.3 for definition of SR-T-ALL and SR-T-LLy)

Standard Risk T-ALL and T-LLy patients will NOT receive CRT. Pretreatment with steroids may preclude Standard Risk status (see Section 3.3).

b. Intermediate Risk T-ALL and T-LLy will be assigned to backbone therapy with 2 IM phases: the first IM phase with High Dose Methotrexate (HDMTX) and the second occurring after Delayed Intensification (DI) with Capizzi Methotrexate (CMTX) ± bortezomib. (See Section 3.3 for definition of IR-T-ALL and IR T-LLy)

Only Intermediate Risk T-ALL and T-LLy patients who are CNS3 will receive CRT (1800 cGy) during 1st cycle (first 4 weeks) of Maintenance.

c. Very High Risk T-ALL patients will be assigned to backbone therapy that includes 3 HR Intensification Blocks. These patients will be risk assessed again after the 3 HR Blocks: T-ALL patients who are MRD positive (detectable by flow cytometry at any level) will be taken off protocol therapy and T-ALL patients who are MRD negative (undetectable at any level by flow cytometry) will remain on protocol therapy and will receive one DI (with or without bortezomib as randomized) and one CMTX IM phase. (See Section 3.3 for definition of VHR-T-ALL)

All VHR T-ALL patients receive CRT during the first cycle of Maintenance. CNS1 or CNS2 will receive 1200 cGy prophylactic CRT. CNS3 will receive 1800 cGy therapeutic CRT.

d. Very High Risk T-LLy patients will initially receive backbone therapy for Induction and Consolidation and then receive 3 HR Intensification Blocks. Disease evaluation will again be performed after the 3 HR Blocks.

1. T-LLy patients with no response or progressive disease as defined in Section 10.4 will be removed from protocol therapy.

2. Patients with a radiographic partial response as defined in Section 10.4 should be re-biopsied. T-LLy patients with biopsy proven persistent disease and/or morphologically positive bone marrow will be taken off protocol therapy. If re-biopsy is not feasible because of surgical morbidity concerns, the study chair should be contacted and the subject may be eligible to continue on therapy.
3. T-LLy patients who are radiographic partial responders with negative biopsies or complete responders will remain on protocol therapy and be treated with backbone therapy with 1 DI and 1 CMTX IM phase in treatment Arm A (without bortezomib)-VHR or Arm B (with bortezomib)-VHR. (See Section 3.3 for definition of VHR-T-LLy)

VHR T-LLy patients who are CNS3 will receive 1800 cGy therapeutic CRT.

4.1.3 Treatment Arms (T-ALL and T-LLy)

Risk Category- Arm A (Without Bortezomib)
(See Appendix I for Therapy Delivery Maps)

Standard Risk (A-SR)	Intermediate Risk (A-IR)	Very High Risk (A-VHR)
Induction (no bortezomib)	Induction (no bortezomib)	Induction (no bortezomib)
Consolidation	Consolidation	Consolidation
IM (CMTX)	IM#1 (HDMTX)	3 HR Intensification blocks
DI (no bortezomib)	DI (no bortezomib)	DI (no bortezomib)
Maintenance	IM#2 (CMTX)	IM (CMTX)
	Maintenance	Maintenance

Risk Category- Arm B (With Bortezomib)
(See Appendix II for Therapy Delivery Maps)

Standard Risk (B-SR)	Intermediate Risk (B-IR)	Very High Risk (B-VHR)
Induction (with bortezomib)	Induction (with bortezomib)	Induction (with bortezomib)
Consolidation	Consolidation	Consolidation
IM (CMTX)	IM#1 (HDMTX)	3 HR Intensification blocks
DI (with bortezomib)	DI (with bortezomib)	DI (with bortezomib)
Maintenance	IM#2 (CMTX)	IM (CMTX)
	Maintenance	Maintenance

4.2 Concomitant Therapy Restrictions

4.2.1 Drug Interactions with Conventional Chemotherapy

Since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with anti-leukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes.[62] Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsant. Azole antifungals (listed in the table below) and the macrolide group of antibiotics (listed in the

table below) may have potent inhibitory effects on drug-metabolizing enzymes, and the doses of some anti-leukemic drugs (e.g., vincristine, anthracyclines, etoposide) may need to be reduced in some patients on chronic azole antifungals or antibiotics (see table below).

DRUG or DRUG CLASS^	POTENTIAL INTERACTION	ACTION TO BE TAKEN
Anticonvulsants	Induction of drug metabolizing enzymes Lowered EFS	AVOID phenytoin, phenobarbital, carbamazepine Consider gabapentin or levetiracetam (Keppra) as alternative
Rifampin	Induction of drug metabolizing enzymes	DO NOT USE
Azole Antifungals fluconazole itraconazole* posaconazole voriconazole ketoconazole	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine*, anthracyclines, etoposide, steroids
Macrolide Antibiotics erythromycin clarithromycin azithromycin roxithromycin telithromycin	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine, anthracyclines, etoposide, steroids

* Itraconazole should NOT be used in patients who are receiving vincristine due to a serious drug-drug interaction leading to severe neurotoxicity.[63,64]

^ For a more complete list of CYP 3A 4/5 Inhibitors and Inducers, go to: http://medicine.iupui.edu/flockhart/

4.2.2 Drug Interactions Specific to Bortezomib

In vitro and *in vivo* studies showed that green tea compounds, ascorbic acid (vitamin C) and other antioxidants, have the potential to significantly inhibit the activity of bortezomib.[135,136] One study concluded that there is not an interaction when plasma concentrations are commensurate with dietary oral intake.[137] To avoid the risk of possible interaction it is recommended that green tea containing products, and supplemental products containing vitamin C, flavonoids or other antioxidants (e.g., vitamins, herbal supplements), be discontinued for at least 24 hours prior to the initiation of bortezomib through 72 hours after the last bortezomib dose. In addition, it is recommended that the total dietary intake of vitamin C not exceed the recommended daily allowance (RDA) for age (i.e., normally balanced diets are acceptable).

4.2.3 Drug Interactions Specific to High-Dose Methotrexate

Possible Drug Interactions with Methotrexate:
Avoid non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim/sulfamethoxazole (TMP/SMX), penicillins, probenecid, IV contrast media, proton pump inhibitors, phenytoin and fosphenytoin. Urinary acidifiers can cause methotrexate to precipitate in the urinary tract.

Hold such agents on the days of a high dose methotrexate infusion and for at least 72 hours after the start of the infusion, until the methotrexate level is < 0.4 µM. If there is delayed methotrexate clearance, continue to hold such medications until the methotrexate level is <

0.1 µM.

4.3 General Guidelines

See Section 6.0, DRUG INFORMATION, for detailed information about drug administration.

4.3.2 Parenteral Chemotherapy Administration Guidelines

See Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

4.3.3 Supportive Care

4.3.3.1 Supportive Care Guidelines Regarding Management of Invasive Fungal Infections.

All treating physicians should have a low index of suspicion for invasive fungal infection (IFI), especially during Induction and during periods of prolonged neutropenia, including consolidation, delayed intensification, and the 3 intensification blocks. In patients with a new or unusual mucocutaneous lesion(s), prompt biopsy of suspicious lesions in an effort to confirm the diagnosis and guide further therapy is recommended as well as targeted imaging and sampling/culture of other clinically suspected areas of infection.

Children with prolonged fever in the setting of neutropenia that does not resolve with the use of antibiotics should receive empiric anti-mold antifungal therapy according to the COG endorsed fever and neutropenia guidelines: (https://childrensoncologygroup.org/downloads/COG_SC_FN_Guideline_Document.pdf). Please follow the guidelines for patients at high risk for Invasive Fungal Infections.

For patients with documented or suspected invasive fungal infection and neutropenia, consider growth factor support with GM-CSF (sargramostim) and/or G-CSF (filgrastim or pegfilgrastim).

While receiving corticosteroids, elevated blood glucose levels may be an additional risk factor. Thus, in patients with sustained hyperglycemia consider endocrinology evaluation. Treating oncologists are encouraged to work in close collaboration with their dermatology, infectious disease, otolaryngology, and surgical colleagues to aggressively and timely treat patients affected by IFIs with medical and surgical interventions, as indicated.

If an IFI is identified, please notify the study chair immediately.

For COG Supportive Care Guidelines see: https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.4 INDUCTION ARM A (without bortezomib)

This Induction is for all T-ALL and T-LLy patients randomized to treatment on Arm A (without bortezomib). See Section 4.1 for details. The therapy delivery map (TDM) for INDUCTION-Arm A (without bortezomib) is in APPENDIX I-A.

CRITERIA TO BEGIN INDUCTION

Patients must complete and sign the appropriate informed consent and undergo bortezomib randomization before starting Induction therapy. Treatment on Arm A is for patients who are randomized to treatment WITHOUT BORTEZOMIB.

Intrathecal Cytarabine: IT

Given at time of diagnostic lumbar puncture (if within 72 hours from the start of protocol therapy) OR Day 1.

Age-based dosing:

Age (yrs)	Dose
1 – 1.99	30 mg
2 – 2.99	50 mg
≥ 3	70 mg

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRIStine: Administer IV push over 1 minute or infusion via minibag per institutional policy
Days: 1, 8, 15 and 22
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (may be given IV)
Days 1-28 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e. total daily dose: 6 mg/m^2/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Of note, corticosteroid pretreatment using prednisone or methylprednisolone DOES NOT CHANGE the number of doses of dexamethasone.

DAUNOrubicin: IV push/infusion (over 1-15 minutes)
Days 1, 8, 15 and 22
Dose: 25 mg/m^2/dose

The reconstituted solution or the commercially available solution (5mg/ml) can be administered diluted or undiluted by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DAUNOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein. Protect from sunlight.

Special precautions: **Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DAUNOrubicin is available in a liposomal formulation (DAUNOrubicin citrate). The conventional and liposomal formulations are NOT interchangeable. The liposomal formulation is not allowed.**

Pegaspargase: IV over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl
Days 4 and 18
Dose: 2500 International units/m^2/dose

Intrathecal Methotrexate: IT
Days 8 and 29 (CNS3 patients ONLY also receive IT MTX on Days 15 & 22).

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

CRITERIA TO BEGIN CONSOLIDATION
Following completion of Induction Arm A, the next course (Consolidation, Section 4.6) starts on Day 36 (7 days following day 29 LP) or when peripheral counts recover, whichever occurs later. If the Day 29 marrow is M2 or M3 or has MRD >5%, the patient should begin Consolidation therapy as soon as possible and should not wait until Day 36 or for count recovery to occur. See below for additional details regarding peripheral count parameters. All patients receive common Consolidation therapy.

TESTICULAR BIOPSY
A testicular biopsy should be performed in patients with persistent testicular disease at the end of Induction if the clinical findings are equivocal.

DAY 29 ± 1 BONE MARROW MRD SAMPLES
THESE SAMPLES MUST BE OBTAINED AND SHIPPED TO THE COG ALL FLOW CYTOMETRY REFERENCE LABORATORY SO THAT RESULTS ARE AVAILABLE FOR RISK STRATIFICATION AT THE END OF CONSOLIDATION. ANY DEVIATION THAT EXCEEDS 1 DAY FROM DAY 29 MUST BE DISCUSSED WITH THE STUDY CHAIR. IF MRD IS NOT SENT THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

4.5 INDUCTION ARM B (with bortezomib)

CRITERIA TO BEGIN INDUCTION

Patients must complete and sign the appropriate informed consent and undergo bortezomib randomization before starting Induction therapy. Treatment on Arm B is for patients who are randomized to treatment WITH BORTEZOMIB. The therapy delivery map (TDM) for INDUCTION ARM B (with bortezomib) is in APPENDIX II-A.

Bortezomib: IV push over 3-5 seconds
Days 1, 4, 8, and 11
Dose: 1.3 mg/m^2/dose

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing bortezomib must be clearly labeled "For intravenous use only -Fatal if given by other routes."

Note: Consecutive doses of bortezomib must be separated by at least 72 hours. Grapefruit and its juice should be avoided for the duration of treatment with bortezomib during each course. To avoid the risk of any possible interaction it is recommended that green tea containing products and any supplemental products containing vitamin C, flavonoids or other antioxidants (e.g., vitamins, herbal supplements) be discontinued from at least 24 hours prior to the initiation of bortezomib through 72 hours after the last bortezomib dose. In addition, it is recommended that the total dietary intake of vitamin C not exceed the RDA for age (i.e., normally balanced diets are acceptable).

Bortezomib is supplied by Millennium Pharmaceuticals and distributed by the NCI DTCD. **Do not use commercially available drug.**

If bortezomib is not available on Day 1 of Induction, then administer the first bortezomib dose as soon as possible and do not delay the start of other Induction chemotherapy. Subsequent bortezomib doses should be given after 72 and 144 hours. All doses must be at least 72 hours apart.

Intrathecal Cytarabine: IT
Given at time of diagnostic lumbar puncture (if within 72 hours from the start of protocol therapy) OR Day 1.

Age-based dosing:

Age (yrs)	Dose
1 – 1.99	30 mg
2 – 2.99	50 mg
≥ 3	70 mg

For IT administration use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRIStine: Administer IV push over 1 minute or infusion via minibag per institutional policy
Days 1, 8, 15 and 22
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (maybe given IV)
Days 1-28 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e. total daily dose: 6 mg/m^2/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

DAUNOrubicin: IV push/infusion over 1-15 minutes
Days 1, 8, 15 and 22
Dose: 25 mg/m^2/dose

The reconstituted solution or the commercially available solution (5mg/ml) can be administered diluted or undiluted by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DAUNOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein or central venous access device. Protect from sunlight.

Special precautions: **Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DAUNOrubicin is available in a liposomal formulation (DAUNOrubicin citrate). The conventional and liposomal formulations are NOT interchangeable. The liposomal formulation is not allowed.**

Pegaspargase: IV over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.
Day 4 and 18
Dose: 2500 International units/m^2/dose

Intrathecal Methotrexate: IT
Administer on Days 8 and 29 (CNS3 patients also receive IT MTX on Days 15 & 22).

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

CRITERIA TO BEGIN CONSOLIDATION

Following completion of INDUCTION ARM B (with bortezomib), the next course (Consolidation, Section 4.6) starts on Day 36 (7 days following day 29 LP) or when peripheral counts recover (whichever occurs later). If the Day 29 marrow is M2 or M3 or has MRD >5%, the patient should begin Consolidation therapy as soon as possible and should not wait until Day 36 or for count recovery to occur. See below for additional details regarding peripheral count parameters. All patients receive common Consolidation therapy.

TESTICULAR BIOPSY

A testicular biopsy should be performed in patients with persistent testicular disease at the end of Induction if the clinical findings are equivocal.

DAY 29 ± 1 BONE MARROW MRD SAMPLES

THESE SAMPLES MUST BE OBTAINED AND SHIPPED TO THE COG ALL FLOW CYTOMETRY REFERENCE LABORATORY SO THAT RESULTS ARE AVAILABLE FOR RISK STRATIFICATION AT THE END OF CONSOLIDATION. ANY DEVIATION THAT EXCEEDS 1 DAY FROM DAY 29 MUST BE DISCUSSED WITH THE STUDY CHAIR. IF MRD IS NOT SENT THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

4.6 CONSOLIDATION-All Patients

This Consolidation course is for all Arm A and Arm B T-ALL and T-LLy patients. See Section 4.1 for details. The therapy delivery map (TDM) for CONSOLIDATION is in APPENDIX I-B (for subjects on Arm A) and APPENDIX II-B (for subjects on Arm B).

CRITERIA TO BEGIN CONSOLIDATION

Start Consolidation on Day 36 from Induction (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later.) T-ALL patients who are M2 or M3 on Day 29 or have MRD >5% should proceed directly to Consolidation without waiting for count recovery, but there should be a minimum of 3 days between Day 29 Induction IT therapy and Day 1 Consolidation IT therapy).

Once Consolidation therapy has begun, interruptions for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) should occur only at Day 29. Once the Day 1 or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Therapy should not be interrupted for fever, if there are no signs of serious infection. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL.

Intrathecal Methotrexate: IT
Days 1, 8, 15[#] and 22[#]
[#] if CNS3 T-ALL or CNS3 T-LLy: omit Days 15 & 22 and administer on days 1 and 8 only

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Cyclophosphamide: IV over 30-60 minutes
Days 1 and 29
Dose: 1000 mg/m^2/dose

May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted. Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Cytarabine: IV (administer over 1-30 minutes) or SubQ
Days 1-4, 8-11, 29-32 and 36-39
Dose: 75 mg/m^2/dose

Subcutaneous Administration: Reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Mercaptopurine: PO
Days 1-14 and 29-42
Dose: 60 mg/m^2/dose once daily*

*See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day.

The liquid or tablet formulation may be used. If using tablets, adjust daily dose using the dosing nomogram in Appendix VI to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. Do not escalate or reduce dose based on blood counts during this cycle.

Pegaspargase: IV over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl
Days 15 and 43
Dose: 2500 International units/m^2/dose

VinCRIStine: Administer IV push over 1 minute or infusion via minibag per institutional policy
Days 15, 22, 43 and 50
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

TESTICULAR RADIATION THERAPY
T-ALL and T-LLy patients with persistent testicular disease at end-Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. During the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 16.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. **Patients with testicular leukemia at diagnosis that clinically resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

BONE MARROW AT END CONSOLIDATION
a. T-ALL SR only:
SR T-ALL patients DO NOT require a bone marrow at the end of Consolidation (see Section 4.1 for definitions of risk assignment). These patients should start the next course of therapy (Interim Maintenance with CMTX) following the completion of Consolidation as soon as counts have recovered with an ANC ≥750/μL and platelets ≥75,000/μl.

BONE MARROW AT END CONSOLIDATION (CONT'D)

b. T-ALL patients who are not SR and with end Induction BM MRD ≥ 0.01% **:**

- Following completion of Consolidation, end of consolidation marrow MRD will determine risk assignment (see Section 4.1 for details) and the next course of therapy.
- The end of Consolidation marrow should occur as close to Day 57 as possible, but should be delayed until counts have recovered with an ANC ≥ 500/µL and platelets ≥ 50,000/µL. The end of Consolidation marrow should not be performed prior to Day 57 even if counts have recovered.
- If on Day 57, the counts have recovered with an ANC ≥ 500/µL and platelets ≥ 50,000/µL, the bone marrow for end of Consolidation MRD should be performed on that day. A one day deviation is allowed, but any deviation that is greater than 1 day after count recovery must be discussed with the study chair.
- If on Day 57, the counts have not recovered (e.g., ANC< 500/µL or platelets < 50,000/µL), the bone marrow for end of Consolidation MRD should be delayed until ANC ≥ 500/µL and platelets ≥ 50,000/µL. The bone marrow for end of consolidation MRD should be performed within 2 days of count recovery (ANC ≥ 500/µL and platelets ≥ 50,000/µL). Any deviation that is greater than 3 days after count recovery must be discussed with the study chair. If counts have not recovered on Day 57, patients should have a CBC checked every 2-3 days (three times a week) at minimum until count recovery to minimize delay in obtaining the bone marrow.
- Patients who have not had count recovery (e.g. ANC ≥ 500/µL and platelets ≥ 50,000/µL) by Day 72 should undergo bone marrow to ensure they are M1 and not M2 or M3.

CRITERIA TO BEGIN NEXT COURSE OF THERAPY FOR T-ALL

a. If the End of Consolidation marrow is M2 or M3, the patient should immediately proceed to Intensification Block 1 and not wait for MRD results to proceed.

b. Patients should begin the next course of therapy (HD MTX if IR, HR BFM Block 1 if VHR) as soon as the results of EOC MRD are available and they have an ANC ≥750/µL and platelets ≥75,000/µl.

c. As there will likely be a few day delay waiting for MRD results between the end of Consolidation marrow and the start of the next course of therapy, the next block of therapy lumbar puncture with intrathecal chemotherapy should not be given early (e.g. at the same time as the end of consolidation bone marrow) and should be given with the next block of therapy.

DAY 57 END OF CONSOLIDATION BONE MARROW FOR MRD

THE END OF CONSOLIDATION BM MRD SAMPLES MUST BE OBTAINED AND SHIPPED TO COG ALL FLOW CYTOMETRY REFERENCE LABORATORY TO HAVE RESULTS AVAILABLE FOR END OF CONSOLIDATION (EOC) RISK STRATIFICATION. THE BONE MARROW FOR MRD MUST BE OBTAINED AS CLOSE TO DAY 57 AS POSSIBLE. DELAYS FOR COUNT RECOVERY AS DESCRIBED ABOVE ARE ALLOWED BUT OTHER DEVIATIONS MUST BE DISCUSSED WITH THE STUDY CHAIR. If MRD IS NOT SENT THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF CONSOLIDATION THERAPY.

c. T-LLy only:

Following completion of Consolidation, the next course (based on risk assignment, see Section 4.1 for details) will start as soon as counts have recovered as described in the relevant block of

therapy. Bone marrow is only required for patients who had morphologic evidence of disease at the end of induction.

4.7 INTERIM MAINTENANCE with CMTX- – All Patients

This IM phase is administered to all patients. SR T-ALL and T-LLy patients receive it after Consolidation. IR T-ALL and T-LLy patients receive it after DI as IM#2. VHR T-ALL and T-LLy patients receive it after DI. See Section 4.1 for details.

The therapy delivery map (TDM) for INTERIM MAINTENANCE with CMTX is in APPENDIX I-C (Arm A-SR) APPENDIX I-G (Arm A-IR), APPENDIX I-L (Arm A-VHR), APPENDIX II-C (Arm B-SR), APPENDIX II-G (Arm B-IR), APPENDIX II-L (Arm B-VHR).

CRITERIA TO BEGIN INTERIM MAINTENANCE WITH CMTX: IR AND VHR PATIENTS

Start when ANC ≥750/µL and platelets ≥75,000/µl and need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.9.

CRITERIA TO BEGIN INTERIM MAINTENANCE WITH CMTX: SR PATIENTS

SR T-ALL and T-LLy patients receive this block immediately after consolidation and **must meet all of following criteria.**

1. Post-Consolidation risk assignment has been completed as described in Section 4.1
2. ANC ≥750/µL and platelets ≥75,000/µl.
3. Need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.9.1, Section 5.9.2, and Section 5.9.3

VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy
Days 1, 11, 21, 31 and 41
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: IV over 2-5 minutes (undiluted) or over 10-15 minutes (diluted).
Days 1, 11, 21, 31 and 41.
Dose: Start dose at 100 mg/m^2/dose and escalate by **50 mg/m^2/dose** on Days 1, 11, 21, 31 and 41 based on blood count requirements as described in Section 5.10.5. Discontinue escalation and resume at 80% of last dose if delay is necessary as described in Section 5.10.5.

Pegaspargase: IV over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.
Days 2 and 22
Dose: 2500 International units/m^2/dose

Intrathecal Methotrexate: IT
Days 1 and 31

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

The therapy delivery map (TDM) for INTERIM MAINTENANCE with CMTX is in APPENDIX I-C (Arm A-SR) APPENDIX I-G (Arm A-IR), APPENDIX I-L (Arm A-VHR), APPENDIX II-C (Arm B-SR), APPENDIX II-G (Arm B-IR), APPENDIX II-L (Arm B-VHR).

Following completion of INTERIM MAINTENANCE with CMTX the next course (based on risk assignment, see Section 4.1 for details) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.8 DELAYED INTENSIFICATION- Arm A (without bortezomib)

This Delayed Intensification (DI) course is for all T-ALL and T-LLy patients randomized to treatment on Arm A (without bortezomib). See Section 4.1 for details.

The therapy delivery maps (TDMs) for DELAYED INTENSIFICATION- ARM A are in APPENDIX I-D (Arm A-SR), APPENDIX I-F (Arm A-IR), and APPENDIX I-K (Arm A-VHR)

CRITERIA TO BEGIN DELAYED INTENSIFICATION SR AND IR T-ALL AND T-LLY:

1. ANC ≥ 750/µL
2. Platelets ≥ 75,000/µL prior to starting therapy.

CRITERIA TO BEGIN DELAYED INTENSIFICATION VHR T-ALL:

VHR T-ALL patients receive this block immediately after HR Intensification 3 and **must meet all of the following criteria**

1. Post-HR Intensification Block 3 MRD is undetectable as described in Section 4.13
2. ANC ≥750/µL
3. Platelets ≥75,000/µl

CRITERIA TO BEGIN DELAYED INTENSIFICATION VHR T-LLY:

VHR T-LLy patients receive this block immediately after HR Intensification 3 and **must meet all of the following criteria**

1. Post-HR Intensification Block 3 disease evaluation demonstrates a radiographic CR OR a radiographic PR with a biopsy showing no residual disease as described in Section 10.4
2. ANC ≥750/µL
3. Platelets ≥75,000/µl

ADDITIONAL GUIDELINES DURING DI FOR ALL RISK GROUPS.

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy. Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated.

VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy.
Days 1, 8, 15, 43 and 50
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (maybe given IV)
Days 1-7 and 15-21
Dose: All patients, regardless of age, receive discontinuous dexamethasone at 5 mg/m^2/dose BID

(i.e. total daily dose: 10 mg/m^2/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

DOXOrubicin: IV push (over 15 minutes)
Days 1, 8 and 15
Dose: 25 mg/m^2/dose

Administer at a concentration not to exceed 2mg/ml by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Special precautions: **Medication errors have occurred due to confusion between DOXOrubicin and DAUNOrubicin. DOXOrubicin is available in a liposomal formulation. The conventional and liposomal formulations are NOT interchangeable.**

Pegaspargase: IV over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl
Days 4, 18 and 43
Dose: 2500 International units/m^2/dose

Intrathecal Methotrexate: IT
Administer on Days 1, 29 and 36.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Cyclophosphamide: IV over 30-60 minutes
Day 29
Dose: 1000 mg/m^2/dose

May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted. Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Cytarabine: IV (Administer over 1-30 minutes) or SubQ
Days 29-32 and 36-39
Dose: 75 mg/m^2/dose

Subcutaneous Administration: Reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Thioguanine: PO
Days 29-42
Dose: 60 mg/m^2/dose

Administer in the **evening** preferably on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix VII for details.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Following completion of DELAYED INTENSIFICATION - Arm A, the next course (based on risk assignment, see Section 4.1 for details) starts on Day 64 or when blood count parameters are met (whichever occurs later).

4.9 DELAYED INTENSIFICATION Arm B (with bortezomib)

This Delayed Intensification (DI) course is for all T-ALL and T-LLy patients randomized to treatment on Arm B (with bortezomib). See Section 4.1 for details.

The therapy delivery maps (TDMs) for DELAYED INTENSIFICATION- Arm B are in APPENDIX II-D (Arm B-SR), APPENDIX II-F (Arm B-IR) and APPENDIX II-K (Arm B-VHR).

CRITERIA TO BEGIN DELAYED INTENSIFICATION SR AND IR T-ALL AND T-LLY:

1. ANC ≥ 750/µL
2. Platelets ≥ 75,000/µL

CRITERIA TO BEGIN DELAYED INTENSIFICATION VHR T-ALL:

VHR T-ALL patients receive this block immediately after HR Intensification 3 and **must meet all of the following criteria**

1. Post-HR Intensification Block 3 MRD was completed and demonstrated undetectable MRD as described in Section 4.13
2. ANC ≥750/µL
3. Platelets ≥75,000/µl

CRITERIA TO BEGIN DELAYED INTENSIFICATION VHR T-LLY:

VHR T-LLy patients receive this block immediately after HR Intensification 3 and **must meet all of the following criteria**

1. Post-HR Intensification Block 3 disease evaluation was completed and demonstrated a radiographic CR OR a radiographic PR and a biopsy showing no residual disease as described in Section 10.4
2. ANC ≥750/µL
3. Platelets ≥75,000/µl

ADDITIONAL GUIDELINES DURING DI FOR ALL RISK GROUPS.

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy. Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL.

Bortezomib: IV push over 3-5 seconds
Days 1, 4, 15, and 18
Dose: 1.3 mg/m^2/dose

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing Bortezomib must be clearly labeled "For intravenous use only - Fatal if given by other routes."

Note: Consecutive doses must be separated by at least 72 hours. Grapefruit and its juice should be avoided for the duration of treatment with bortezomib during each course. To avoid the risk of any possible interaction it is recommended that green tea containing products and any supplemental products containing vitamin C, flavonoids or other antioxidants (e.g., vitamins, herbal supplements) be discontinued from at least 24 hours prior to the initiation of bortezomib through 72 hours after the last bortezomib dose. In addition, it is recommended that the total dietary intake of vitamin C not exceed the RDA for age (i.e., normally balanced diets are acceptable).

Bortezomib is supplied by Millennium Pharmaceuticals and distributed by the NCI DTCD. **Do not use commercially available drug.**

VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy.
Days 1, 8, 15, 43 and 50
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (maybe given IV)
Days 1-7 and 15-21
Dose: All patients, regardless of age, receive discontinuous dexamethasone: 5 mg/m^2/dose BID (i.e. total daily dose 10 mg/m^2/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

DOXOrubicin: IV push (over 15 minutes)
25 mg/m^2/dose on Days 1, 8 and 15

Administer at a concentration not to exceed 2mg/ml by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

Special precautions: **Medication errors have occurred due to confusion between DOXOrubicin and DAUNOrubicin. DOXOrubicin is available in a liposomal formulation. The conventional and liposomal formulations are NOT interchangeable.**

Pegaspargase: IV over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl
Day 4, 18 and 43
Dose: 2500 International units/m^2/dose

Intrathecal Methotrexate: IT
Administer on Days 1, 29 and 36.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Cyclophosphamide: IV over 30-60 minutes
Day 29
Dose: 1000 mg/m^2/dose

May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted. Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Cytarabine: IV (Administer over 1-30 minutes) or SubQ
Days 29-32 and 36-39
Dose: 75 mg/m^2/dose

Subcutaneous Administration: Reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Thioguanine: PO
Days 29-42
Dose: 60 mg/m^2/dose

Administer in the evening preferably on an empty stomach (at least 1 hour before or 2 hours after food or drink except water). Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix X for details.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Following completion of DELAYED INTENSIFICATION- Arm B (with bortezomib), the next course (based on risk assignment, see Section 4.1 for details) starts on Day 64 or when blood count parameters are met (whichever occurs later).

4.10 INTERIM MAINTENANCE #1 with HD MTX- ALL INTERMEDIATE RISK SUBJECTS

This is IM#1 for all IR T-ALL and T-LLy patients randomized to either treatment Arm. SR and VHR T-ALL and T-LLy patients do not receive this block. See Section 4.1 for details.

The therapy delivery maps (TDMs) for Interim Maintenance #1 with HD MTX are in APPENDIX I-E (Arm A-IR) and APPENDIX II-E (Arm B-IR).

CRITERIA TO BEGIN INTERIM MAINTENANCE WITH HD MTX: IR PATIENTS ONLY

IR T-ALL and T-LLy patients receive this block immediately after consolidation and **must meet all of the following criteria**

1. Post-consolidation risk assignment completed as described in Section 4.1
2. ANC ≥750/µL and platelets ≥75,000/µl.
3. Need to meet renal and hepatic function to receive HD MTX as defined in Section 5.9.1, Section 5.9.2, and Section 5.9.3

High Dose Methotrexate: **IV over 24 hours**
Days 1, 15, 29, and 43
Dose: 5000 mg/m^2/dose (no maximum dose)

For HD MTX Infusion Guidelines and liver and kidney requirements to administer drug see Section 5.9 and Appendix IV.

Leucovorin: PO/IV
Days 3-4, 17-18, 31-32, and 45-46
Dose: 15mg/m^2/dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of the HD MTX infusion. See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.

VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy.
Days 1, 15, 29, 43
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Mercaptopurine: PO
Days 1-56
Dose: 25 mg/m^2/dose once daily*

*Other Considerations:
*See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day.

The liquid or tablet formulation may be used. If using tablets, adjust daily dose using the dosing nomogram in Appendix VI to attain a weekly cumulative dose as close to 175 mg/m2/week as possible. Do not escalate or reduce dose based on blood counts during this cycle. Mercaptopurine should be held for ANC < 750/µL or platelets < 75 000/µL. Do not make up missed doses (see Section 5.11.1).

Intrathecal Methotrexate: IT
Days 1 and 29

When IT therapy and HD MTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

Age-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Following completion of Interim Maintenance #1 the next course (based on randomization assignment, see Section 4.1 for details) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.11 INTENSIFICATION BLOCK 1 (HR1)- ALL VERY HIGH RISK SUBJECTS

This phase of treatment is for all VHR T-ALL and T-LLy patients who are randomized to either treatment Arm. SR and IR T-ALL and T-LLy patients do not receive this block.

The therapy delivery maps (TDMs) for INTENSIFICATION BLOCK 1 are in APPENDIX I-H (Arm A-VHR) and APPENDIX II-H (Arm B-VHR).

CRITERIA TO BEGIN INTENSIFICATION BLOCK 1

T-ALL patients who are M2 or M3 at the end of Consolidation should proceed directly to Intensification Block 1 without waiting for count recovery or MRD results to proceed.

VHR T-ALL and T-LLy patients receive this block immediately after consolidation and **must meet all of the following criteria**

1. Post-consolidation risk assignment must have been completed as described in Section 4.1
2. ANC≥750/μL
3. Platelets ≥75,000/μl
4. Need to meet renal and hepatic function requirements to receive HD MTX as defined in Section 5.9.2, Section 5.9.3, and Section 5.9.4.
5. Need to meet renal function requirements to receive HD ARAC as defined in Section 5.4.4

The 3 High Risk Intensification blocks are profoundly myelosuppressive and since they also include 5 days of high dose dexamethasone, clinical signs of infection may be blunted. Therefore, the following precautions are required for all subjects during each high risk block:

- CBC with differential every 2 days after completion of chemotherapy until there is evidence of marrow recovery. Recovery is defined as ANC >0.2 x 10^9/L (200μ/L) and platelet transfusion independence.
- G-CSF 5 μg/kg/day SC or IV starting anytime from 7 days to 11 days from the start of the block (e.g., at least 24 hours after completion of chemotherapy in each HR block) until the WBC count is >3.0 x 109/L (>3000/mm^3). [Pegfilgrastim 100 μg/kg (max 6 mg/dose) s.c. given once during the 7-11th day from the start of the block may be considered as an alternative.]

Additionally the following precautions are STRONGLY recommended for all subjects during each high risk block:

- Hospitalization of patients for close observation after each intensive block of chemotherapy, particularly during the period of profound myelosuppression, until there is evidence of blood count recovery because this is the intervention most likely to reduce the death rate.
- A very low threshold should be used for institution of empiric antimicrobial therapy since dexamethasone may blunt the signs of a life threatening infection.

Dexamethasone: PO (maybe given IV)
Days 1-5
Dose: 10 mg/m^2/dose (i.e. total daily dose: 20 mg/m^2/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

High Dose Methotrexate: IV over 24 hours
Day 1
Dose: 5000 mg/m^2/dose (no maximum dose)

For HD MTX Infusion Guidelines and renal and hepatic function requirements see Section 5.9 and Appendix IV):

Leucovorin: PO/IV
Days 3-4
Dose: 15 mg/m^2/dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of the HD MTX infusion. See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.

VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy.
Days 1 and 6
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide: IV over 1-6 hours
Day 2-4
Dose: 200 mg/m^2/dose Q12 hours x5doses

May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

High Dose Cytarabine: IV (infuse over 3 hours)
Day 5
Dose: 2000 mg/m^2/dose Q12 hours x 2 doses

Suggested premedications and supportive care: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2-4 hour schedule.

Pegaspargase: IV over 1-2 hours
Day 6*
Dose: 2500 International units/m^2/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.
*Administer 3 hours after completion of the second High Dose Cytarabine infusion.

Triple Intrathecal Therapy: IT
Day 1*

Age-based dosing:
1 to < 2 yrs: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 3 yrs: MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 9 yrs: MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9 yrs: MTX 15 mg, HC: 15 mg, ARAC: 30 mg

*Should be given 2 hours after start of High Dose MTX infusion (window of -6 to +6 hours in relation to start of HD-MTX is acceptable)

Filgrastim: SubQ/IV
5 mcg/kg/dose daily beginning on Day 7 and until WBC > 3000/µL.
Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

*Pegfilgrastim 100 mcg/kg (max 6 mg/dose) s.c. once during the 7-11th day from the start of the block may be considered as an alternative

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Following completion of INTENSIFICATION BLOCK 1 Arm, the next course (INTENSIFICATION BLOCK 2 Section 4.12) starts on Day 22 or when blood count parameters are met (whichever occurs later).

4.12 INTENSIFICATION BLOCK 2- ALL VERY HIGH RISK SUBJECTS

This phase of treatment is for all VHR T-ALL and T-LLy patients who are randomized to either treatment Arm. SR and IR T-ALL and T-LLy patients do not receive this block.

The therapy delivery maps (TDMs) for INTENSIFICATION BLOCK 2 are in APPENDIX I-I (Arm A-VHR) and APPENDIX II-I (Arm B-VHR).

Start Day 1 when ANC ≥750/μL and platelets ≥75,000/μL. Need to meet renal and hepatic function requirements described in Section 5.9.2, Section 5.9.3, and Section 5.9.4. in order to receive HD MTX. HR2 lasts 21 days.

The 3 High Risk Intensification blocks are profoundly myelosuppressive and since they also include 5 days of high dose dexamethasone, clinical signs of infection may be blunted. Therefore, the following precautions are required for all subjects during each high risk block:

- CBC with differential every 2 days after completion of chemotherapy until there is evidence of marrow recovery. Recovery is defined as ANC >0.2 x 10^9/L (200μ/L) and platelet transfusion independence.
- G-CSF 5 μg/kg/day SC or IV starting anytime from 7 days to 11 days from the start of the block (e.g., at least 24 hours after completion of chemotherapy in each HR block) until the WBC count is >3.0 x 109/L (>3000/mm^3). [Pegfilgrastim 100 μg/kg (max 6 mg/dose) SC. given once during the 7-11^{th} day from the start of the block may be considered as an alternative.]

Additionally, the following precautions are STRONGLY recommended for all subjects during each high risk block:

- Hospitalization of patients for close observation after each intensive block of chemotherapy, particularly during the period of profound myelosuppression, until there is evidence of blood count recovery because this is the intervention most likely to reduce the death rate.
- A very low threshold should be used for institution of empiric antimicrobial therapy since dexamethasone may blunt the signs of a life threatening infection.

Dexamethasone: PO (maybe given IV)
Days 1-5
Dose: 10 mg/m^2/dose BID (i.e. total daily dose: 20 mg/m^2/day)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

High Dose Methotrexate: IV over 24 hours
Day 1
Dose: 5000 mg/m^2/dose (no maximum dose)

For HD MTX Infusion Guidelines and renal and hepatic requirements to administer see Section 5.9 and Appendix IV

Leucovorin: PO/IV
Days 3-4
Dose: 15mg/m^2/dose x minimum of 3 doses given at 42, 48, and 54 hours after the start of the HD MTX infusion. See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.

VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy.
Days 1 and 6
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Ifosfamide: IV over 1 hour
Days 2-4*
Dose: 800 mg/m^2/dose Q12hours x5 doses

*Start immediately after completion of HD-MTX infusion

Suggested hydration: Administer 3,000 mL/m²/day (125 mL/m²/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Monitor for adequate urine output as per institution guidelines. May use diuretics (e.g., furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Mesna: IV
Days: 2-4
Dose: 300 mg/m^2/dose Hour 0, 4, and 8 from start of each ifosfamide infusion

Hydration following ifosfamide administration: If patient stops methotrexate hydration for whatever reason, need to continue until 12 hours post ifosfamide infusion.

DAUNOrubicin: IV push/infusion over 1-15 minutes
Day 5
Dose: 30 mg/m^2/dose

The reconstituted solution or the commercially available solution (5mg/ml) can be administered diluted or undiluted by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DAUNOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein or central venous access device. Protect from sunlight.

Special precautions: **Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DAUNOrubicin is available in a liposomal formulation (DAUNOrubicin citrate). The conventional and liposomal formulations are NOT interchangeable. The liposomal formulation is not allowed.**

Pegaspargase: IV over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl
Day 6
Dose: 2500 International units/m^2/dose IV

Triple Intrathecal Therapy: Day 1*
Age-based dosing:
1 to < 2 yrs: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 3 yrs: MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 9 yrs: MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9 yrs: MTX 15 mg, HC: 15 mg, ARAC: 30 mg

*Should be given 2 hours after start of High Dose MTX infusion (window of -6 to +6 hours in relation to start of HD-MTX is acceptable)

Filgrastim*: SubQ/IV
Day 7
Dose 5 mcg/kg/dose daily until WBC > 3000/µl

*Pegfilgrastim 100 mcg/kg (max 6 mg/dose) s.c. once during the 7-11th day from the start of the block may be considered as an alternative.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

CRITERIA FOR INITIATION OF INTENSIFICATION BLOCK 3
Following completion of INTENSIFICATION BLOCK 2 Arm, the next course (INTENSIFICATION BLOCK 3, Section 4.13) starts on Day 22 or when blood count parameters are met (whichever occurs later).

4.13 INTENSIFICATION BLOCK 3 (HR3) ALL VERY HIGH RISK SUBJECTS

This phase of treatment is for all VHR T-ALL and T-LLy patients who are randomized to either treatment Arm. SR and IR T-ALL and T-LLy patients do not receive this block.

The therapy delivery maps (TDMs) for INTENSIFICATION BLOCK 3 are in APPENDIX I-J (Arm A-VHR) and APPENDIX II-J (Arm B-VHR).

CRITERIA FOR INITIATION OF INTENSIFICATION BLOCK 3

Start Day 1 when ANC ≥ 750/μL and platelets ≥ 75,000/μL. HR3 lasts 21 days. Patients must meet renal function requirements described in Section 5.4.4.

The 3 High Risk Intensification blocks are profoundly myelosuppressive and since they also include 5 days of high dose dexamethasone, clinical signs of infection may be blunted. Therefore, the following precautions are required for all subjects during each high risk block:

- CBC with differential every 2 days after completion of chemotherapy until there is evidence of marrow recovery. Recovery is defined as ANC >0.2 x 10^9/L (200μ/L) and platelet transfusion independence.
- G-CSF 5 μg/kg/day SC or IV starting anytime from 7 days to 11 days from the start of the block (e.g., at least 24 hours after completion of chemotherapy in each HR block) until the WBC count is >3.0 x 109/L (>3000/mm^3). [Pegfilgrastim 100 μg/kg (max 6 mg/dose) s.c. given once during the 7-11^{th} day from the start of the block may be considered as an alternative.]

Additionally the following precautions are STRONGLY recommended for all subjects during each high risk block:

- Hospitalization of patients for close observation after each intensive block of chemotherapy, particularly during the period of profound myelosuppression, until there is evidence of blood count recovery because this is the intervention most likely to reduce the death rate.
- A very low threshold should be used for institution of empiric antimicrobial therapy since dexamethasone may blunt the signs of a life threatening infection.

Dexamethasone: PO (maybe given IV)
Days 1-5
Dose: 10 mg/m^2/dose BID (i.e. total daily dose: 20 mg/m^2/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

High Dose Cytarabine: IV (over 3 hours)
Days 1-2
Dose: 2 gm/m^2/dose Q12 hours x 4 doses

Suggested premedications and supportive care: Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2-4 hour schedule.

Etoposide: IV over 1-2 hours
100 mg/m^2/dose Q12 hours x 5 doses on Days 3-5
The first dose of etoposide should be given approximately 12 hours after the start of the 4^{th} dose of high dose cytarabine on Day 2. Etoposide will be administered every 12 hours thereafter for a total of 5 doses.

Infuse diluted solution (concentration ≤ 0.4 mg/mL) over at least 60-120 minutes; slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m^2/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W. Avoid use of large volumes of D_5W due to potential development of hyponatremia.

Pegaspargase: IV, administer over 1-2 hours through the tubing of a freely infusing solution of D_5W or 0.9% NaCl
Day 6
Dose: 2500 International units/m^2/dose

Triple Intrathecal Therapy: IT Methotrexate (MTX), Hydrocortisone (HC), Cytarabine (ARAC)
Day 5

Age-based dosing:
1 to < 2 yrs.: MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 3 yrs.: MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 9 yrs.: MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9 yrs.: MTX 15 mg, HC: 15 mg, ARAC: 30 mg

Filgrastim: SubQ/IV*
5 mcg/kg/dose daily beginning on Day 7 and until WBC > 3000/µl.

Administer undiluted by subcutaneous injection (preferred). May also administer diluted in D5W by IV infusion over 15-30 minutes or by continuous infusion.

*Pegfilgrastim 100 mcg/kg (max 6 mg/dose) SC. once during the 7-11th day from the start of the block may be considered as an alternative.

T-ALL: After completing the 3 HR Intensification Blocks, T-ALL patients continue on protocol therapy resuming at DI with or without bortezomib as randomized if MRD is undetectable. If MRD is detectable, patients are no longer eligible to continue on protocol therapy.

T-LLy: After completing the 3 HR Intensification Blocks, T-LLy patients continue on protocol therapy resuming at DI with or without bortezomib as randomized if they have a complete response as defined in Section 10.4 and a morphologically negative marrow. Patients with persistent disease by imaging should be re-biopsied. If there is active disease by pathologic examination, patients are no longer eligible to continue on protocol therapy.

TIMING OF BONE MARROW MRD FOR PATIENTS WITH VHR T-ALL.
The marrow for MRD that is obtained after Intensification HR3 should occur as close to Day 21 as possible, but should be delayed until counts have recovered with an ANC ≥ 500/µL and platelets ≥ 50,000/µL. OF NOTE, this is different from Day 29 MRD which must be sent on Day 29 regardless of counts. The end of HR3 marrow should not be performed before Day 21 even if the counts have recovered.

If on Day 21, the counts have recovered with an ANC ≥ 500/µL and platelets ≥ 50,000/µL, the bone marrow for end of HR3 MRD should be performed that day. A 1 day deviation is allowed, but any deviation that is greater than 1 day after count recovery must be discussed with the study chair.

If on Day 21, the counts have not recovered (e.g., ANC< 500/µL or platelets < 50,000/µL), the bone marrow for end of HR3 MRD should be delayed until ANC ≥ 500/µL and platelets ≥ 50,000/µL. The bone marrow for end of HR3 MRD should be performed within 2 days of count recovery (ANC ≥ 500/µL and platelets ≥ 50,000/µL). Any deviation that is greater than 2 days after count recovery must be discussed with the study chair. If counts have not recovered on Day 21, patients should have a CBC checked every 2-3 days (three times a week) at minimum until count recovery to minimize delay in obtaining the bone marrow.

As there will likely be a delay of a few days waiting for MRD results between the end of HR3 marrow and the start of the next course of therapy (DI), the DI lumbar puncture with intrathecal chemotherapy should not be given early (e.g. at the same time as the end of HR3 bone marrow) and should be given with the next block of therapy.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Following completion of INTENSIFICATION BLOCK 3 Arm A-VHR, subjects will either stop treatment due to lack of response or continue on to next course. The next course (based on randomization, see Section 4.1 for details) starts on Day 22 or when blood count parameters are met (whichever occurs later).

4.14 MAINTENANCE - All Patients

This Maintenance course is for all patients irrespective of study phase or treatment randomization assignment.

CRITERIA FOR STARTING MAINTENANCE

1. ANC ≥ 750/µL
2. Platelets ≥ 75,000/µL.

VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy.
Days 1, 29 and 57
Dose: 1.5 mg/m^2/dose (max dose 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Dexamethasone: PO (may be given IV)
Days 1-5, 29-33, 57-61
Dose: 3 mg/m^2/dose BID (i.e. total daily dose: 6 mg/m^2/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Mercaptopurine: PO
Days 1-84
Dose: 75 mg/m^2/dose*

Other Considerations:
*See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day.

If using tablets, adjust daily dose using the dosing nomogram in Appendix VI to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Section 5.11.2 for dose modifications during Maintenance.

Methotrexate: PO
Days 8, 15, 22, 29*, 36, 43, 50, 57, 64, 71 and 78
Dose: 20 mg/m^2/dose weekly
* Omit Day 29 of first 4 cycles for SR T-ALL and T-LLy patients and for first 2 cycles of Maintenance for IR T-ALL and T-LLy patients.

Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water).

Intrathecal Methotrexate: IT
Administer on Day 1 **(also on Day 29 of the first 4 cycles of Maintenance for Standard Risk T-ALL and T-LLy patients ONLY and on Day 29 of the first 2 cycles of Maintenance for Intermediate Risk T-ALL and T-LLy patients ONLY)**.

Aged-based dosing:

Age (yrs)	Dose
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Cranial Radiation Therapy

All CRT will be given during the 1st cycle (first 4 weeks) of Maintenance. See the tables below to determine which subjects will receive CRT. See Section 16.1 for details.

T-ALL- Cranial Radiation Therapy

	SR	IR	VHR
CNS 1	none	none	CRT (1200 cGy)
CNS 2	none	none	CRT (1200 cGy)
CNS 3	n/a	CRT (1800 cGy)	CRT (1800 cGy)

T-LLy- Cranial Radiation Therapy

	SR	IR	VHR
CNS 1	none	none	none
CNS 2	none	none	none
CNS 3	n/a	CRT (1800 cGy)	CRT (1800 cGy)

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

SEE SECTION 6.0, DRUG INFORMATION, FOR DETAILED INFORMATION ABOUT DRUG ADMINISTRATION.

The therapy delivery maps (TDMs) for MAINTENANCE are in APPENDIX I-M (Arm A) and APPENDIX II-M (Arm B).

CRITERIA TO BEGIN MAINTENANCE CYCLES

Begin subsequent Maintenance cycles regardless of counts. Only mercaptopurine and PO methotrexate will be interrupted for myelosuppression as outlined in Section 5.10.

DOSE MODIFICATIONS FOR MYELOSUPPRESSION DURING MAINTENANCE

Only mercaptopurine and PO methotrexate will be interrupted for myelosuppression as outlined in Section 5.10.

DURATION OF THERAPY

1. GIRLS SR and IR T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **two** years from the start of Interim Maintenance (~ Week 119).

2. GIRLS VHR T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **two** years from the start of Intensification Block #1 (~ Week 119).

3. BOYS SR and IR T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **three** years from the start of Interim Maintenance (~ Week 171).

4. BOYS VHR T-ALL: Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **three** years from the start of Intensification Block #1 (~ Week 171).

5. T-LLy patients (regardless of gender): Continue to repeat 12-week cycles of Maintenance therapy until the total duration of therapy is **two** years from the start of Interim Maintenance (~Week 119)

6. May stop therapy on anniversary date if dexamethasone is completed for the 5-day dexamethasone pulse. Anniversary date is defined as the date marking two (2) years (for T-ALL girls and all T-LLy patients, regardless of gender) and three (3) years (for T-ALL boys) from the start of Interim Maintenance #1 for SR and IR patients, and from the start of Intensification Block #1 for VHR patients.

5.0 DOSE MODIFICATION FOR TOXICITIES

Notify the Study Chair at the time of removing a patient from protocol therapy for toxicity. The drugs are listed in alphabetical order.

5.1 Asparaginase [E.coli, Pegaspargase (PEG-Asparaginase) or Erwinia]

5.1.1 Allergy

Local Allergic Reactions (inflammation at injection site, swelling): Note these recommendations only apply when the asparaginase product is administered intramuscularly. Continue asparaginase administration in the presence of Grade 1 allergy as defined by CTCAE v4.0 (transient flushing or rash; drug fever < 38ºC).

Systemic Allergic Reactions: In the event of Grade 1 reactions, characterized by transient flushing or rash and drug fever < 38ºC, without the need for treatment with antihistamines or steroids, the dose of asparaginase being administered intravenously may be continued with close observation.

Discontinuation is recommended for Grade 2 or higher allergic reactions, as defined by CTCAE v4.0, that require medical intervention.

Note: Premedication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged since anti-histamine use may mask the appearance of systemic allergy. Systemic allergy is frequently associated with the presence of asparaginase neutralizing antibodies, which render asparaginase therapy ineffective. In the event of Grade 2 or higher systemic or recurrent local allergic reaction, Erwinia asparaginase should be substituted.

Arm A ONLY: Patients with allergy/anaphylaxis to pegaspargase may be eligible to receive IV pegcrisantaspase, a pegylated form of Erwinia asparaginase, on COG AALL1421 at doses prescribed on that protocol. Patients who have previously received *Erwinia* asparaginase or are receiving other investigational agents (including patients on Arm B of AALL1231) are **not** eligible for AALL1421.

5.1.2 Anaphylaxis

Discontinue pegaspargase or *E. coli* if the patient develops Grade 3 anaphylaxis as defined by CTCAE v4.0 (symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, Erwinia asparaginase should be substituted.

Erwinia asparaginase has a shorter half-life and is associated with a shorter duration of asparagine depletion than native *E. coli* asparaginase, with "head-to-head" comparisons of Erwinia and *E. coli* asparaginase, using the same dose and schedule for both preparations, demonstrating a superior outcome, favoring *E. coli* asparaginase.[138,139] Pegaspargase has a longer half-life and is associated with more prolonged asparagine depletion than native *E. coli* asparaginase, but the largest randomized trial comparing weekly native to bi-weekly pegaspargase wasn't powered to detect a difference in outcome.[140] Current COG trials have adopted pegaspargase as the preparation of choice, based on the results of CCG 1962.[141] COG AALL07P2 showed that Erwinia asparaginase was well tolerated and achieved nadir serum asparaginase activity at both 48 and 72 hours after dosing that was similar to that achieved with pegaspargase. Based on these and other data, the FDA approved Erwinia asparaginase for use following allergy to pegaspargase, with a dose of Erwinia 25,000 IU/m^2 x 6 doses IM on a Monday/Wednesday/Friday schedule substituted for a single dose of pegaspargase.

PATIENTS ENROLLED IN AALL0932, AALL1131 OR AALL1231 MAY BE ELIGIBLE TO ENROLL IN AALL1421 IF THEY DEVELOP AN ALLERGIC REACTION TO PEGASPARGASE THAT PRECLUDES FURTHER ADMINISTRATION OF THAT DRUG. The new AALL1421 trial was developed to study the pharmacokinetics and tolerability of pegcrisantaspase in patients with hypersensitivity to PEG-asparaginase. On AALL1421 patients will receive pegcrisantaspase at the assigned dose via 1 hour IV infusion as a replacement for each scheduled dose of PEG-asparaginase remaining on the original treatment protocol. Please see the AALL1421 protocol web page for more information.

The dose modification guidelines for ALL trials recommend the substitution for replacement of Erwinia asparaginase for either native or pegaspargase utilizing the following schedule:

Phase(s) of Treatment	**Drug(s)**	**Replacement Schedule for Erwinia asparaginase[#]**	**Important Notes**
Induction, Consolidation, Interim Maintenance (CMTX), Delayed Intensification, Intensification Blocks 1, 2, and 3	One or more doses of pegaspargase (2,500 IU/m^2)	25,000 IU/m^2/dose IM or IV# M/W/F x 6 doses for each dose of pegaspargase.	

[#]If a patient develops a Grade 3 or higher anaphylaxis to Erwinia, discontinue future asparaginase therapy. Consider discontinuation for severe Grade 2 or higher allergic reactions

To replace a dose of intravenous pegaspargase that was discontinued during the infusion due to an allergic reaction, the following recommendations may be used to guide patient care.

In the event that a pegaspargase infusion is discontinued for an allergic reaction, regardless of amount received, substitution with *Erwinia* asparaginase should begin approximately 48 hours after pegaspargase has been discontinued and preferably to coincide with the recommended Monday/Wednesday/Friday administration schedule detailed above in patients who are clinically stable. Up to 6 doses of *Erwinia* asparaginase may be administered, as tolerated, to replace the incomplete intravenous pegaspargase dose. Of note, *Erwinia* asparaginase is recommended only for pegaspargase hypersensitivity reactions, and not for pancreatitis, hepatitis, coagulation abnormalities, or other non-hypersensitivity toxicities associated with pegaspargase. To best suit the needs of each individual patient, additional modifications to these recommendations may be made at the discretion of the treating physician.

5.1.3 Coagulopathy

If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

5.1.4 Hyperbilirubinemia
Asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity. No specific guidelines are available.

5.1.5 Hyperglycemia
Do not modify dose. Treat hyperglycemia as medically indicated.

5.1.6 Hyperlipidemia
Do not modify dose

5.1.7 Ketoacidosis
Hold asparaginase until blood glucose can be regulated with insulin.

5.1.8 Pancreatitis
Discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until symptoms and signs subside, and amylase/lipase levels return to normal and then resumed. Grade 3 or 4 pancreatitis is a contraindication to additional asparaginase administration.

5.1.9 Thrombosis
Withhold asparaginase until symptoms have resolved, and treat with appropriate antithrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing LMWH or antithrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate. For significant thrombosis, which is not catheter-related, consider evaluation for inherited predisposition to thrombosis.

CNS Events (bleed, thrombosis or infarction): Hold asparaginase. Treat with FFP, factors or anticoagulation as appropriate. Consider resuming at full dose when all symptoms have resolved (and evidence of recanalization in case of thrombosis by CT/MRI). Consider evaluation for inherited predisposition to thrombosis.

Centers may elect to discontinue pegasparaginase and switch to erwinia asparaginase based upon laboratory evidence of silent inactivation of asparaginase activity in the absence of clinical symptoms of hypersensitivity at their discretion.

5.2 Bortezomib Related Toxicities

Special criteria will be followed for peripheral neuropathy and pulmonary toxicities thought to be possibly, probably or definitely related to bortezomib

5.2.1 Bortezomib-related peripheral neuropathy
Peripheral neuropathy will be closely monitored during each block of treatment that includes bortezomib and toxicities graded.

Neuropathy grading should be based on the maximum toxicity occurring during the previous block. Neuropathy should be graded using the "BALIS" scale (see Section 5.13). All dose modifications should be based on the worst preceding toxicity. Bortezomib dose will be decreased for sensory peripheral neuropathy as follows:

Table 2: Dose Modifications for Bortezomib-Related Neuropathic Pain and / or Peripheral Sensory Neuropathy

Severity of peripheral sensory neuropathy	Bortezomib modification
Grades 1-2 without pain	None
Grade 1 with pain	Decrease bortezomib to 1 mg/m^2/dose
Grade 2 with pain or any Grade 3	Hold bortezomib treatment until symptoms ≤ Grade 1. Do not make up missed doses. When toxicity resolves, re-initiate bortezomib at 1 mg/m^2/dose
Grade 2 with or any Grade 3 > 2 weeks duration or recurrence after prior dose reduction	Discontinue bortezomib
Grade 4	Discontinue bortezomib

5.2.2 Bortezomib-associated pulmonary toxicity

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib. For this reason, pulmonary toxicity will be monitored carefully during the study. See below for management of new-onset dyspnea, hypoxia or chest infiltrates not explained by infection or other known cause.

5.2.2.1 Identification and Management of Bortezomib-Related Pulmonary Toxicity

Pulmonary toxicities are more commonly seen when bortezomib is given to elderly adults. Pulmonary toxicity due to bortezomib may be delayed and can occur up to 3 weeks after the final dose of bortezomib is administered. Bortezomib-related pulmonary toxicities are rare in children and were not seen during AALL0P1. Nevertheless, as pulmonary toxicities secondary to bortezomib can be serious, a low threshold to evaluate for pulmonary toxicity is recommended. Patients with abnormal respiratory symptoms, including dyspnea, cough, or pleuritic chest pain or abnormal respiratory findings on exam, including tachypnea, increased work of breathing, or ausculatory abnormalities should have a chest radiograph and pulse oximetry performed.

If the patient develops pulmonary toxicity, including a decrease in oxygen saturation to < 90%, and/or bilateral infiltrates on chest x-ray, and/or pulmonary opacities on CT scan, in the absence of evidence of pneumonia or congestive heart failure, the following steroid therapy is recommended. Therapy can be tailored based on the severity of the pulmonary toxicity:

- Methylprednisolone 200-400 mg/m^2 IV X 1, followed by 250 mg/m^2 IV daily for 3 days (max dose 1000 mg/day), or
- Dexamethasone 6 mg/m^2 IV BID hrs. or
- Prednisone 40 mg/m^2 PO daily divided BID.

Other similar steroid regimens suitable for treatment of non-infectious pneumonitis may be used. In addition, it is suggested that a formal consultation from a pulmonologist be obtained. Bronchoscopy is encouraged if clinically indicated. The steroid dosage should be tapered as clinically appropriate once the clinical condition improves.

5.2.2.2 Dose De-escalation or Discontinuation of Bortezomib for Pulmonary Toxicity and

Other Bortezomib-Related Toxicities (Excluding Peripheral Neuropathy)
Bortezomib will be dose de-escalated to 1 mg/m^2 for any resolving Grade 3 pulmonary toxicity (excluding voice changes/laryngitis), including hypoxia (oxygen saturation below the threshold listed in 5.2.2.1) that is possibly, probably or definitely related to bortezomib. Patients that experience a Grade 4 pulmonary toxicity possibly, probably or definitely related to bortezomib (excluding voice changes/laryngitis) will discontinue bortezomib.

5.2.2.3 Patients re-experiencing the same bortezomib-related qualifying Grade 3 pulmonary toxicity following a single bortezomib dose reduction will discontinue bortezomib.

5.2.3 Bortezomib-Related Electrolyte Abnormalities
Bortezomib has been associated with hyponatremia, hypophosphatemia, and hypokalemia in some studies. Serum sodium, potassium, and phosphorus should be checked at the beginning of Induction and DI. Consider correcting low levels as clinically appropriate, balancing the risk of correction of these abnormalities with the risks of developing hyperkalemia or hyperphosphatemia from tumor lysis during induction chemotherapy. Also, consider monitoring electrolyte levels periodically during induction and DI and correcting if clinically indicated. Bortezomib will not be dose de-escalated for bortezomib-related electrolyte abnormalities

5.2.4 Non-Hematologic and non-Electrolyte Grade 3 or 4 Bortezomib-Related Toxicity
The bortezomib dose should be de-escalated to 1 mg/m^2 for non-hematologic and non-electrolyte Grade 3 and 4 toxicities that are possibly, probably or definitely related to bortezomib (see below).

Dose de-escalation within a block (Induction or DI):
If a patient experiences a Grade 3 or 4 bortezomib-related toxicity that does not require cessation of bortezomib (see above), and once this Grade 3 or 4 toxicity resolves to ≤ Grade 1, bortezomib can be restarted at a decreased dose of 1 mg/m^2 for **subsequent** doses. Missed doses of bortezomib will not be made up. Patients who have a qualifying Grade 3 pulmonary toxicity that worsens (i.e., > Grade 3) by the next scheduled dose of bortezomib should discontinue bortezomib.

Dose de-escalation between Induction and DI:
The bortezomib dose will be decreased to 1 mg/m^2 for qualifying Grade 3 or 4 toxicities (see above) that resolve to ≤ Grade 1 prior to the beginning of DI. Doses reduced for an adverse event will not be re-escalated, even if there is minimal or no toxicity at the reduced dose.

5.2.5 Bortezomib Dose Reductions for Hyperbilirubinemia:
Patients with mild hepatic impairment do not require dose adjustment of bortezomib. Patients with moderate or severe hepatic impairment should receive bortezomib at modified doses as outlined below:

	Direct Bilirubin Level	Bortezomib Dose Modification
Moderate	> 1.5x – 3x upper limit of normal	Reduce bortezomib to 0.7 mg/m^2 for all doses in the cycle in which hepatotoxicity is present.

Severe	> 3x upper limit of normal	Consider dose escalation to 1 mg/m^2 in subsequent cycles if transaminitis and hyperbilirubinemia resolves and hepatic toxicity was not possibly, probably, or definitively related to bortezomib.

* No adjustment necessary for elevated SGOT (ALT).

5.3 Cyclophosphamide

5.3.1 Hematuria

5.3.1.1 Omit in the presence of macroscopic hematuria.

5.3.1.2 If there is a history of previous significant hematuria:

- Hydrate before cyclophosphamide until specific gravity is <1.010
- Hydrate at 125 mL/m^2/hr for 24 hours after dose
- Monitor for adequate urine output as per institutional guidelines.
- Give IV mesna at a total dose that is 60% of the cyclophosphamide dose divided to 3 doses (e.g., if the cyclophosphamide dose is 1000 mg/m^2, the total mesna dose is 600 mg/m^2 or 200 mg/m^2/dose). Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat 4 and 8 hours after the start of cyclophosphamide. This total daily dose of mesna can also be administered as IV continuous infusion. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion.

5.3.2 Renal Dysfunction

If creatinine clearance or radioisotope GFR is < 10 mL/min/1.73 m^2, reduce dose of cyclophosphamide by 50%. Prior to dose adjustment of cyclophosphamide, the creatinine clearance should be repeated with good hydration.

5.4 Cytarabine (ARAC)

5.4.1 Fever

- Do not withhold ARAC for fever if it is likely to have been caused by the ARAC (ARAC Syndrome).
- Obtain blood cultures if a central line is present.

5.4.2 Rash or Conjunctivitis

For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis.

5.4.3 Myelosuppression

Once Consolidation (C) or Delayed Intensification (DI) has started do not interrupt for uncomplicated myelosuppression; do hold for proven or presumed serious infection. Do make up missed doses.

5.4.4 Renal Function

Adequate renal function (defined as creatinine within normal range) is required for the administration of high dose ARAC. Creatinine Clearance should be measured for patients with elevated creatinine or suspected renal insufficiency. For CrCl < 60 mL/min/1.73 m^2, hold pending recovery and omit if recovery requires > 3 weeks.

5.5 Daunorubicin and Doxorubicin

5.5.1 Cardiac Toxicity

Discontinue for clinical or echocardiographic evidence of cardiomyopathy (SF < 27% or EF < 50%) or Grade 3-4 left ventricular systolic dysfunction (LVSD) per CTCAE version 4.0.

5.5.2 Myelosuppression (beyond Induction)

If patient has severe infection or severe mucositis (Grade 3-4) and an ANC < 500/µL delay anthracycline during phases other than Induction. During Induction, continue with anthracycline administration. Subsequent doses should be given at full dose.

5.5.3 Hyperbilirubinemia [142]

Direct Bili	% Dose Reduction
< 1.2 mg/dL	Full dose
1.2 – 3.0 mg/dL	50%
3.1 – 5.0 mg/dL	75%
> 5.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved.

Do not make up missed doses.

5.5.7 Extravasation

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines.

5.6 Etoposide

5.6.1 Allergic Reaction

Premedicate with diphenhydramine (1-2 mg/kg slow IV push, maximum dose -50 mg). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension.

5.6.2 Hypotension

If diastolic or systolic blood pressure (BP) falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of NS 10 mL/kg if BP fails to recover or falls further. Stop infusion if BP does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% NaCl at 10 mL/kg/hr for 2 hours prior to any subsequent infusion.

5.6.3 Renal Insufficiency

If renal function decreases, adjust etoposide as follows: CrCl 10-50 mL/min/1.73 m^2, decrease dose by 25%; if CrCl < 10 mL/min/1.73 m^2, decrease dose by 50%.

5.6.4 Hyperbilirubinemia

If direct bilirubin is > 2 mg/dL, decrease dose by 50%. If direct bilirubin is > 5 mg/dL, hold etoposide.

5.7 Ifosfamide

5.7.1 Hematuria

Grade 2 – 3: Administer Mesna as under Section 4.12 with ifosfamide. Grade 4 notify Study Chair.

5.8 Intrathecal Methotrexate/Triple Intrathecal Therapy

5.8.1 Systemic toxicity

The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5 mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC < 500/µL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

5.8.2 Dose modifications following an episode of acute neurotoxicity

Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.[143-145] These toxicities are poorly understood and currently it is impossible to predict who will suffer these complications. In addition, there are no data clearly linking the occurrence of an acute neurotoxic event with an increased risk of long-term neurocognitive dysfunction, nor do changes present on MRI at the time of an acute event clearly correlate with or predict outcome.[145-150] It is clear however, that CNS prophylaxis is a mandatory component of curative therapy for children with ALL. Effective prophylaxis generally takes 2 forms; cranial, or less commonly, craniospinal radiation, with a limited number of doses of IT therapy or prolonged IT therapy with either IT MTX or triple IT therapy (MTX, ARAC and hydrocortisone). Certain protocols, for example BFM 2000,[151] include fewer doses of IT MTX, with an acceptably low frequency of CNS relapse, but the backbone of the BFM therapies is not the same as those currently used by the Children's Oncology Group. The exclusive use of IT ARAC has not been studied or described in the context of ALL therapy nor can one demonstrate the safety of omitting multiple doses of IT therapy without concomitant use of cranial radiation therapy or high dose methotrexate.

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches or any others. Thus the treating physician must evaluate the patient and, with the family, make the best possible decision with respect to the relative risk and benefit of continued therapy.

Following an acute neurotoxic event, a history and physical exam should guide the differential diagnosis. A neurology consult may be of value and should be considered. Seizures and other transient events may be linked to fever, infection, encephalitis, meningitis, hypertension, electrolyte disturbance, hypoglycemia, trauma, intracranial hemorrhage or thrombosis, narcotic withdrawal, illicit drug use, or other causes in addition to the direct side effects of chemotherapy. Appropriate laboratory studies may include, but are not limited to, blood cultures, a CBC, electrolytes, including glucose, calcium, magnesium and phosphorus, renal and liver function studies and/or an examination of the CSF. Imaging studies may include a CT scan and/or an MRI. The CT is commonly normal, in the absence of stroke, but if calcifications are present, this finding may be indicative of a more severe mineralizing leukoencephalopathy.[152] MRI abnormalities may be pronounced, but transient. Posterior reversible encephalopathy may be present on MR with extensive diffusion abnormalities, but these do not appear to correlate with subsequent demyelination or gliosis.[153-155] Additional studies, including MR angiography and/or venogram should be considered, if clinically indicated (e.g., focal deficits).

Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration.[156] For patients who return to their "pre-event" status, without residual deficits of physical or neurologic exam, there are few data to support or guide therapeutic interventions. It is reasonable to hold the next dose of IT therapy, or, substitute IT Ara-C for 1 dose of IT MTX, or triple IT therapy. It is also reasonable to include leucovorin rescue at a dose of 5 mg/m^2 q 12 hrs x 2 doses beginning 48 hours after the LP. This pattern of rescue was associated with a clear diminution in the incidence of acute neurotoxicity in one case series.[156] There have been questions about potential interference of leucovorin with the efficacy of the IT MTX, but there are little data to support or refute this position. Moreover, the administration 48 hours later would minimize any potential interference. If the event does not recur, resumption of standard therapy should be considered, following 1 modified or omitted IT dose. In the face of multiply recurrent events, or evidence of progressive encephalopathy, another evaluation is warranted and the treating physician may consider a more prolonged or definitive change in therapy. These decisions are extremely difficult and may hinge on an individual's view of the importance of quality of life versus an increase in the risk of relapse. Since the greatest impact of CNS prophylaxis occurs early in therapy, the timing of these events may also influence clinical decisions. Cranial radiation has been suggested as an alternative to continued IT therapy though much of the literature on long-term neurocognitive dysfunction supports a more deleterious effect from CRT than IT therapy.[157-160] Dramatic deviations from protocol recommended therapy might result in the child being taken off protocol therapy.

The use of dextromethorphan (DM) has been suggested as a neuroprotectant, capable of preventing NMDA mediated neurotoxicity without prohibitive toxicity. Low dose therapy has been recommended, in part, based on data suggesting that DM is concentrated in brain relative to serum. However, the literature on the use of DM supports a tight dose response relationship, with the likelihood of sparing an initially unaffected area, following ischemic damage, linked to dose, in both clinical trials and animal models of CNS ischemia.[161-164] At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander et al[165] have raised concerns about the potential deleterious effects of long-term NMDA receptor blockade on memory because hippocampal long-term potentiation is dependent on the activation of the NMDA receptor. Thus in the absence of a clinical trial there are few data to support the addition of DM.

5.8.3 Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture

Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by LP. NOTE: Obstruction to CSF flow may be a contraindication to intrathecal and/or intraventricular therapy.

5.8.4 Viral, bacterial, or fungal meningitis

Omit until resolved.

5.9 **High-Dose Methotrexate (HDMTX) and Leucovorin Rescue**

[Please note that **HDMTX** refers to IV MTX **5g/m^2 given over 24 hrs**]

Note: Review of methotrexate dosing on BFM-based protocols indicated that excessive methotrexate toxicity has not been encountered in patients larger than 2 m^2 who receive more than

10 grams of methotrexate. The investigator should base the methotrexate on the patient's meter-squared dosing and not cap at 10 grams of methotrexate.

5.9.1 HD MTX Infusion Guidelines

See Appendix IV for a flowchart of the HDMTX / LCV guidelines.

When IT therapy and HDMTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

Hold TMP-SMX on the days of HDMTX infusion and for at least 72 hours after the start of the HDMTX infusion and until the MTX level is less than 0.4 µM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Hold any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HDMTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 µM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. An acetate or bicarbonate bolus (0.5-1 mEq/kg over 15 min) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HDMTX infusion, and for a minimum of 54 hours after the MTX bolus started for patients who meet expected clearance parameters. In patients with delayed MTX clearance, continue hydration and leucovorin as instructed (Appendix IV) until the plasma MTX concentration is below 0.1uM.

Hour 0: MTX 500 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the HDMTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Hours 24, (36), 42 and 48: Draw MTX level and serum creatinine. NOTE: 36 hour level is only drawn if needed (see below).

For MTX levels that exceed these expected values modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly (serum CR >125% of baseline), at any time point, assure appropriate urine pH and urine volume as above and draw a 42 hour level. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see below). For patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m^2/hr). If subsequent course is not associated with delayed clearance, attempt to use standard hydration.

If the 24 hour level is < 150 µM draw the next level at hour 42 and refer to table below.

If the 24 hour level is ≥ 150 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc., described above and repeat the level with a serum Cr at hour 36. Then refer to the table below.

If the 42 and 48 hour levels are ≤ 1 and 0.4 µM, respectively, give Leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin.

36 hr MTX level	42 hr MTX level	48 hr MTX level	Leucovorin Rescue++
Only required if 24 hr level is ≥ 150 µM.**	1.01 to 9.9 µM	0.41 to 5.9 µM	Continue 15 mg/m^2 q 6h until MTX level < 0.1 µM (draw q12-24 h).
	10 to 19.9 µM	6 to 9.9 µM	Increase to 15 mg/m^2 q 3h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	20 to 200 µM	10 to 100 µM	Increase to 100 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	> 200 µM	> 100 µM	Increase to 1000 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.

** **If the 36 hour level exceeds 3** µM, increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also **consider glucarpidase if 36 hour MTX level exceeds 10** µM (see below).

++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

5.9.2 Nephrotoxicity

Postpone course if pre-treatment (MTX) serum creatinine is > 1.5x baseline or GFR creatinine clearance < 65 mL/minute/1.73m^2. If renal function does not recover, omit MTX. Do not give HDMTX to a patient with this degree or renal impairment, assuming that prolonged excretion can be managed with glucarpidase.

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G_2, Voraxaze™).[166,167] To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue will remain on study.

5.9.3 Elevated Transaminases

Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of intravenous MTX. Blood samples for ALT should not be drawn following the start of MTX infusions as MTX causes significant short term elevation in ALT levels.

ALT	IV MTX
< 10 X ULN	Continue with therapy as scheduled
10 – 20 X ULN	Continue with therapy as scheduled for 1 cycle
10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full dose at point of interruption. Do not skip doses.
> 20 X ULN	Hold therapy until ALT < 10 X ULN, then resume at full dose at point of interruption. Do not skip doses.
> 20 X ULN for > 2 weeks	Evaluate with AST, bili, alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given. Notify Study Chair.

* *Please see COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp for TMP/SMX substitutions.

5.9.4 Hyperbilirubinemia

Hold IV MTX for direct hyperbilirubinemia of > 2.0 mg/dL.

5.9.5 Mucositis

For Grade 3-4 mucositis, withhold IV MTX until resolved. Increase leucovorin rescue following the next course from 3 to 5 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3-4 mucositis, attempt to decrease the leucovorin. If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25%, increase hydration to 200 mL/m^2/hr and continue increased leucovorin as above. Should subsequent courses be well tolerated, use a stepwise approach to resuming a standard approach to drug delivery. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

5.9.6 Myelosuppression

All chemotherapy should be held for ANC < 750/µL and platelets < 75 000/µL.

5.10 Capizzi Methotrexate Regimens

5.10.1 Liver Dysfunction

Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of intravenous MTX. Blood samples for ALT should not be drawn following the start of MTX infusions as MTX causes significant short term elevation in ALT levels.

ALT	IV MTX
< 10 X ULN	Continue with therapy as scheduled
10 – 20 X ULN	Continue with therapy as scheduled for 1 cycle
10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20 X ULN	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption. Do not skip doses.
> 20 X ULN for > 2 weeks	Evaluate with AST, bili, alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given.

* Please see COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp for TMP/SMX substitutions.

5.10.2 Nephrotoxicity

Postpone course if serum creatinine is >1.5 x baseline or GFR creatinine clearance < 65 mL/1.73m²/minute.

5.10.3 Hyperbilirubinia

Hold IV MTX for direct hyperbilirubinemia of > 2.0 mg/dL.

5.10.4 Mucositis

For Grade 3-4 mucositis, withhold IV MTX until resolved. Discontinue MTX dose escalation and resume at 80% of last dose if therapy is delayed for myelosuppression or Grade 3 or greater mucositis. If mucositis persist or recurs, consider culturing lesions for herpes simplex.

5.10.5 Myelosuppression

A) If ANC is < 500/µL or platelets < 50 000/µL, hold all chemotherapy and repeat blood counts in 4 days.
   1. In 4 days, if ANC ≥ 500/µL and platelets ≥ 50 000/µL, give same dose of methotrexate as previous cycle.
   2. In 4 days, if ANC is still < 500/µL or platelets < 50 000/µL, give VCR (and IT MTX if Day 31) and pegaspargase (if due) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.
      a. If after 7 days ANC ≥ 500/µL or platelets ≥ 50 000/µL, reduce dose of IV MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.

b. If after 7 days ANC is still < 500/µL or platelets < 50 000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50,000/µL. When ANC ≥ 500/µL and platelets ≥ 50 000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A-C.

B) If ANC ≥ 500 but < 750/µL and platelets ≥ 50 000 but < 75 000/µL, give same dose of MTX as previously (i.e., no escalation).

C) If ANC ≥ 750 and platelets ≥ 75 000 escalate MTX by 50 mg/m^2.

D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A-C.

5.11 PO Methotrexate (MTX) and 6-Mercaptopurine (MP)

5.11.1 Interim Maintenance #1 with HDMTX

If ANC is < 750/µL and/or platelets < 75 000/µL, hold mercaptopurine. Restart mercaptopurine at full dose with next cycle of HD MTX when ANC is ≥ 750/µL and platelets are ≥ 75 000/µL. Do not make up missed doses. Consider a marrow evaluation in the face of persistent or prolonged cytopenias. If patient develops severe or unexpected myelosuppression, see section below on thiopurine pharmacology testing.

If patient develops severe or unexpected myelosuppression, see section below on thiopurine pharmacology testing.

5.11.2 Maintenance:

a) Dose reduction for myelosuppression:

If neutrophil count falls below 500/µL or if platelet count falls below 50,000/µL during Maintenance, MP and MTX will be held until recovery above these levels. For the first drop in ANC or platelets, resume chemotherapy (both MP and MTX) at the same dose the patient was taking prior to the episode of myelosuppression. If neutrophil count falls below 500/µL or if platelet count falls below 50 000/µL for a second (or greater) time, discontinue doses of MP and MTX until ANC is ≥ 750/µL and platelets are ≥ 75 000/µL. Restart both MP and MTX at 50% of the dose prescribed at the time the medication was stopped. Then continue to increase to 75% and then 100% of the dose prescribed prior to stopping the medication at 2-4 week intervals provided ANC remains ≥ 750/µL and platelets remain ≥ 75 000/µL. May increase both MP and MTX simultaneously. Consider discontinuing TMP/SMX as per COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp. If neutrophil count falls below 500/µL or if platelet count falls below 50 000/µL on > 2 occasions during Maintenance, perform thiopurine pharmacology testing as described below. Should therapy be withheld for myelosuppression or elevated transaminase, do not "make up" that week. Resume therapy at the correct point, chronologically.

b) Dose escalation:

For ANC ≥ 1500/µL on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s) alternately increase doses of MTX or MP by 25%. As a general rule, do not increase doses more often than every 4 weeks. If both MTX and MP are increased once without a fall in ANC, consider noncompliance as a possibility. Noncompliance can be assessed by obtaining a sample for RBC thioguanine nucleotides (TGNs). Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2-4

hours later. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance.

c) Mucositis Grade 3-4:
MTX should be reduced to 50% if Grade 3 toxicity develops; withhold in the presence of Grade 4 toxicity until there is a resolution, then resume at 50% of original dose with gradual dose escalation. If mucositis persists or recurs, consider culturing for herpes simplex.

d) Liver Dysfunction:
For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total bilirubin. Monitor SGPT/ALT or SGOT/AST and total bilirubin every 2 weeks during Consolidation and every 4 weeks during Maintenance as long as transaminases remain over 5x ULN.

Continue full dose therapy unless either of the following occurs:
1) Direct bilirubin > 2.0 mg/dL
2) SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) on 2 determinations at least 1 week apart.

If either of these occurs, hold MTX and monitor labs as above, weekly. Restart at full dose therapy when the transaminase is less than 5x ULN, if bilirubin is normal. If liver dysfunction persists, consider a trial period with MTX but without MP, especially if red cell MP methylated derivatives are elevated. Also consider liver biopsy.

Exclude infectious hepatitis (A, B, C) for persistent (> 1 month) elevations in SGPT/ALT or SGOT/AST above 5x ULN.

5.11.3 Thiopurine Pharmacology Testing and Dosage Adjustments in All Blocks that Contain Thiopurines

MP and 6-TG are methylated directly by thiopurine methyltransferase (TPMT) to an inactive metabolite. TPMT activity varies tremendously among patients, because of a common inherited genetic defect in TPMT. One in 300 patients is completely deficient (homozygous defective) and 10% of the population is moderately deficient in TPMT activity because they have inherited one variant (non-functional) TPMT allele (i.e., heterozygotes).[168-171] Patients with low TPMT form higher concentrations of the 6-thioguanine nucleotides (6-TGN) and are more susceptible to acute thiopurine toxicity (primarily myelosuppression, involving neutropenia, thrombocytopenia, and anemia). Patients with the complete deficiency of TPMT tolerate less than 10% of protocol doses of MP (10 to 30 mg/m^2/day 3 days per week). About 35% of heterozygotes require a lower dose of MP to avoid dose-limiting myelosuppression.[172]

Recently, germline variants in the gene encoding the nucleoside diphosphate–linked moiety X-type motif 15 (NUDT15) were reported in approximately 4% of Hispanic/Native American and nearly 10% of East Asian children with ALL; these polymorphisms are strongly associated with 6-MP intolerance. [173]

There are now CLIA certified tests for TPMT genotype and phenotype, for thiopurine metabolites (6-methyl mercaptopurine [6-MMP] and 6-TGN) measurements, and for *NUDT15* polymorphisms. Only 3 SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide.[168,174-177] Thus, the genotyping test has a low false negative rate, and may be preferable to TPMT phenotype testing in cases where a history of red cell transfusions

would potentially confound assessments of RBC TPMT activity. When the genotyping result is coupled with a phenotyping test for TPMT or with thiopurine metabolite concentrations in erythrocytes, the reliability of the tests will be even greater. Moreover, metabolite levels can provide an index of patient compliance with thiopurine therapy.

Recommendations for Thiopurine Monitoring and Dosage Adjustments:
When myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy, thiopurine testing should be performed:

- For subjects who have received full dose thiopurine therapy during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status
- TPMT genotyping will be informative in all subjects, if at least 1 mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5%-10% of mutants. NOTE: *Genotyping can be done despite recent transfusions.*

5.11.4 Suggested Dose Adjustments in Patients With Unacceptable Myelosuppression

- If the subject is *homozygous deficient* for TPMT or *NUDT15*, the thiopurine dose should be *reduced to* 10-20 mg/m^2/day 3 days per week. If the subject is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30%-50%. It is not yet clear how the dose of thiopurine should be adjusted for patients who are heterozygous for *NUDT15* but such patients should be monitored carefully while on thiopurines. If a patient has two polymorphisms in *NUDT15* (i.e. heterozygous for both the R139C and R139H), they should be treated as if they were homozygous deficient. Gradual dose escalations should be attempted as outlined below.
- Do not increase the dose in response to a high ANC for 4 weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are not often necessary.
- If the subject is homozygous wild-type (high activity) for TPMT or *NUDT15*, then discontinue TMP/SMX and use pentamidine or dapsone. For modifications of the oral MP and MTX see the beginning of this Section.

5.12 Steroids (Dexamethasone and Prednisone)

5.12.1 Hypertension

Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

5.12.2 Hyperglycemia

Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

5.12.3 Pancreatitis
Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis.

5.12.4 Osteonecrosis (ON)
Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) during Induction or Delayed Intensification. Consider omitting Maintenance steroid for osteonecrosis Grade 1 (clinically asymptomatic, radiographic finding only). Omit Maintenance steroid for osteonecrosis Grade 2 or greater, and notify study chair. Consider resuming Maintenance steroid after 6 months if joint symptoms have resolved and if MRI findings have significantly improved or normalized.

5.12.5 Varicella
Steroids should be held during active infection except during Induction. Do not hold during incubation period following exposure.

5.12.6 Inability to use oral doses
For dexamethasone, substitute the IV preparation mg for mg. For prednisone, substitute IV methylprednisolone at 80% of the oral prednisone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same; prednisone is converted in the liver to prednisolone.

5.12.7 Severe infection
Do not hold or discontinue steroids during Induction without serious consideration, as this is a critical period in the treatment of ALL. Later in therapy, one may consider holding steroid until patient achieves cardiovascular stability, except for "stress doses."

5.12.8 Severe psychosis
Dexamethasone dose may be reduced by 50% for severe psychosis. If symptoms persist, consider switching to an equivalent dose of prednisone.

5.13 **PO 6-Thioguanine (TG)**
Delayed Intensification
Oral TG will be held for suspected or proven serious infection.

For severe and/or unexpected myelosuppression, evaluate for TPMT activity as described in Section 5.10.

5.14 **Vincristine**
PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (See text box below)

5.14.1 Severe neuropathic pain (Grade 3 or greater)
Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. NOTE: neuropathic pain can be not only severe but difficult to treat. However, because vincristine is an important component of curative therapy and the majority of neuropathies are ultimately reversible, vincristine therapy may be given at full dose at investigator discretion. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies. Drugs such as gabapentin may be of value.

5.14.2 Vocal Cord paralysis
Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. See above for comment on CMT.

5.14.3 Foot Drop, paresis
Should be Grade 3 to consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vincristine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. See above for comment on CMT. Physical therapy may be beneficial to maintain range of motion and provide AFO's and other forms of support. Drugs such as gabapentin may be of value.

5.14.3 Jaw pain
Treat with analgesics; do not modify vincristine dose.

5.14.4 Hyperbilirubinemia[178,179]

Direct Bili	Dose reduction
< 3.1 mg/dL	Full dose (maximum dose: 2 mg),
3.1- 5.0 mg/dL	50% of calculated dose (maximum dose: 1 mg),
5.1-6.0 mg/dL	75% of calculated dose (maximum dose: 0.5 mg),
> 6.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

5.14.5 Constipation or ileus (≥ Grade 3) or typhlitis
Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% of calculated dose (maximum dose: 1 mg) and escalate to full dose as tolerated.

5.14.6 Extravasation
In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG guidelines.

Modified ("Balis") Pediatric Scale of Peripheral Neuropathies

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.

- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.

- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.

- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.

- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).

- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required & Optional Clinical, Laboratory and Disease Evaluations: Diagnosis, Induction, Consolidation Arm A and Arm B: T-ALL ONLY

STUDIES**	Diagnosis	Induction	Consolidation
Required Observations: Arms A and B T-ALL ONLY			
Hx/PE with VS/Wt (BSA)	X	Weekly	Start of Course
CBC/diff/plts	X	Weekly	Weekly
CSF cell count & cytospin	X	With each IT	With each IT
Bilirubin (total and direct), ALT, AST creatinine	Baseline	Days 1 and 29	Start of Course
Performance Status	Baseline		Prior to Day 1 therapy
Pregnancy Test[1]	Baseline		
Bone Marrow MRD and cytomorphology Assessment	X[$]	End of Induction[5]	End of Consolidation[2,5]
Chest x-ray	Baseline		
Required Observations: Patients receiving bortezomib (Arm B) T-ALL ONLY			
Pulse Oximetry (O2 saturation) and Chest x-ray		X[3]	
Electrolytes including PO_4		Start of Course[6]	
Optional Observations: Arms A and B T-ALL ONLY (All optional studies require patient consent)			
Bone Marrow (BM)/Peripheral Blood (PB) for bortezomib response (ETP-ALL) study (**open to Arm A and B**)[4]	BM: Pre-treatment	PB:Day 1 Hour 0, 6, 24 BM &PB:End of Induction	
Cell Banking[7]	Baseline[7]	End of Induction[7]	
Recommended Observations: Arms A and B T-ALL ONLY			
TPMT and NUDT15 genotype (if available)		During Induction	

[1] Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control

[2] End of consolidation bone marrow is not performed on SR T-ALL patients. It is REQUIRED for T-ALL patients with end Induction BM MRD ≥ 0.01% ONLY

[3] Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

[4] See Section 15.1 for details. Peripheral blood can be substituted if >80% blasts. Please send AALL1231 specimen transmittal form and institutional immunophenotype report with the sample submission to the laboratory

[5] Patients who are not in a morphologic remission at end of induction or consolidation remain on protocol therapy.

[6] Bortezomib has been associated with hyponatremia, hypophosphatemia, and hypokalemia in some studies. Serum phosphorus should be checked at the beginning of Induction. See Section 5.2.4 for optional recommendations on correction and monitoring.

[7] Done as part of AALL08B1 or APEC14B1. See AALL08B1 or APEC14B1 Manual of Procedures for details. Also note that specimens are requested at time of relapse as part of AALL08B1 or APEC14B1.

7.2 Required & Optional Clinical, Laboratory and Disease Evaluations: Diagnosis, Induction, Consolidation: Arm A and Arm B: T-LLy ONLY

STUDIES**	Diagnosis	Induction	Consolidation
Required Observations: Arms A and B T-LLy ONLY			
Hx/PE with VS/Wt (BSA)	Baseline	Weekly	Start of Course
CBC/diff/plts	Baseline	Weekly	Weekly
CSF cell count & cytospin	X	With each IT	With each IT
Bilirubin (total and direct), ALT, AST, creatinine	Baseline	Days 1 and 29	Start of Course
Performance Status	Baseline		Prior to Day 1 therapy
Pregnancy Test[1]	Baseline		
Disease Evaluation			
Chest & neck CT/Chest x-ray[2]	Baseline[2]	End of Induction[2]	End of Course[2]
Abdomen/Pelvis CT or MRI [8]	Baseline	End of Induction[8]	End of Course[8]
Bone scan[5]	Baseline	End of Induction[5]	End of Course[5]
Diagnostic Biopsy/Cytology[4]	Baseline		End of Course if PD or NR
Bone Marrow MRD Assessment[7]	X		
Bilateral bone marrow aspirate and biopsy cytomorphology [4]	X[7]	End of Induction only if positive at diagnosis	End of Course only if + at end of Induction
Required Observations: Patients receiving bortezomib (Arm B) T-LLy ONLY			
Pulse Oximetry (O2 saturation),chest x-ray[3]		X[3]	
Electrolytes including PO_4		Start of Course[6]	
Optional Observations: Arms A and B T-LLy ONLY (All optional studies require patient consent)			
Cell Banking[7]	Baseline[7]		
Bone Marrow MRD Assessment		End of Induction[9]	
Recommended Observations: Arms A and B T-LLy ONLY			
PET Scan (Recommended)	Diagnosis	End of Induction#	PET Scan (If + at End Induction)
TPMT and NUDT15 genotype (if available)		During Induction	

[1]Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control

[2] Obtain chest CT for all T-LLy patients at Baseline and at end-Induction. The baseline chest CT may be delayed until the patient is stable. If patient has CR at end-Induction, no subsequent chest CT is required but a chest x-ray will be performed at end-Consolidation and end of therapy. If patient does not have CR at end-Induction, a chest CT will be performed at end-Consolidation. Patients who have PD at end of consolidation are off protocol therapy.

[3] Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

[4] Determined by morphology on bilateral bone marrow aspirates/biopsies (not MRD or flow). Bilateral bone marrow aspirates and biopsies are strongly preferred but not required for study eligibility. A unilateral bone marrow aspirate for morphology and for central MRD bone marrow assessment are required to be eligible.

[5] Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease. A PET scan can be used as a substitute for bone scan; however, a bone scan is preferred in patients with bone symptoms.

[6] Bortezomib has been associated with hyponatremia, hypophosphatemia, and hypokalemia in some studies. Phosphorus should be checked at the beginning of Induction. See Section 5.2.3 for optional recommendations on correction and monitoring.

[7] If enrolled on APEC14B1, submit as a part of APEC14B1. If not enrolled on APEC14B1, submit as part of this protocol (see Section 14.2 for details).

[8] Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at baseline are negative, no repeat scans are required.

[9] See Section 14.2 for details. # If positive at diagnosis or a residual mass present

7.3 Required Clinical, Laboratory and Disease Evaluations Post-Consolidation Therapy: Arm A-SR and Arm B-SR (T-ALL and T-LLy)

STUDIES**	IM (CMTX)	Delayed Intensification	Maintenance
Required Observations: Arms A-SR and B-SR T-ALL and T-LLy			
Hx/PE with VS/Wt (BSA)	Start of Course	Start of Course	Every 4 weeks
CBC/diff/plts	Prior to each MTX dose	Weekly	Every 4 weeks
CSF cell count & cytospin	With each IT	With each IT	With each IT
Bilirubin, ALT, creatinine	Prior to each MTX dose	Day 1, 29	Prior to each 12 wk cycle
Thiopurine metabolites			As clinically Indicated [1,4]
Required Observations: Patients receiving bortezomib (Arm B-SR) ONLY (T-ALL and T-LLy)			
Pulse Oximetry (O2 saturation) and Chest x-ray		X[3]	
Electrolytes including PO_4		Start of Course[6]	
Required Observations: T-LLy ONLY			
Chest CT/Chest x-ray[2]			Completion of Therapy[2]
Abdomen/Pelvis CT or MRI			Completion of Therapy[7]
Bone scan[5]			Completion of Therapy
Diagnostic Biopsy/Cytology[8]			At relapse[8]
PET scan[#]			Post-treatment[#]
Optional Observations: T-ALL and T-LLy			
Optional Banking/Biology[8]			At relapse[8]

[1] For patients in whom TPMT and/or NUDT15 genotyping was not previously performed (see Section 5.10).

[2] If patient has CR at end-Induction, no subsequent chest CT is required but a chest x-ray will be performed at end-Consolidation and end of therapy. If patient has CR at end-Consolidation, a chest x-ray will be performed at end of therapy. If patient does not have CR at end-Consolidation, a chest CT will be performed at end of therapy. For patients who had PET-CT at diagnosis, a PET-CT can be used instead of standard CT to follow disease response.
Note: Patients who have NR and have not achieved at least a PR at end-Consolidation are off protocol therapy.

[3] Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

[4] Recommended only for HR-ALL patients during any Maintenance cycle in which 6MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.10).

[5] Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease. A PET scan can be used as a substitute for bone scan; however, a bone scan is preferred in patients with bone symptoms.

[6] Bortezomib has been associated with hyponatremia, hypophosphatemia, and hypokalemia in some studies. Serum phosphorus should be checked at the beginning of Delayed Intensification. See Section 5.2.3 for optional recommendations on correction and monitoring.

[7] Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at Baseline are negative, no repeat scans are required.

[8] **T-ALL:** Done as part of AALL08B1 or APEC14B1

[8] **T-LLy**: If enrolled on APEC14B1, submit as a part of APEC14B1. If not enrolled on APEC14B1, submit as part of this protocol (see Section 13.6 for details)

#Patients with post treatment residual masses only

7.4 Required Clinical, Laboratory and Disease Evaluations Post-Consolidation Therapy: Arm A-IR and Arm B-IR (T-ALL and T-LLy)

STUDIES**	IM#1 (HD MTX)	Delayed Intensification	IM#2 (CMTX)	Maintenance
Required Observations: Arms A-IR and B-IR (T-ALL and T-LLy)				
Hx/PE with VS/Wt (BSA)	Start of Course	Start of Course	Start of Course	Every 4 weeks
CBC/diff/plts	Prior to each MTX dose	Weekly	Prior to each MTX dose	Every 4 weeks
CSF cell count & cytospin	With each IT	With each IT	With each IT	With each IT
Bilirubin, ALT, creatinine	Prior to each MTX dose	Day 1, 29	Prior to each MTX dose	Prior to each 12 wk cycle
Thiopurine metabolites				As clinically Indicated [1,2]
Required Observations: Patients receiving bortezomib (Arm B-IR) ONLY (T-ALL and T-LLy)				
Pulse Oximetry (O2 saturation) and Chest x-ray		X[8]		
Electrolytes including PO_4		Start of Course[6]		
Required Observations: T-LLy ONLY				
Chest CT/Chest x-ray[3]				Completion of Therapy[3]
Abdomen/Pelvis CT or MRI				Completion of Therapy[4]
Bone scan[5]				Completion of Therapy
Diagnostic Biopsy/Cytology[7]				At relapse[7]
PET scan[#]				Post-treatment[#]
Optional Observations: T-ALL and T-LLy				
Optional Banking/Biology[7]				At relapse[7]

[1]For patients in whom TPMT and/or NUDT15 genotyping was not previously performed (see Section 5.10).

[2]Recommended only for HR-ALL patients during any Maintenance cycle in which 6MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (Section 5.10).

[3]Obtain chest CT for all patients at Baseline and at end-Induction. The baseline chest CT may be delayed until the patient is stable. If patient has CR at end-Induction, no subsequent chest CT is required but a chest x-ray will be performed at end-Consolidation and end of therapy. If patient does not have CR at end-Induction, a chest CT will be performed at end-Consolidation. If patient has CR at end-Consolidation, a chest x-ray will be performed at end of therapy. If patient does not have CR at end-Consolidation, a chest CT will be performed at end of therapy. For patients who had PET-CT at diagnosis, a PET-CT can be used instead of standard CT to follow disease response.

[4] Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at Baseline are negative, no repeat scans are required.

[5] Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease. . A PET scan can be used as substitute for bone scan; however, a bone scan is preferred in patients with bone symptoms.

[6] Bortezomib has been associated with hyponatremia, hypophosphatemia, and hypokalemia in some studies. Serum phosphorus should be checked at the beginning of Delayed Intensification. See Section 5.2.3 for optional recommendations on correction and monitoring.

[7] **T-ALL:** Done as part of AALL08B1 or APEC14B1

[7] **T-LLy**: If enrolled on APEC14B1, submit as a part of APEC14B1. If not enrolled on APEC14B1, submit as part of this protocol (see Section 13.6 for details)

[8] Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

Patients with post treatment residual masses only

7.5 Required & Optional Clinical, Laboratory and Disease Evaluations for Arm A-VHR and Arm B-VHR (T-ALL and T-LLy)

STUDIES**	3 HR BFM Blocks	Delayed Intensification	IM (CMTX)	Maintenance
Required Observations: Arms A-VHR and B-VHR				
Hx/PE with VS/Wt (BSA)	Start of each Block	Start of Course	Start of Course	Every 4 weeks
CBC/diff/plts	Start of Course & every 2 days after completion of chemotherapy	Weekly	Prior to each MTX dose	Every 4 weeks
CSF cell count & cytospin	With each IT	With each IT	With each IT	With each IT
Bilirubin, ALT, creatinine	Start of Course	Day 1, 29	Prior to each MTX dose	Prior to each 12 wk cycle
T-ALL only: Bone Marrow MRD & cytomorphology Assessment	End of 3 HR BFM blocks[8,9]			
Thiopurine metabolites				As clinically Indicated [1,2]
Required Observations: Patients receiving bortezomib (Arm B-VHR T-ALL and T-LLy) ONLY				
Pulse Oximetry (O2 saturation) and CXR[3]		X[10]		
Electrolytes including PO_4		Start of Course[6]		
Required Observations: T-LLy ONLY				
Chest CT[3]	End of 3 HR BFM blocks			Completion of Therapy[3]
Abdomen/Pelvis CT or MRI	End of 3 HR BFM blocks			Completion of Therapy[4]
Bone scan[5]	End of 3 HR BFM blocks			Completion of Therapy
Diagnostic Biopsy/Cytology (bilateral Bone Marrow aspirate and biopsy) [8,9]	End of 3 HR BFM blocks if PR or NR			At relapse[8]
PET scan[#]				Post-treatment[#]
Optional Observations: T-ALL and T-LLy				
Optional Banking/Biology [8]				At relapse [8]

[1]For patients in whom TPMT and/or NUDT15 genotyping was not previously performed (see Section 5.10).
[2]Recommended only for HR-ALL patients during any Maintenance cycle in which 6MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.10).
[3]For patients who had PET-CT at diagnosis, a PET-CT can be used instead of standard CT to follow disease response.
[4]Reimage if positive at end of consolidation.
[5] Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at Baseline are negative, no repeat scans are required. A PET scan can be used as substitute for bone scan; however, a bone scan is preferred in patients with bone symptoms.
[6] Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease.
[7] Bortezomib has been associated with hyponatremia, hypophosphatemia, and hypokalemia in some studies. Serum phosphorus should be checked at the beginning of Delayed Intensification. See Section 5.2.3 for optional recommendations on correction and monitoring.
[8] **T-ALL:** Done as part of AALL08B1 or APEC14B1
T-LLy: If enrolled on APEC14B1, submit as a part of APEC14B1. If not enrolled on APEC14B1, submit as part of this protocol (see Section 13.6 for details)
[9] T-ALL Only. See Section 14.1 for details
[10] Patients who have detectable MRD and/or are not in morphologic remission at the end of 3 HR BFM blocks are removed from protocol therapy
[11] Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.
#Patients with post treatment residual masses only

7.6 **Studies Suggested to be Obtained After Stopping Therapy (T-ALL Patients)**

Note: See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org

1st year	PE, CBC/diff/platelets q 4 weeks, CXR, BMA, CSF, as clinically indicated*
2nd year	PE, CBC/diff/ platelets q 2 months CXR, as clinically indicated*
3rd year	PE, CBC/diff/ platelets q 3 months CXR, as clinically indicated*
4th year	PE, CBC/diff/ platelets q 6 months CXR, as clinically indicated*
5th year	PE, CBC/diff/ platelets q 6-12 months

* Obtain at any point after the end of therapy when it is clinically indicated.

7.7 **Studies Suggested to be Obtained After Stopping Therapy (T-LLy Patients)**

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org

1st year	PE, CBC/diff/platelets q 3 months CT of primary site, BMA, CSF, as clinically indicated*
2nd year	PE, CBC/diff/ platelets q 3 months CT of primary site, as clinically indicated*
3rd year	PE, CBC/diff/ platelets q 4 months CT of primary site, as clinically indicated*
4th year	PE, CBC/diff/ platelets q 6 months CT of primary site, as clinically indicated*
5th year	PE, CBC/diff/ platelets q 12 months

* Obtain at any point after the end of therapy when it is clinically indicated.

7.8 **At Relapse**

T-ALL patients who relapse should have samples of bone marrow sent to the Molecular Reference Laboratory for cell banking as part of AALL08B1 or Project:EveryChild (APEC14B1, if open for ALL relapse specimens).

T-LLy patients who enrolled on APEC14B1: T-LLy patients who relapse should have samples of bone marrow sent to the Molecular Reference Laboratory for cell banking as part of Project:EveryChild (APEC14B1).

T-LLy patients who did not enroll on APEC14B1: samples should be sent as part of this protocol (See Section 13.6)

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Relapse/ progressive disease
b) VHR T-ALL who have an M2/M3 marrow and/or detectable MRD at the end of the 3 HR Intensification Blocks
c) VHR T-LLy with biopsy-proven persistent disease and/or morphologically positive bone marrow at end of 3 HR Intensification Blocks
d) Identified to have Ph+ T-ALL*
e) Identified to have Ph+ T-LLy**
f) Refusal of further protocol therapy by patient/parent/guardian.
g) Completion of planned therapy
h) Physician determines it is in patient's best interest
i) Development of a second malignancy
j) Inevaluable
k) Adverse events requiring removal from protocol therapy

[#]As assessed by CT with persistent active disease by biopsy or morphologically positive bone marrow at end of 3 HR Intensification Blocks

*Ph+ T-ALL patients are not eligible for post-induction therapy on AALL1231 and should be removed from protocol therapy prior to Day 15 of Induction therapy.
**Ph+ T-LLy patients are not eligible for post-induction therapy on AALL1231 and should be removed from protocol therapy prior to or at the end of Induction.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence) with the exception of COG AALL1421, a Phase 2 study of IV pegcrisantaspase, a pegylated Erwinia asparaginase, as a replacement for pegaspargase in patients with pegaspargase hypersensitivity.
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design and Endpoints

This is a randomized Phase III trial, with patients randomized 1:1 to backbone chemotherapy +/- bortezomib. Patients will be stratified at enrollment as T-ALL or T-LLy and will be randomized within each stratum.

Primary Endpoint: Comparison of EFS between modified ABFM backbone +/- bortezomib in all randomized patients.

Secondary Endpoints:

(a) To compare EFS and cumulative incidence rates for isolated CNS, isolated bone marrow, and combined bone marrow relapse between IR patients on the non-bortezomib containing arm of this study (no CRT) with similar patients on AALL0434 (+ CRT)
(b) To assess toxicities associated with administering modified standard therapy for T-ALL and T-LLy, which includes dexamethasone and additional doses of pegaspargase.

(c) To compare EFS between VHR T-ALL patients treated with HR BFM intensification blocks who become MRD negative and those who remain MRD positive at the end of HR Block 3. Comparison of EFS between VHR T-LLy patients treated with HR BFM intensification blocks who have PR or CR with those who do not respond (NR).

9.2 Patient Accrual and Expected Duration of Trial

Based on accrual rates observed on AALL0434, this study is projected to accrue around 250/year T-ALL and 75/year T-LLy patients. This study is expected to accrue up to a maximum of 1400 patients over a 4.4 year period with a minimum follow up of 3 years, adjusting for ineligible and inevaluable patients, patient withdrawals, and losses due to other reasons.

Projected distribution of accrual by risk group:
Standard Risk (SR) T-ALL: 40-50% of T-ALL patients;
Intermediate Risk (IR) T-ALL: 35-50% of patients;
Very High Risk (VHR) T-ALL: 10-15% of patients;
SR T-LLy: 65% of T-LLy patients;
IR T-LLy: 25% of T-LLy patients; and,
VHR T-LLy: <10% of T-LLy patients.

9.3 Statistical Analysis Methods

9.3.1 Power Calculation for Phase 3 Bortezomib Primary End-point:

With 1200 eligible, evaluable patients randomized to the +/- bortezomib arms, there is 90.5% power to detect improvement in 4-year EFS from 85% to 90% with an alpha of 0.05, using a one-sided log rank test (HR =0.6483) (comparison of the two EFS curves). There is sufficient power to detect a difference if the baseline EFS is different from the projected 85%. A baseline 4 year-EFS of 80% would allow detection of an improvement to 85% (HR=0.7283), with power of 82.1%; and there is 83.4% power to detect an improvement in EFS from 88% to 92% (HR=0.6523). Interim monitoring for efficacy and futility will be performed. The efficacy stopping boundaries to be used will allocate greater importance to the later analyses. The upper boundaries selected are based on the alpha × $(\text{time})^2$ spending function. The study will also be monitored for futility using the method of Freidlin and Korn. The lower boundaries are based on repeated testing of the alternative hypothesis at the 0.05 level (1-sided). The comparative analyses of regimen outcome will occur at approximately 20%, 40%, 60%, 80% and 100% of the projected combined EFS event horizon (217 events assuming baseline EFS rate of 85%) for the overall randomized group.

9.3.1.1 Amendment #6 (05/29/2019)

The COG DSMC recommended permanent closure of the study to accrual during the spring 2019 meeting; primarily due to concerns about the impact the positive results from AALL0434 for the nelarabine randomization could have on the conduct and interpretability of AALL1231. With the permanent closure to accrual as of 05/24/2019, this study will not have the required number of randomized patients (+/- Bortezomib) to have sufficient power to meet the primary objective. Last patient was randomized in November 2017. Per the recommendation of the DSMC, final analyses comparing EFS for the randomized arms, will be conducted based on the 3/31/2020 database freeze.

9.3.2 Secondary End-points:

Power calculation for CNS therapy changes primary end-point: The risk group definitions on this proposed study are different than AALL0434, and EOC MRD data will not be available on many AALL0434 patients. In order to determine if eliminating CRT and the multiple backbone modifications affect EFS and relapse rates, similar populations must be compared.

Any subject on either trial who is all of the following: [<9.99 years old, initial WBC <50,000/mm^3, day 29 MRD <0.1%, CNS1, testicular disease negative, not steroid pretreated] will be eliminated from the analysis, because they did not receive CRT on 0434 and will not receive CRT on AALL1231. We will also eliminate any subject on either trial who is an induction failure (M3 marrow on day 29) or CNS3 because they would have received CRT on 0434 and will still get CRT on AALL1231. Outcomes (EFS) for the remaining patients (about 49% of all T-ALL patients) on both studies will be compared. It is important not only to compare CNS relapse rates but also to compare BM, combined BM and CNS, and total relapse rates, because the elimination of prophylactic CRT may change the distribution of relapse, but not change overall relapse rate. Cumulative incidence rates for isolated CNS, isolated marrow, and combined marrow relapses will be monitored for these patients and compared with that seen for similar patients on AALL0434. Assuming approximately 584 patients (as identified by our definitions earlier excluding various subgroups) in 0434 meet these criteria and received CRT, there will be around the same number of patients who meet these criteria on this study and will not be getting CRT. Outcomes on AALL0434 are blinded at this time, hence the table below gives the power and detectable differences in cumulative incidence rates assuming a range of baseline rates on AALL0434 for the different types of relapse (isolated CNS, isolated marrow, combined marrow+CNS) for the above monitoring, using a one-sided log-rank test with a 5% significance level. Interim monitoring will be done using an alpha x (time)^2 spending function with 5 looks occurring at 20%, 40%, 60%, 80%, and 100% information.

Comparison of 2-year cumulative incidence rates on AALL0434 vs. AALL1231	Hazard ratio	Total expected events	Power
1.5% vs. 4%	2.7	32	81%
2% vs. 4.7%	2.38	39	80%
2.5% vs. 5.5%	2.23	47	81%
3% vs. 6.2%	2.1	54	81%
3.5% vs. 6.8%	1.98	60	80%

Evaluation of the modified backbone: Event-free survival (EFS) of patients treated on the control arm (no bortezomib) of AALL1231 will be compared with the EFS and OS of patients treated on the control arm (no nelarabine and Capizzi MTX with PEG-ASP arm) of the previous study AALL0434. Safety data will also be compared between the two arms.

Evaluation of HR blocks:
The proportion of VHR T-ALL patients with EOC MRD ≥0.1% who become MRD negative (MRD undetectable) after the three high-risk BFM blocks of therapy, will be estimated. EFS for these patients (who continue on chemotherapy) will be compared with those who continue to have detectable MRD and who may receive other treatment options including HSCT. It is anticipated that there will be about 100 – 120 VHR T-ALL patients accrued on this study. With this, the proportion who become MRD negative after the HR blocks can be estimated with a maximum standard error of 5%. It is projected that 80% of patients will become MRD negative after the HR blocks. With small numbers, the comparison of EFS between the two groups above will be essentially descriptive.

There will be a total of about 25 to 30 VHR T-LLy patients on study. Comparison of EFS between VHR T-LLy patients treated with HR BFM intensification blocks who are PR or CR with those who do not respond (NR) will essentially be descriptive due to small patient numbers.

9.3.3 Interim Monitoring

Induction Mortality. It is expected that a small percentage of patients will experience treatment related mortality (TRM) during induction. It is possible that induction mortality may increase based on the modifications that include dexamethasone, an additional dose of PEG-ASP, and +/- bortezomib randomization. Induction deaths on the two randomized arms will be closely monitored. The induction mortality rate on UKALL 2003 was 2.4% for patients treated with the anthracycline containing induction, dexamethasone at 6mg/m^2/day, and an extra dose of pegaspargase on day 18. This TRM rate is quite similar to that seen in other recent studies using a four-drug induction regimen, including AIEOP-BFM ALL 2000 (2% on dexamethasone-containing arm) and COG AALL0232 (2.16% for AYA pts vs. 1.67% for younger pts.[46,47,51] Due to the changes in induction compared to previous trials, the overall induction death rate will be closely monitored. All patients enrolled on study who receive induction will be included in this monitoring. Assuming a 'null' induction mortality rate of 2.5%. A Pocock boundary (truncated at 3 standard deviations) with 7 interim looks (after first 100 patients and then after every 200 patients enrolled, up to the first 1000 patients). The probability of crossing the boundary at any time when the true induction mortality rate is 2.5% is 10%. The boundary is given in the table below. If the boundary is crossed, the study will be temporarily closed for review of deaths and possible modifications to therapy.

Sample size	Number of induction deaths to trigger concern (Pocock boundary, alpha = 10%)	Percent of induction deaths that trigger concern (Pocock boundary, alpha = 10%)
100	7	7.0%
200	11	5.5%
400	17	4.25%
600	23	3.83%
800	29	3.63%
1000	35	3.50%
1200	41	3.42%

The induction death rates on the two randomized arms will also be compared and monitored closely for increased rates on the bortezomib arm. The induction death rates will be monitored using a Pocock type boundary (truncated at 3 standard deviations) to provide a greater chance of stopping early if the death rate looks excessive, using a one-sided test with an alpha of 10%. There will be 6 planned looks after every 200 patients randomized to the two arms. With this plan, there is 80% power to detect a difference if the induction death rates on the two arms are 2% vs. 4% or 3% vs. 5%. Since the induction regimen using dexamethasone and the addition of bortezomib, is hoped to result in some potential improvement in EFS, the above monitoring rule for induction deaths needs always to be considered in conjunction with EFS results (i.e., a slightly increased induction death rate would possibly be acceptable if the observed early EFS results looked promising).

Grade 4-5 infections. It is expected that a percentage of patients will experience Grade 4-5 infections. It is possible that Grade 4-5 infections may increase based on the modifications during induction that include dexamethasone, an additional dose of PEG-ASP, and +/- bortezomib randomization and during DI that include an additional dose of PEG-ASP and +/- bortezomib randomization. In AALL0232, 84.8% of subjects had a grade 3-5 infection during protocol therapy; however, only 13.7% had a grade 4 infection and 1.5% had a grade 5 infection (AALL0232, Study Progress Report, September 30 2011). The overall grade 4+ infection rate together with other toxicities of concern, among all patients will be estimated every six months at the time of interim monitoring to the COG Data Safety Monitoring Committee (DSMC). If the rate seems excessive compared to that seen on earlier studies (AALL0232, AALL0434),

the data will reviewed for possible modifications to therapy. In addition, the grade 4+ infection rates will be compared between the two randomized arms (+/- bortezomib). Significant differences will be brought to the attention of the COG DSMC for review and possible therapy modifications.

Osteonecrosis. It is expected that a modest percentage of patients will experience osteonecrosis (ON). The reported rates of osteonecrosis vary widely between studies and increased incidence occurs with older age and female gender. Three-year ON rates on CCG-1882 were 14.2% +/- 1.3% for children greater than 10 years of age.[180] On CCG-1961, the 5-year ON incidence rates were 9.9% +/-1.5% and 20% +/- 4.3% for the 10 to 15 and 16 to 21 year age groups, respectively.[181] On AALL0232, the rates in children over 10 years were 17.2% for patients randomized to receive dexamethasone and 12.6% on the prednisone arm.[182] On the St Jude Total XV ALL trial, the cumulative incidence of symptomatic ON (grade 2-4) was 14.6% +/- 1.6%.[183] Finally, on UKALL 2003 the rate of ON in intermediate risk patients of all ages, which included most of the T-ALL patients, was 9.4% (Vora, personal communication). As of February 2013, AALL0434 had a total of 85/1406 (6%) grade 2-3 osteonecrosis reported. There were no reports of grade 4 ON. It is possible that osteonecrosis rates may increase based on the increased use of dexamethasone and extra doses of PEG-ASP. The incidence of grade 2-4 symptomatic osteonecrosis will be closely monitored on the trial. Very detailed information is captured on osteonecrosis with a specific case report form on the COG ALL trials and will also be done for this study. Rates of osteonecrosis will be summarized overall, and by age-group and gender in the biannual study progress reports and reviewed by the study committee. Any indication of an increase in rates will be reviewed closely and reported to the COG DSMC for review and possible therapy modifications.

Targeted Toxicities (Bortezomib). Peripheral neuropathy and pulmonary toxicity are of special concern with bortezomib treatment, although these toxicities are more commonly found in adults than children. Both of these will be closely monitored and reported to the DSMC for biannual review and on an *ad hoc* basis as required for judging the safety of bortezomib. In addition, the specific dose modifications and supportive care guidelines are provided in Section 5.2.

Adverse Event Monitoring

The study will be monitored to ensure that bortezomib is feasible and does not result in excessive toxicities or death during induction or DI. In addition, the study will be monitored to ensure changes in the backbone do not result in excessive toxicities. As described above, specific monitoring rules will be followed for TRM, grade 4-5 infections, osteonecrosis, peripheral neuropathy, and pulmonary toxicity. The incidence rates of the following key adverse events (in addition to any Grade 4 non hematologic toxicities) will be estimated across all patient subgroups on this trial.

1. CNS hemorrhage requiring medical intervention (Grade 2 and higher)
2. GI bleed requiring operative or interventional radiology intervention (Grade 3 and higher)
3. Pancreatitis requiring medical intervention (Grades 2 and higher)
4. Transient ischemic attacks (All grades)
6. Stroke (All grades)
7. Encephalopathy (Grade 3 and higher)
8. Neuropathy; motor or sensory, interfering with ADL (Grade 3 and higher)*
9. Seizure (Grade 2 and higher)
10. Allergic reaction (Grade 3 and higher)
11. Ileus (Grade 3 and higher)

12. Mucositis/stomatitis; functional (Grade 3 and higher)
13. Bilirubin (Grade 3 and higher)
14. Thrombosis (Grade 3 and higher)
15. Hyponatremia (Grade 3 and higher)
16. Hypophosphatemia (Grade 3 and higher)
17. Osteonecrosis (Grade 2 and higher)

9.4 Gender and Minority Accrual Estimates

Based on the distribution derived from AALL0434, the gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	57	144	201
Not Hispanic or Latino	320	879	1199
Ethnic Category: Total of all subjects	377	1023	*1400
Racial Category			
American Indian or Alaskan Native	1	6	7
Asian	22	56	78
Black or African American	64	148	212
Native Hawaiian or other Pacific Islander	5	8	13
White	285	805	1090
Racial Category: Total of all subjects	377	1023	*1400

* These totals must agree

9.5 Correlative Studies

9.5.1 Minimal Residual Disease Determination at Serial Time Points During Therapy

Patients with newly diagnosed T-ALL will have MRD measured in the bone marrow (BM) at the end of the first block of Induction therapy (Day 29). Those patients (~50%) with MRD levels <0.01% in BM at Day 29 will be considered Standard Risk and assigned to the least intensive cytotoxic therapy. For the remaining patients (~50%), MRD will be assessed in BM at the end of Consolidation (EOC) therapy. Those with MRD <0.1% (~40%) will be considered Intermediate Risk and receive intermediate intensity therapy. The remainder (~10%) will be considered Very High Risk and receive intensified therapy followed by an additional MRD assessment with those positive for MRD taken off study. Specimens from all patients will also be assayed at study entry in order to define an abnormal phenotype that will facilitate detection of MRD.

Part of the diagnostic immunophenotyping at study entry will include the marginal cost for early thymic precursor (ETP) sub classification, a subset whose outcome is an important secondary endpoint of the study. Early studies suggested patients with ETP ALL do poorly, but more recent data suggest the prognosis may not be dire (see Section 2.2 for background and rationale on ETP ALL). It is critical to understand whether or not ETP phenotype independently predicts outcome in T-ALL. Multivariate analysis will be performed to determine if ETP ALL is an independent predictor of poor outcome based on MRD rates at End Induction and End of Consolidation. Preliminary data suggest ETP represents 12.4% of

T-ALL in AALL0434, yielding 118 ETP patients of the 952 T-ALL anticipated on AALL1231. There are few data available to predict the proportion of ETP+ patients that will have MRD <0.1% at EOC. Overall, we expect that ~10% of T-ALL patients will have MRD ≥0.1% at EOC while ~90% will have MRD <0.1%. Given the known higher percentage of end induction MRD+ patients among the ETP+ subset, we hypothesize that ~50% of ETP+ patients (n=59) will have MRD ≥0.1% at EOC (5-fold higher rate than MRD-negative), while ~50% (n=59) will have MRD <0.1%. If the 4-year EFS of these ETP+, EOC MRD <0.1% patients is ~50% or better, it would suggest that ETP patients can be risk stratified based on MRD alone (unless there is a specific therapy available for ETP patients). However, if this assumption is incorrect and ETP+ patients with MRD <0.1% at EOC have an EFS < 50%, it would suggest that MRD alone cannot be used to risk stratify these patients and alternative strategies (stem cell transplant in CR1 or other novel therapies) should be pursued for all ETP patients. Hence, we will see if the lower limit of the 95% confidence interval for the 4-year EFS estimate for ETP+, EOC MRD <0.1% patients exceeds 50%. With a sample size of 59 ETP+, EOC MRD < 0.1% cases (assuming no censoring before 4 years), the lower bound on an exact 95% CI for 4-year EFS will exceed 50% with at least 86% probability (=Prob[number event free at four years is at least 38]) if the true 4-year EFS is at least 70%. The EFS will also be compared between ETP+, EOC MRD<0.1% versus ETP+, EOC MRD≥0.1%. Due to small numbers (59 patients in each group), this comparison will essentially be descriptive.

Patients with T-LLy will have the level of marrow involvement assessed at diagnosis to facilitate risk stratification into Standard and Intermediate risk groups. T-LLy patients will also be assessed for MRD at Day 29, as this study will enroll more T-LLy patients than any to date and offers a unique opportunity to establish risk factors for this understudied patient population. We hypothesize that T-LLy patients with <0.01% MRD at End of Induction will have the best outcome, consistent with existing data in T-ALL. No data exist on the frequency of marrow MRD following therapy for T-LLy, although the frequency of marrow involvement at diagnosis > 0.01% is 66% in AALL0434. Assuming that about 80% of T-LLy patients will have MRD < 0.01% at End of Induction, this yields roughly 198 T-LLy patients on this study with MRD<0.01% and 50 patients with MRD≥0.01%. Assuming an overall 4-year EFS of 80% for T-LLy, there is over 99% power to detect a difference in EFS between the two MRD groups (90% vs. 40% 4-year EFS, HR=0.1155). There is over 98% power to detect a difference in EFS if the EFS rates are 85% and 60% in the two groups (HR=0.3181).

Additional statistical details are included in Appendix XI.

9.5.2 Evaluating Mechanisms of Bortezomib Response and Mechanisms of Bortezomib Resistance in T- ALL

Statistical analysis, including sample sizes are included in Appendix XII.

9.5.3 Identifying Biomarkers and Mechanisms of Chemotherapy Resistance and Response in T-ALL, Focusing on ETP ALL

Statistical analysis, including sample sizes are included in Appendix XII.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (i.e., v4.02 and all subsequent iterations prior to version 5.0).

10.2 T-ALL and T-LLy: Relapse

Any recurrence of disease whether in marrow or extramedullary. Relapse should be histopathologically/biopsy confirmed.

10.2.1 CNS Relapse

Positive cytomorphology and WBC ≥ 5/μL OR clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome. If any CSF evaluation shows positive cytomorphology and < 5 WBC/μL, a second CSF evaluation is required within 2-4 weeks. While identification of a leukemic clone in CSF by flow cytometry (CD2, CD3, CD34, or the same T-cell immunophenotypic markers that were identified at diagnosis) or FISH for diagnostic karyotypic abnormality may be useful, definitive evidence of CNS involvement (i.e. WBC ≥ 5/μl or clinical signs of CNS leukemia) is required for a diagnosis of CNS relapse.

10.2.2 Testicular Relapse

Must be documented by testicular biopsy, if not associated with a marrow relapse.

10.2.3 Bone Marrow Relapse

Patients with an M3 marrow at any point after achieving remission.

10.2.4 Combined extramedullary and Bone Marrow Relapse

Patients with a CNS or testicular relapse and a M2 or M3 marrow.

10.3 T-ALL: Response

See definitions in Section 3.3.

10.4 T-LLy: Response

These criteria are derived from published international consensus guidelines.[184,185]

Prior to therapy: Patients will have a bilateral bone marrow biopsies and aspirate, CT of the neck, chest, abdomen and pelvis, CXR, and, if indicated, a bone scan. On Day 29 patients will have a repeat CT of chest and CT of areas of active disease at diagnosis (neck, abdomen, and/or pelvis), CXR and if positive at diagnosis a bone scan. Patients with morphologic evidence of bone marrow disease at diagnosis will repeat the bilateral bone marrow aspirates and biopsies (>5-25% blasts by morphology) at Day 29. At end of consolidation, patients not in a CR at the end of Induction will have repeat CT imaging of active sites of disease and if positive at end of Induction a bone scan. Patients with morphologic evidence of bone marrow disease (>5-25% blasts by morphology) at end of Induction will repeat the bilateral bone marrow aspirates and biopsies at the end of consolidation. VHR patients will have repeat imaging at the end of 3 HR BFM blocks of sites demonstrating active disease at the end of consolidation. Patients with morphologic evidence of bone marrow disease at end of consolidation will have a repeat bilateral bone marrow aspirates and biopsies at the end of the 3 HR BFM blocks. A PET scan is highly recommended but not required at diagnosis, at the end of Induction, and, if there are residual masses, at the end of Consolidation and for VHR patients if there are residual masses at the end of the 3 HR BFM blocks.

Of note, if a PET scan is obtained at baseline, PET imaging should be continued with subsequent response assessment until patient no longer has PET-avid disease. A bone scan is the preferred method to follow bone disease however, PET scan can be used as a substitute for a bone scan in patients with bone symptoms. For patients who had a PET-CT at diagnosis, a PET-CT can be used instead of a regular CT to follow disease response.

10.4.1 Complete Response (CR)

Defined as disappearance of all detectable clinical evidence of disease from all sites as determined by physical examination and appropriate imaging studies. Lymph nodes must have decreased to less or equal 1.5cm. Any macroscopic nodules in any organs detectable by CT should be gone. Bone marrow aspirate/biopsy must be morphologically normal. MRD will be sent on D29 on those patients consenting but will not be used in clinical decision making on this study.

For patients with a previous positive PET scan, PET scan must be negative.

A post-treatment residual mass of any size is considered a CR as long as it is PET negative. A negative PET is required in patients with post-treatment residual masses to be considered a CR. Patients with post-treatment residual masses must be followed by PET and remain PET negative to be considered CR.

Bone lesions that remain positive by MRI/CT and/or PET will be considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation. No new lesions.

10.4.2 Partial Response (PR)

At least a 50% decrease in the sum of the product of diameters (SPD) of the lesions of up to six of the largest dominant nodes or nodal masses. Splenic and hepatic nodules must decrease by at least 50% in their SPD. No new lesions.

In patients with a positive PET scan prior to therapy, the post-treatment PET must be positive in at least one previously involved site. No new lesions.

10.4.3 Stable Disease (SD) / No response (NR)

Failure to qualify for a PR or PD. No new lesions.

In patients with a positive PET scan prior to therapy, the PET must be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

10.4.4 Relapsed/Progressive Disease (PD)

Greater than 25% increase in the size of any lesions or appearance of new lesion(s) more than 1.5 cm in any axis. In patients with a positive PET scan prior to therapy, lesions must be PET positive.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) 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. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 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.

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

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "*Disease progression*" in the system organ class (SOC) "*General disorders and administration site conditions*". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.4.5 Second Malignancy:

A **second malignancy** is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the "***Pregnancy, puerperium and perinatal conditions"*** SOC.

There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, **pregnancy in partners of men on study needs be reported and followed in the same manner as a patient pregnancy**.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero*." Any Pregnancy loss should be be reported expeditiously, as **Grade 4 "*Pregnancy loss*" under the "*Pregnancy, puerperium and perinatal conditions*" SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*", should be reported expeditiously as **Grade 4, "*Death neonatal*" under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners

of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301)897-7497.
In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the

ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 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.

Any medical documentation supporting an expedited report (e.g., H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404.

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
<tr><td colspan="5">NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
“24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
“7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.</td></tr>
<tr><td colspan="5">[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
• All Grade 4, and Grade 5 AEs
Expedited 7 calendar day reports for:
• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
• Grade 3 adverse events</td></tr>
</table>

11.10 **Protocol Specific Additional Instructions and Reporting Exceptions**

- All Grade 3-Grade 5 pulmonary toxicities (with the exception of laryngitis) **must** be reported as SAEs. **Sites are required to complete the patient Medidata/Rave screens on-line within 24 hours of any Grade 3-5 pulmonary toxicity.**
- **Grades 1-4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.**

11.11 **Reporting of Adverse Events for <u>commercial</u> agents – CTEP-AERS abbreviated pathway**

The following are expedited reporting requirements for adverse events experienced by patients on study who have <u>not</u> received any doses of an investigational agent on this study.
Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

<u>Table B</u>
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

11.12 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 4 and higher nonhematologic Adverse Events as well as the following specific toxicities:

1. CNS hemorrhage requiring medical intervention (Grade 2 and higher)
2. GI bleed requiring operative or interventional radiology intervention (Grade 3 and higher)
3. Pancreatitis requiring medical intervention (Grades 2 and higher)
4. Transient ischemic attacks (All grades)
6. Stroke (All grades)
7. Encephalopathy (Grade 3 and higher)
8. Neuropathy; motor or sensory, interfering with ADL (Grade 3 and higher)*
9. Seizure (Grade 2 and higher)
10. Allergic reaction (Grade 3 and higher)
11. Ileus (Grade 3 and higher)
12. Mucositis/stomatitis; functional (Grade 3 and higher)
13. Bilirubin (Grade 3 and higher)
14. Thrombosis (Grade 3 and higher)
15. Hyponatremia (Grade 3 and higher)
16. Hypophosphatemia (Grade 3 and higher)
17. Osteonecrosis (Grade 2 and higher)

*Please use Balis scale (Section 5.13.6) grading for neuropathy (motor or sensory).

See Section 5.2 for identification, management and reporting of bortezomib-related toxicities.

12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

12.2 **CTA/CRADA**

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).
Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13.0 PATHOLOGY GUIDELINES FOR T-LLy

13.1 Pathology Goals

To provide accurate diagnosis and classification of pediatric lymphoblastic lymphoma through central pathologic review of morphology and immunophenotypic data. **This study is limited to T-cell lymphoblastic lymphoma (Stages II-IV)**. The central review will employ the 2008 World Health Organization (WHO) Lymphoma Classification[98] to facilitate concordance in diagnosis and correlate morphologic, immunophenotypic and cytogenetic data.

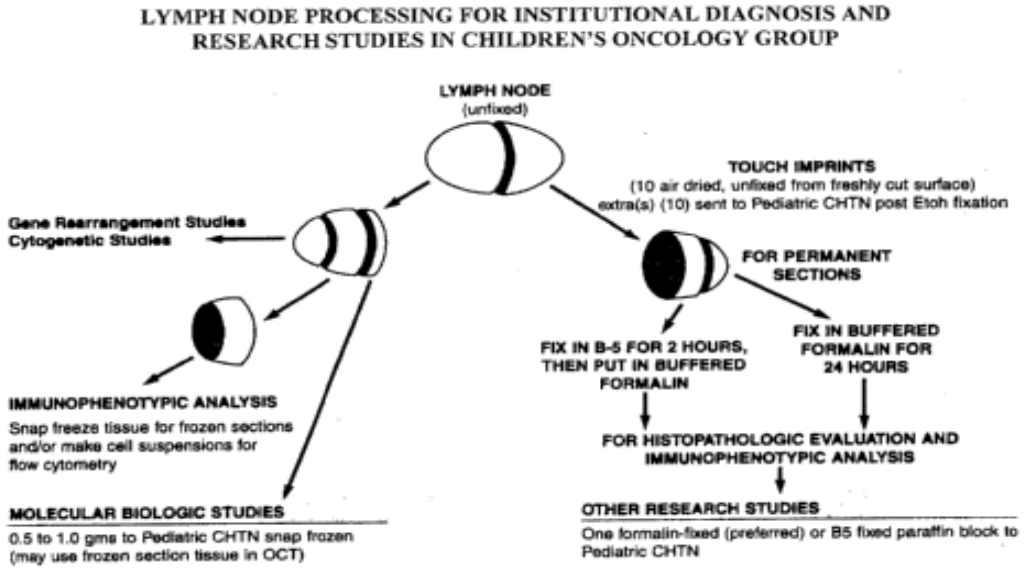
NOTE: Tissue for central review is strongly encouraged but not required for enrollment. The distinction between T-ALL and T-LLy is based on morphology on bone marrow aspirate as determined by local institutions and not by central MRD. Bilateral bone marrow aspirates and biopsies are strongly preferred but not required for study eligibility. A unilateral bone marrow aspirate for morphology and for central MRD bone marrow assessment are required to be eligible.

13.2 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions

13.2.1 Tissue Specimens

Tissue should preferentially, whenever possible, be obtained fresh and delivered immediately to the Pathology Laboratory for optimal handling and distribution (fixation, snap freezing, cytogenetics, etc.). Refer to diagram entitled 'Lymph Node Processing For Institutional Diagnosis And Research Studies In Children's Oncology Group' (Figure 13.1). Submit representative tissue sections for fixation including at least one block with 10% buffered formalin.

Figure 13.1



13.2.2 Cytology Specimens

Cytology or body fluid specimens (i.e. pleural fluid) should be delivered promptly to the pathology laboratory, and handled per primary institutional procedures. Sufficient material should be utilized for morphologic evaluation by cytocentrifuge preparations stained with a Romanowsky stain (i.e. Giemsa or Wright's stains). Provided enough specimen is available, at least one cell block should be prepared with specification of the fixative utilized and the time in fixative

13.3 **Immunophenotyping Recommendations for Primary Institutions**

For eligibility in this study, the methodology and criteria for immunophenotypic analysis defined by the submitting institution will be accepted. Recognized methods include: paraffin section immunohistochemistry, frozen section immunohistochemistry, cytocentrifuge (cytospin) immunocytochemistry, and flow cytometry.

For eligibility in this study, an extensive panel of antibodies should be employed for immunophenotypic evaluation. This can be done on snap frozen tissue by immunohistochemistry, and body fluid/cytology specimens by flow cytometry or cytocentrifuge (cytospin) immunocytochemistry. This panel of antibodies is listed as follows:

T-Cell: CD1a, CD2, CD3, CD4, CD5, CD7, CD8.
B-Cell: CD19, CD20, Kappa, Lambda.
Myeloid: CD13, CD14, CD33.
Other: CD10, CD25, CD34, CD45, TdT.

The method of TdT evaluation should be specified (i.e. flow cytometry, immunofluorescence, immunohistochemistry).

For cases in which no paraffin embedded tissue has been prepared, and only stained cytospin slides remain available, these cases will be acceptable for protocol submission and pathology review when

adequate immunophenotypic data is available from the primary institution. This situation may occur with cases evaluated by cytospin immunocytochemistry or flow cytometry immunophenotyping.

If specimen is limited, preventing a complete immunophenotypic evaluation, a recommended minimum panel of antibodies should include: CD3, CD5, CD19, CD79a and TdT. If specimen is limited to paraffin embedded tissue only, a preferred panel of antibodies should include at least: CD45RO (UCHL-1), CD79a, and TdT. If additional antibodies that may be utilized in paraffin embedded tissue are available at the primary institution, the panel may include: CD3 (polyclonal), CD43 (Leu22), CD22, PAX5[99,100], and CD45RA (4KB5). If immunophenotyping studies are not available locally, the case may be sent as a consultation case for evaluation including immunophenotyping studies to Dr. Rodney Miles (see address in Section 13.5.6).

13.4 Pathology Staging Criteria

Cerebrospinal Fluid: Leukocyte count greater than or equal to 5/µL, with presence of blasts. TdT evaluation is strongly recommended.

Bone Marrow: The presence of greater than 5% and less than 25% blasts in a bone marrow aspirate, or focal infiltration in a bone marrow biopsy, represents involvement of the marrow by lymphoblastic lymphoma.

13.5 Retrospective Central Pathology Review

13.5.1 Requested Materials

Materials to be submitted for retrospective pathology review to the COG Biopathology Center include the following:

- Initial diagnostic material prior to therapy
- Specimens demonstrating relapse of lymphoma at any time
- Specimens from residual masses demonstrating residual lymphoma or complete response to therapy
- A copy of all final pathology reports (see details in Section 13.5.1d)
- Pathology Data Collection Form
- AALL1231 Transmittal Form

Please label all materials with the patient's COG patient identification number and the institutional pathology number and block number found on the corresponding pathology report. The materials to be submitted are described below and listed in Table 13-1.

a.) Paraffin Blocks

If possible, it is preferred that paraffin blocks be submitted to the COG Biopathology Center. For surgical biopsy specimens, this should include a paraffin block of tissue prepared in 10% Buffered Formalin (as described in Section 13.5.4). For cytology specimens, a paraffin block may be available as a cell block preparation (see Section 13.5.1.5). If paraffin blocks cannot be submitted, then submit twenty (20) unstained sections (4 microns thick) of unbaked slides air-dried at room temperature from one representative block and two (2) H&E stained slides from each block. These sections should be place on sialinized slides (i.e. Fisher Superfrost Plus).

b.) Cytology Slides

When paraffin blocks have not been prepared, a cytologic preparation of one stained, air-dried cytospin slide (i.e. Romanowsky stain such as Giemsa or Wright's stain) and 10 unstained slides should be submitted.

c.) Biopsies of Residual Masses
For these biopsy specimens, send a recut slide (hematoxylin and eosin stain) from all of the paraffin blocks for review. The corresponding pathology report should accompany the slides for review.

d.) Pathology Reports
A copy of all pathology reports on each case should be submitted. This should include: Final reports of diagnostic biopsy and bone marrow specimens (even if negative) All immunophenotyping reports of diagnostic biopsy and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available) Results of any genotypic studies (i.e. gene rearrangement studies) Results of any cytogenetic (karyotypic) analysis

e.) Pathology Data Collection Forms
A separate pathology data collection form (Institutional Pathology Form) should be completed and submitted along with the above materials. Also, indicate the primary institution pathology diagnosis utilizing the WHO Lymphoma Classification[98] on the data collection form.

13.5.2 Transmittal Form
An AALL1231 specimen transmittal form must be submitted along with the pathology review materials.

13.5.3 Biopathology Center Address
All material submitted for central pathology review should be sent via regular mail or using your institutional courier account to:

COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA 1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCParaffinTeam@nationwidechildrens.org

* The room number is required. Packages not listing the room number could be denied and returned to sender.

13.5.4 Paraffin Blocks and Cytologic Slides-Storage/Return
Paraffin blocks and cytologic slides will be retained at the COG Biopathology Center indefinitely, unless the institution requests their return.

13.5.5 Lymphoma Classification
Morphologic evaluation and classification of the study cases will utilize the criteria described in the WHO Lymphoma Classification.[98] Eligible pediatric lymphomas will be classified as precursor T-cell lymphoblastic lymphoma.

13.5.6 Review Pathologists
For any questions regarding the pathology protocol, please contact:

Rodney R. Miles, MD PhD
ARUP Laboratories Hematopathology
500 Chipeta Way
Salt Lake City, UT 84108
Phone: (801) 213-3448 (801) 581-5854

Email: rodney.miles@path.utah.edu

13.6 **Preparation of Tissue Banking Samples at Time of Diagnosis or Relapse- for T-LLy patients not enrolled on Project:EveryChild (APEC14B1)**

At diagnosis, at least one square centimeter of snap frozen tumor is requested in addition to the material required for central review (described in Section 13.5). If more than 1 gram is available, cut tissue into 1 gram aliquots. Wrap each piece of tissue in a separate piece of foil and snap freeze in vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen) or cold isopentane. Label the foil with either "P" or "M" to designate whether the tissue submitted is primary or metastatic. Place tissue in the appropriate zip-lock bag (primary or metastatic) and, using a waterproof marker, label the bag with the patient's BPC number, specimen type and date obtained. Document the anatomic site of collection on the transmittal form. Store specimens at -70°C or colder until shipped. Include a transmittal form and pathology with each shipment of specimens.

If tumor tissue is obtained at the time of relapse for clinical purposes, additional material (as described above for diagnosis) is requested for banking and subsequent biologic studies.

The Biopathology Center (BPC) will bank the tissue for future distribution and use including the studies listed above.

13.6.1 Specimen Shipping Instructions

Specimen Procurement Kits for shipping frozen tumor tissue to the BPC are provided upon request. To request a Specimen Procurement Kit, use the following link:

https://ricapps.nationwidechildrens.org/KitManagement/

Select 'AALL1231' from the protocol list to order kits for the submission of frozen tumor tissue from T-LLy patients.

Frozen specimens must be shipped to the BPC, Monday through Thursday for delivery Tuesday through Friday.

1. Before the frozen tissue is placed into the Specimen Procurement Kit, it must first be placed in three separate layers of packaging :
    a. Place the tissue in a zip-lock bag.
    b. Place the zip-lock bag in the biohazard diagnostic envelope. Expel as much air as possible and seal the envelope securely.
    c. Place the biohazard envelope inside the Tyvek envelope. Expel as much air as possible and seal securely.
2. Place the tissue inside the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.
3. Place the transmittal form and pathology report inside the compartment.
4. Place the foam lid on top to secure specimens during shipment.
5. Close the outer lid of the Specimen Procurement Kit and tape with filament or other durable sealing tape.
6. Access Kit Management to print a Federal Express shipping label. A blank adhesive label is provided in the Specimen Procurement Kit to use when printing the shipping label.

Attach the shipping label to the top of the kit. Complete the dry ice label (UN 1845). Attach the dry ice and Exempt Human Specimen labels to the side of the kit.. Arrange for Federal Express pick-up per your usual institutional procedure or by calling 1-800-238-5355.

Ship specimens to:
COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, Room WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Email: BPCBank@nationwidechildrens.org

* The room number is required. Packages not listing the room number could be denied and returned to sender.

14.0 MRD ANALYSIS GUIDELINES AND REQUIREMENTS

14.1 Minimal Residual Disease- Required and Optional Specimens: T-ALL patients

The following MRD assessments are **required** for T-ALL patients. Bone marrow will be collected and shipped at the following time points:

- Diagnosis (done as part of AALL08B1 or Project:EveryChild)
- *End of Induction
- *End of Consolidation (IR and VHR patients with end of Induction MRD ≥ 0.01%)
- *End of High Risk Block #3 (for VHR T-ALL patients) in order to assess disease involvement in the bone marrow and for subsequent risk stratification.

***These samples will be shipped to the COG ALL Reference Flow Cytometry Lab using the shipping and handling requirements in Appendix IX.**

NOTE: Day 8 peripheral blood MRD is NOT sent on this study

14.2 Minimal Residual Disease- Required and Optional Specimens: T-LLy Only*

The following MRD assessments are **REQUIRED** for T-LLy patients as a part of AALL1231. Bone marrow will be collected and shipped at the following time point:

- Diagnosis

***NOTE: Only a unilateral specimen should be sent for MRD testing at diagnosis.**

The following MRD assessments are **OPTIONAL** for T-LLy patients as part of AALL1231. Bone marrow will be collected and shipped at the following time point to assess whether MRD can predict EFS and OS in T-LLy:

- **End of Induction

**** These samples will be shipped to the COG ALL Reference Flow Cytometry Lab using the shipping and handling requirements in Appendix IX. Only a unilateral specimen should be sent for MRD testing at end of Induction.**

15.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

Correlative studies are **optional**, and **not required** for risk-stratification or treatment assignment. These tests are not required for treatment decisions but are essential for advancing the field.

15.1 **Evaluating Mechanisms of Bortezomib Response and Resistance in T-ALL and Identifying Biomarkers and Mechanisms of Chemotherapy Resistance and Response in T-ALL, Focusing on Early Thymic Precursor (ETP) ALL.**

This optional study is open to **all** T-ALL patients (Arm A and B and is NOT limited to patients receiving bortezomib.). Peripheral blood and bone marrow will be collected. Please check the protocol website for updates.

The goal of this study is to understand the mechanisms of bortezomib action and the mechanisms of bortezomib resistance and to compare signaling pathway abnormalities between ETP ALL and non-ETP ALL. Appendix XII provides additional details regarding experimental design.

For consenting patients of Arm A and Arm B, we are requesting a pretreatment and end of Induction bone marrow sample (peripheral blood can be substituted if >80% blasts), and 4 peripheral blood samples. Peripheral blood will be collected at the following time points:

- Pre-treatment
- 4-8 hours (ideally at 6 hours) after initiating Induction chemotherapy
- 22-26 hours (ideally at 24 hours) after initiating Induction chemotherapy
- End of Induction.

If randomized to the bortezomib-containing arm post-treatment samples are timed relative to first dose of bortezomib.

See Appendix X for sample collection, processing, and shipping information for the Horton Lab.

15.2 **OPTIONAL TISSUE BANKING**

15.2.1 Studies of Genomic Variation

There is substantial evidence that both inherited germline constitutional and somatically-acquired ALL-specific genomic variation may contribute to variations in response[186-195] AALL08B1 and successor study Project:EveryChild (APEC14B1) will serve as the mechanism by which materials will be collected and banked for genomic research, all of which must be approved by the ALL Biology committee. The AALL08B1 protocol and the Project:EveryChild (APEC14B1) protocol and Manual of Procedures include information on consent, collection, shipping, processing, analysis, and storage of diagnostic samples. The same guidelines and instructions for collection, shipping, processing, analysis, and storage will be used for subsequent samples, including End of Induction, End of Consolidation, and relapse.

A blood sample at Day 29 is being requested specifically for the purpose of providing constitutional (germline) DNA from each patient. Whenever possible, an aliquot of diagnostic BM or PB will also be set aside for extraction of somatic tumor DNA. In some cases, RNA may be used as the starting material.

COG maintains an ALL cell bank that includes specimens from legacy CCG and POG ALL cell banks, COG ALL classification protocols (AALL03B1 and AALL08B1) and specimens collected prospectively from patients enrolled in current trials, including Project:EveryChild (APEC14B1). Specimens are available to any qualified investigator, from COG and non-COG institutions. Applications are submitted electronically to the Chair of the COG ALL Cell Bank Committee and reviewed by the Cell Bank Committee following established policies. In general, every effort is made to supply qualified investigators with small numbers (10-20) of non-scarce specimens. For large studies and

particularly those that request scarce specimens (e.g., those from low frequency genetic or clinical subsets, relapsed samples or sample sets containing patients of defined outcomes), the committee prioritizes the use of samples based on scientific merit to ensure adequate supply for future research questions.

Specimens from the COG ALL cell bank are supplied to investigators following scientific review and approval of their proposal. Released samples may include vials of cryopreserved cells, or aliquots of nucleic acids, depending upon the needs of the investigator and the supplies that are available. Following scientific approval, investigators must sign a formal letter of collaboration and provide evidence of local IRB approval for the proposed laboratory studies. Any proposal that involves greater than 100 patients must also be approved by CTEP prior to sample release (for banked tissue request form, see https://members.childrensoncologygroup.org/News/Newsitem.asp?ID=11427). The samples that are sent to investigators are coded.

16.0 RADIATION THERAPY GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

Radiation therapy (RT) for patients on COG protocols can only be delivered at approved COG RT facilities (per COG administrative policy 3.9).

16.1 Cranial Radiation Therapy

All CRT will be given during the 1st cycle (first 4 weeks) of Maintenance. See the tables below to determine which subjects will receive CRT.

T-ALL- Cranial Radiation Therapy

	SR	IR	VHR
CNS 1	none	none	CRT (1200 cGy)
CNS 2	none	none	CRT (1200 cGy)
CNS 3	n/a	CRT (1800 cGy)	CRT (1800 cGy)

T-LLy- Cranial Radiation Therapy

	SR	IR	VHR
CNS 1	none	none	none
CNS 2	none	none	none
CNS 3	n/a	CRT (1800 cGy)	CRT (1800 cGy)

16.1.1 Equipment and Calibration

16.1.1.1 Modality

X-ray beams with a nominal energy between 4 and 6 MV are permitted. The use of IMRT is not permitted in this study.

16.1.1.2 Calibration
Calibrations of therapy units used in this protocol shall be verified by the Radiological Physics Center (RPC).

16.1.1.3 Target Volume
The target volume consists of the entire brain and meninges, including the frontal lobe as well as posterior halves of the globes of the eyes, with the optic disc and nerve, extending superior to the vertex and posterior to the occiput. The caudal border will be below the skull base at the C2 vertebral level.

The target volume shall be defined by means of CT or conventional simulation. Care must be taken to avoid shielding the posterior orbit and cribriform plate. In case of conventional simulation, radio-opaque markers should be placed on the surface of the fleshy canthus to aid in localizing this point.

16.1.2 Target Dose

16.1.2.1 Prescription Point
The prescription point in the cranial volume is at or near the center. For multi-convergent beams, the prescription point is usually at intersection of the beam axes. Note: Regardless of the location of central axis, dose should be prescribed at or near the center of the cranial volume (midway between the maximum separation).

16.1.2.2 Dose Definition
Absorbed dose is specified in centigrays (cGy)-to-muscle.

16.1.2.3 Tissue Heterogeneity
No tissue heterogeneity corrections, such as for bone attenuation, will be made.

16.1.2.4 Prescribed Dose and Fractionation
Very High Risk T -ALL patients who are CNS 1 or 2
These patients will receive prophylactic cranial radiation, consisting of a total dose of 1200 cGy given in 8 daily fractions of 150 cGy per fraction, administered Monday through Friday.

All T-ALL and T-LLy who are CNS3
All patients who are CNS3 at diagnosis will receive cranial radiation consisting of a total dose of 1800 cGy given in 10 daily fractions of 180 cGy per fraction, administered Monday through Friday.

16.1.2.5 Dose Uniformity
Dose variations in target volume will be within +7%, -5% of prescription-point dose. (From ICRU Report 50: small high-dose volumes can be excluded from evaluation of dose uniformity but not small low-dose volumes.)

16.1.2.6 Treatment Interruptions
No corrections will be made for treatment interruptions less than 7 days. For interruptions greater than 7 days, contact the Study Radiation Oncology Coordinator.

16.1.3 Treatment Technique

16.1.3.1 Patient Position
It is recommended that the patient be treated in supine with immobilization appropriate for the child such as a face mask and well-fitting headrest.

16.1.3.2 Beam Configuration
The cranial volume is treated with two lateral, equally-weighted photon beams. Fields shall extend at least 1 cm beyond periphery of the scalp.

16.1.3.3 Field Shaping
Field-shaping will be done with blocks which are at least 5 half-value layers (HVLs) thick. Multi-leaf collimators are acceptable.

16.1.2.11 Eye Protection
A simple method to minimize lens irradiation, while treating posterior halves of eyes, is to let central axes of the horizontal cranial beams go through both orbits. The anterior edges of beams are defined by an external block or by an independently controlled collimator and meet at a point 1 cm anterior to frontal lobe meninges. Shielding blocks cover the anterior halves of eyes and protect nose and mouth. Essentially the same geometry can be achieved with by placing central axes through center of head by angling lateral fields so rays through the eyes lie in the same horizontal plane. It is acceptable to use a parallel-opposed beam-pair, without such angling, with shielding blocks that cover the anterior half of proximal eye. The dose to contralateral lens will then increase

16.2 **Testicular Radiation**
T-ALL and T-LLy patients with persistent testicular disease at end-Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. During the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy. Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. **Patients with testicular leukemia at diagnosis that clinically resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular radiation.**

16.2.1 Equipment and Calibration

16.2.1.1 Modality
High-energy photon or electron beams are permitted. Selection of energy is determined by dose uniformity criterion, and with electrons, lowest possible energy should be used to spare tissues outside target volume. IMRT is not permitted in this study.

16.2.1.2 Calibration
Calibrations of therapy machines used in this protocol will be verified by the Radiological Physics Center.

16.2.1.3 Target Volume
The target volume consists of testes in the scrotal sac. (Note: The cremasteric reflex may move testes high up in inguinal canal.) The field may be reduced as the palpably enlarged mass decreases in size during treatment.

16.2.2 Target Dose

16.2.2.1 Prescription Point
Prescription point is at or near center of planning target volume.

16.2.2.2 Dose Definition
Absorbed dose is specified as centigrays (cGy)-to-muscle.

16.2.2.3 Prescribed Dose and Fractionation
Total dose to prescription point will be 2400 cGy in 12 daily fractions of 200 cGy per fraction, administered Monday through Friday.

16.2.2.4 Dose Uniformity
Variations of dose within planning target volume will be within +7%, -5% of dose to prescription point. The uniformity requirement can be met with electron beam of appropriate energy provided bolus is used, which is simplest technique. Bolus may also be needed for photon beams to fulfill dose uniformity requirement. (From ICRU Report 50: small high-dose volumes can be excluded from evaluation of dose uniformity, but not small low-dose volumes.)

16.2.2.5 Treatment Interruptions
No corrections will be made for treatment interruptions less than 7 days. For interruptions greater than 7 days, contact the Study Radiation Oncology Coordinator.

16.2.3 Treatment Technique

16.2.3.1 Patient Position
Patient will be treated in supine position.

16.2.3.2 Field Shaping
Field shaping can be done with blocks of at least 5 HVLs thick. Multi-leaf collimators are acceptable.

16.2.3.3 Normal Tissue Sparing
Testes will be supported posteriorly and, if possible, extended caudally in order to minimize perineal irradiation. Field shall not be angled towards perineum. The penis shall be excluded from field by fixing it to skin over the symphysis pubis.

16.3 Quality Assurance Documentation

16.3.1 IROC RHODE ISLAND (FORMERLY QARC) Post Treatment Review
Patients receiving RT on this study will have a review only of the dose delivered. There is no on-treatment review and no target volume review.
Within one week of the completion of radiotherapy, the following data will be submitted:

"RT-2 Radiotherapy Total Dose Record" form.
Copy of patient's radiation therapy chart, including prescription, and daily and cumulative doses.

16.3.2 Data must be sent to

IROC Rhode Island (formerly QARC)
Building B, Suite 201
640 George Washington Highway

Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

16.3.3 Questions regarding the dose calculations or documentation should be directed to

COG Protocol Dosimetrist
IROC Rhode Island (formerly QARC)
Building B, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

16.3.4 Questions regarding the radiation therapy section of this protocol should be directed to the Study Radiation Oncology Coordinator

Samir I. Patel, MD
University of Alberta-Stollery Children's Hospital
11560 University Avenue
Edmonton, AB T6L 6J5
Phone: (780) 432-8518
Fax: (780) 432-8380
E-mail: samir.patel2@albertahealthservices.ca

16.4 Definitions of Deviation in Protocol Performance

16.4.1 Minor Deviation
Dose to prescription point differs from that in protocol between 6% and 10%.

16.4.2 Major Deviation
Dose to the prescription point differs from that in the protocol by more than 10%.

APPENDIX I: THERAPY DELIVERY MAPS – ARM A (T-ALL and T-LLy)

APPENDIX I-A

INDUCTION- Arm A (without bortezomib)

This Induction course is for patients randomized to treatment on Arm A (no bortezomib) See Section 4.3 for details.

_____ Patient name or initials _____ DOB

Patients must complete and sign the appropriate informed consent and undergo bortezomib randomization before starting Induction therapy. This Course lasts 5 weeks (35 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) Dose 1 – 1.99 30 mg 2 – 2.99 50 mg ≥ 3 70 mg	Given at time of diagnostic lumbar puncture (LP)* **OR** Day 1	May give prior to randomization **Note age-based dosing**	a. Hx/PE with VS/Wt (BSA), CBC/diff/plts b. Bilirubin (total and direct), ALT, AST creatinine c. CSF cell count & cytospin[2] d. TPMT and NUDT15 genotype (if available) e. BM MRD f. Performance status g. Pregnancy test h. BM cytomorphology i. CXR j. Cell Banking (optional) **T-LLy Only** k. Chest CT l. Abdomen/pelvis CT (or MRI) m. Bone scan n. Diagnostic biopsy/cytology[4] o. PET scan **Optional Studies T-ALL ONLY** Bortezomib Response Study (open to Arms A and B): See Section 15.1 for details p. PB sample q. BM sample **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV Push Over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15 & 22	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Dexamethasone (DEX)	PO (may be given IV)	3 mg/m²/dose BID	Days 1-28 (no taper)	Total daily dose: 6 mg/m²/day, divided BID	
DAUNOrubicin (DAUN)	IV Push/infusion Over 1-15 min	25 mg/m²/dose	Days 1, 8, 15 & 22		
PEG aspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m² **x 1 dose**	Days 4 & 18	Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 8 & 29 (Days 15 & 22 **for CNS3 ONLY)**	**Note age-based doing** **Please note CNS3**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m**

Date Due	Date Given	Day	IT ARAC ____mg	VCR ____mg	DEX ____mg ____mg	DAUN ____mg	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		-2/-1/0/LP							(a,b,f,g,h,i,j$)@ (k,l,m[8],n)[4,@] (p)[5,^] (e)$	
		1	____mg*	____mg	____mg ____mg	____mg			b,c*, d[11],n[1,5]	
		4					____IU **(1 dose)**			
		8		____mg		____mg		____mg	a, c	
		15		____mg		____mg		____mg#	a, c#,	
		18					____IU **(1 dose)**			
		22		____mg		____mg		____mg#	a, c#	
		29						____mg	a, b,c,e[3],h[10], (i ,k[12],l[7],m[8],o[9]) [4] (p,q)[5]	
		36	**Start next course (Consolidation, Appendix I-B) on Day 36 or when blood count parameters are met (whichever occurs later) Patients with Day 29 marrow M2 or M3 or MRD >5% should start as soon as possible (not wait for Day 36 or count recovery to occur.)**							

*On Day 1 **OR** at the time of diagnostic lumbar puncture (LP) if < than 72 hours from the start of protocol therapy.

$ **T-ALL:** Done as part of AALL08B1 or APEC14B1 **T-LLy**: If enrolled on APEC14B1, submit as a part of APEC14B1. If not enrolled on APEC14B1, submit as part of this protocol (see Section 13.6 for details) #CNS3 patients ONLY @Baseline ^ Pre-treatment

[1] For all patients who consent, collect at hours 0, 6 and 24. See Section 15.1 for details. [2] Obtain with each IT administration

[3] Optional for T-LLy. Required for T-ALL [4] T-LLy ONLY [5]T-ALL ONLY [6] follow-up exams only if baseline demonstrates disease.

[7] Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at Baseline are negative, no repeat scans are required.

[8] Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease. A PET scan can be used as a substitute for bone scans; however, a bone scan is preferred in patients with bone symptoms.

[9] PET scan is recommended but not required at baseline. If a PET is obtained at baseline, PET imaging should be continued with subsequent response assessments until patient no longer has PET-avid disease.

[10] **T-LLy:** only if positive at diagnosis

[11] To be performed any time during Induction [12]If a PET-CT was obtained at diagnosis, it can be used instead of a regular CT to follow response.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX I-B

CONSOLIDATION Arm-A This Consolidation course is for patients on Arm A. See Section 4.6 for details.	_____ Patient name or initials	_____ DOB

Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). Patients with Day 29 marrow M2 or M3 or MRD >5% should start as soon as possible (not wait for Day 36 or count recovery to occur.) Once Consolidation therapy has begun, interruptions for myelosuppression should occur only at Day 29. Patients with T-ALL and persistent testicular disease at end-Induction will receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Within the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (See Section 16.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 8, 15, 22 **Omit Days 15 & 22 for CNS3 patients ONLY**	**Note age-based dosing** **Please note CNS3**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[2] d. Bilirubin (total and direct), ALT, AST creatinine e. Performance Status f. BM MRD[1,4] g. Bone Marrow cytomorphology T-LLy Only h. Chest CT/CXR i. Abdomen/pelvis CT (or MRI), Bone scan, PET scan **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 30-60 minutes	1000 mg/m^2/dose	Days 1 & 29	See Section 4.6 for admin guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m^2/dose	Days 1-4, 8-11, 29-32 & 36-39		
Mercaptopurine (MP)	PO	60 mg/m^2/dose	Days 1-14 & 29-42	See Section 4.6 and Appendix VI for administration guidelines	
VinCRIStine (VCR)	IV Push over 1 min$^+$	1.5 mg/m^2/dose	Days 15, 22, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Days 15 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
T-ALL patients with biopsy proven testicular disease at end-Induction will receive testicular XRT. See Section 4.4 & Section 16.0 for additional details.					

APPENDIX I-B

CONSOLIDATION Arm-A
This Consolidation course is for patients on Arm A. See Section 4.6 for details.

_____ Patient name or initials _____ DOB

Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). Patients with Day 29 marrow M2 or M3 or MRD >5% should start as soon as possible (not wait for Day 36 or count recovery to occur.) Once Consolidation therapy has begun, interruptions for myelosuppression should occur only at Day 29. Patients with T-ALL and persistent testicular disease at end-Induction will receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Within the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (See Section 16.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **two (2)** pages.

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	IT MTX ____mg		CPM ____mg	ARAC ____mg	MP ____mg	VCR ____mg	PEG-ASP ____IU	Studies	Comments
			CNS3 T-ALL	**All other patients**							
			Enter calculated dose above and actual dose administered below								
		1$	____mg	____mg	____mg	____mg	____mg			a,b,c,d,e[5]	
		2				____mg					
		3				____mg					
		4				____mg					
		8	____mg	____mg		____mg				b,c	
		9				____mg					
		10				____mg					
		11				____mg					
		14									
		15		____mg				____mg	____IU	b,c	
		22		____mg				____mg		b,c	
		29			____mg	____mg	____mg			b	
		30				____mg					
		31				____mg					
		32				____mg					
		36				____mg				b	
		37				____mg					
		38				____mg					
		39				____mg					
		43						____mg	____IU	b	
		50						____mg		b	
		56								b,g[6], (i[7],j[8])[3]	
		57								f[1,4]	
			Start next course (Based on Risk Assignment See Section 4.1.2) on Day 57 or when blood count parameters are met (whichever occurs later).								

[1] End of Consolidation bone marrow is not performed on SR T-ALL patients. It is REQUIRED for T-ALL patients with end Induction BM MRD ≥ 0.01% ONLY

[2] Obtain with each IT administration [3] T-LLy ONLY [4] T-ALL only [5] Prior to Day 1 therapy

[6] T-LLy: Only if positive at end Induction. See section 7.0 for additional details.

[7] If patient has CR at end-Induction perform a CXR. If PR or NR at end-Induction perform a chest CT (If a PET-CT was obtained at diagnosis, it can be used instead of a regular CT to follow response)

[8] If baseline is negative, no repeat scans are required.

[$] T-ALL and T-LLy patients with persistent testicular disease at end-Induction should receive radiation to the testes during Consolidation. See Section 16.2 for details.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

THERAPY DELIVERY MAPS – ARM A-SR (T-ALL and T-LLy)

APPENDIX I-C

INTERIM MAINTENANCE with CMTX- Arm A-SR This IM course is for patients assigned to Arm A-SR. See Section 4.7 for details.	_____ Patient name or initials _____ DOB

Post-consolidation risk assignment must have been completed as described in Section 4.1. Start when ANC ≥750/µL and platelets ≥75,000/µl. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.10.1, Section 5.10.2, and Section 5.10.3. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] [1] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (CMTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m^2 **escalate by 50 mg/m^2/dose**	Days 1, 11, 21, 31 & 41	See Section 4.7 and Section 5.10 for details	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) – Dose 1 – 1.99 – 8 mg 2 – 2.99 – 10 mg 3 – 8.99 – 12 mg ≥ 9 – 15 mg	Days 1 & 31	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m^2**

Date Due	Date Given	Day	VCR ____mg	IV MTX *(escalating dose)*	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg		____mg	a,b*,c	
		2			____IU			

		11	____mg	____mg			b*	

		21	____mg	____mg			b*	
		22			____IU			

		31	____mg	____mg		____mg	b*,c	

		41	____mg	____mg			b*	

		56						
		57	**Start next course (Delayed Intensification, Appendix I-D) on Day 57 or when blood count parameters are met (whichever occurs later).**					

[1] Obtain with each IT administration

*To be performed prior to each dose of methotrexate

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Page 1 of 1

APPENDIX I-D

DELAYED INTENSIFICATION Arm A-SR (without bortezomib) This Delayed Intensification course is for patients randomized to treatment on Arm A-SR (no bortezomib) See Section 4.8 for details.	_____ Patient name or initials _____ DOB

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy. Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (may be given IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 1-15 min	25 mg/m²/dose	Days 1, 8, & 15		
PEG aspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	PEG-ASP ____IU	IT MTX _____mg	Studies	Comments
				Enter calculated dose above and actual dose administered below					
		1	____mg	____mg ____mg	____mg		_____mg	a,b,c,d	
		2							
		3							
		4				____IU			
		5							
		6							
		7							
		8	____mg		____mg			b	

		15	____mg	____mg ____mg	____mg			b	
		16							
		17							
		18				____IU			
		19							
		20							
		21							
		22						b	
			This therapy delivery map continues on the next page with Day 29.						

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

DELAYED INTENSIFICATION Arm A-SR (without bortezomib)

This Delayed Intensification course is for patients randomized to treatment on Arm A-SR (no bortezomib). See Section 4.8 for details.

Patient name or initials

DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 minutes	1000 mg/m²/dose	Day 29	See Section 4.8 for administration guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42	See Section 4.8, Section 5.13 & Appendix VII for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 1, 29 & 36	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	PEG-ASP ____IU	CPM ____mg	ARAC _____mg	TG _____mg	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29			____mg	_____mg	_____mg	_____mg	b,d,c	
		30				↓	↓			
		31				↓	↓			
		32				↓	↓			
		33					↓			
		---					↓			
		36				_____mg	↓	_____mg	b,c	
		37				↓	↓			
		38				↓	↓			
		39				↓	↓			
		40					↓			
		41					↓			
		42					↓			
		43	____mg	____IU					b	
		44								
		45								
		46								
		47								
		48								
		49								
		50	____mg						b	

		57							b	

		63							b	
		64	**Start next course (Maintenance, Appendix I-M) on Day 64 or when blood count parameters are met (whichever occurs later)**							

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

THERAPY DELIVERY MAPS – ARM A-IR (T-ALL and T-LLy)

APPENDIX I-E

INTERIM MAINTENANCE #1 with HDMTX- Arm A-IR
This IM course is only for patients randomized to Arm A-IR. See Section 4.10 for details.

_____ Patient name or initials

_____ DOB

Patients receive this block immediately after consolidation and must meet all of the following criteria: Post-consolidation risk assignment must have been completed as described in Section 4.1. Start when ANC ≥750/µL and platelets ≥75,000/µl. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.9.1, Section 5.9.2, and Section 5.9.3. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High-Dose Methotrexate (HD MTX)	IV over 24 hours	5000 mg/m^2/dose	Days 1, 15, 29 & 43	See Section 5.9 & Appendix IV for administration guidelines. **Note: 2 stage administration**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	42, 48, and 54 hours after the start of the HD MTX infusion	See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.	
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1, 15, 29 & 43	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Mercaptopurine (MP)	PO	25 mg/m^2/dose	Days 1-56	See Section 4.10, Section 5.11and Appendix VI for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 1 & 29	Deliver within 6 hours of the start of IV MTX (hr -6 to +6) **Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m^2**

Date Due	Date Given	Day	HD MTX ____mg	LCV	VCR ____mg	MP ____mg	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	____mg		____mg	____mg	____mg	a,b*,c	
		2							
		3		____mg$					
		4							
		5							

		15	____mg		____mg			b*	
		16							
		17		____mg$					
		18							
		19							

		29	____mg		____mg		____mg	b*,c	
		30							
		31		____mg$					
		32							
		33							
		34							

		43	____mg		____mg			b*	
		44							
		45		____mg$					
		46							
		47							

		56							
		57	**Start next course (Delayed Intensification, Appendix I-F) on Day 57 or when blood count parameters are met (whichever occurs later).**						

[1] Obtain with each IT administration

*To be performed prior to each dose of methotrexate

$Please document the number of doses of leucovorin administered

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX I-F

DELAYED INTENSIFICATION Arm A-IR (without bortezomib)

This Delayed Intensification course is for patients randomized to treatment on Arm A-IR (no bortezomib) See Section 4.8 for details.

_____ Patient name or initials

_____ DOB

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy. Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (May be given IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 1-15 min	25 mg/m²/dose	Days 1, 8, & 15		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) – Dose 1 – 1.99 – 8 mg 2 – 2.99 – 10 mg 3 – 8.99 – 12 mg ≥ 9 – 15 mg	Days 1, 29 & 36	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	PEG-ASP ____IU	IT MTX _____mg	Studies	Comments
				Enter calculated dose above and actual dose administered below					
		1	____mg	____mg ____mg	____mg		_____mg	a,b,c,d	
		2							
		3							
		4				____IU			
		5							
		6							
		7							
		8	____mg		____mg			b	

		15	____mg	____mg ____mg	____mg			b	
		16							
		17							
		18				____IU			
		19							
		20							
		21							
		22						b	
			This therapy delivery map continues on the next page with Day 29.						

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

DELAYED INTENSIFICATION Arm A-IR (without bortezomib)

This Delayed Intensification course is for patients randomized to treatment on Arm A-IR (no bortezomib) See Section 4.8 for details.

_____ Patient name or initials

_____ DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1, 8, 15, 43, & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	**Note age-based dosing**	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29	See Section 4.8 for administration guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m^2/dose	Days 29-42	See Section 4.8, Section 5.13 & Appendix VII for administration guidelines	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m^2**

Date Due	Date Given	Day	VCR ___mg	PEG-ASP ___IU	IT MTX ___mg	CPM ___mg	ARAC ___mg	TG ___mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29			___mg	___mg	___mg	___mg	b,d,c	
		30								
		31								
		32								
		33								

		36			___mg		___mg		b,c	
		37								
		38								
		39								
		40								
		41								
		42								
		43	___mg	___IU					b	
		44								
		45								
		46								
		47								
		48								
		49								
		50	___mg						b	

		57							b	

		63							b	
		64	**Start next course (IM #2 CMTX, APPENDIX I-G) on Day 64 or when blood count parameters are met (whichever occurs later)**							

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX I-G

INTERIM MAINTENANCE #2 with CMTX- Arm A-IR This IM course is for patients randomized to Arm A-IR. See Section 4.7 for details.	_____ Patient name or initials _____ DOB

Begin IM when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.10. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (CMTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m² **escalate by 50 mg/m²/dose**	Days 1, 11, 21, 31 & 41	See Section 4.7 and Section 5.10 for details	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1 – 1.99 — 8 mg 2 – 2.99 — 10 mg 3 – 8.99 — 12 mg ≥ 9 — 15 mg	Days 1 & 31	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	IV MTX *(escalating dose)*	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg		____mg	a,b*,c	
		2			____IU			

		11	____mg	____mg			b*	

		21	____mg	____mg			b*	
		22			____IU			

		31	____mg	____mg		____mg	b*,c	

		41	____mg	____mg			b*	

		56						
		57	**Start next course (Maintenance Appendix I-M) on Day 57 or when blood count parameters are met (whichever occurs later).**					

[1] Obtain with each IT administration

*To be performed prior to each dose of methotrexate

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

THERAPY DELIVERY MAPS – ARM A-VHR (T-ALL and T-LLy)

APPENDIX I-H

Intensification Block (1) – Arm A-VHR

This course is only for patients randomized/assigned to treatment on Arm A-VHR. See Section 4.11 for details

Patient name or initials _____ DOB _____

T-ALL patients who are M2 or M3 at the end of Consolidation should proceed directly to Intensification Block 1 without waiting for count recovery or MRD results to proceed. Patients receive this block immediately after consolidation and **must meet all of the following criteria:** Post-consolidation risk assignment must have been completed as described in Section 4.1. **T-ALL only:** Begin Intensification Block #1 after collection of end of consolidation bone marrow for MRD, when ANC ≥750/µL and platelets ≥75,000/µl, and organ function requirements are met as defined in Sections 5.9.1, 5.9.2, and 5.9.3, or whichever occurs later. **T-LLy only:** Start when ANC ≥750/µL and platelets ≥75,000/µl. This Cycle lasts 21 days and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (May be given IV)	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day, divided BID	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High dose methotrexate (HD-MTX)	IV	5000 mg/m^2/dose	Day 1	See Section 5.9 & Appendix IV for administration guidelines	
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	Days 3-4	Minimum of 3 doses given at 42, 48, and 54 hours after the start of the HD MTX infusion See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.	
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1 & 6	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Cyclophosphamide (CPM)	IV over 1-6 hours	200 mg/m^2/dose Q12 hrs x5 doses	Days 2-4	See Section 4.11 for administration guidelines	
High dose cytarabine (ARAC)	IV over 3 hours	2000 mg/m^2/dose Q12 hrs x2 doses	Day 5		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 6	Administer 3 hours after completion of the second HD-AraC infusion through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	**MTX and HC dosing:** Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg **ARAC dosing:** Age (yrs) Dose 1 – 1.99 16 mg 2 – 2.99 20 mg 3 – 8.99 24 mg ≥ 9 30 mg	Day 1	**Note age-based dosing** **Delivery within 6 hrs of IV MTX infusion**	
Filgrastim (G-CSF)	SubQ	5 mcg/kg/dose	Daily beginning on Day 7	Continue until WBC > 3000/µL	

Enter Cycle #_____ Ht_____cm Wt_____kg BSA____m^2

Date Due	Date Given	Day	DEX ___mg	IV MTX ____mg	LCV ____mg$	VCR ____mg	CPM ____mg	ARAC ____mg	PEG-ASP ____IU	ITT ____mg (MTX) ____mg (HC) ____mg (ARAC)	G-CSF ____mcg	Studies	Comments
			Enter calculated dose above and actual dose administered below										
		1	___mg ___mg	____mg		____mg				____mg (MTX) ____mg (HC) ____mg (ARAC)		a,b,c,d	
		2	___mg ___mg				____mg ___mg						
		3	___mg ___mg		____mg$		____mg ___mg						
		4	___mg ___mg				____mg						
		5	___mg ___mg					____mg ___mg					
		6				____mg			____IU				
		7									____mcg	b*	
		21	**Start next course (Intensification Block 2 Appendix I-I) on Day 22 or when blood count parameters are met (whichever occurs later).**										

[1] Obtain with each IT administration *Every 2 days after completion of chemotherapy until count recovery

$Please document the number of doses of leucovorin administered

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX I-I

Intensification Block (2) -Arm A-VHR This course is only for patients randomized to treatment on Arm A-VHR .See Section 4.12 for details.	_____ Patient name or initials _____ DOB

Start Day 1 when ANC ≥750/µL and platelets ≥75,000/µL. This Cycle lasts 21 days and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (May be given IV)	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day, divided BID	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High dose methotrexate (HD-MTX)	IV over 24 hours	5000 mg/m^2/dose	Day 1	See Section 5.9 & Appendix IV for administration guidelines	
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	Days 3-4	Minimum of 3 doses given at 42, 48, and 54 hours after the start of the HD MTX infusion See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.	
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1 & 6	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Mesna	IV	300 mg/m^2/dose Hour 0, 4, and 8 from start of each ifosfamide infusion	Days 2-4	Hydration following ifosfamide administration: If patient stops methotrexate hydration for whatever reason, need to continue until 12 hours post ifosfamide infusion.	
Ifosfamide (IFOS)	IV over 1 hr	800 mg/m^2/dose Q12 hours x5 doses	Days 2-4	Suggested hydration: Administer 3000 mL/m^2/day (125 mL/m^2/hr) using fluid containing 0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity < 1.010 and urine output > 3 mL/kg/hr prior to start of ifosfamide **Start immediately after HD-MTX**	
DAUNOrubicin (DAUN)	IV Push/infusion Over 1-15 min	30 mg/m^2/dose	Day 5		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 6	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	**MTX and HC dosing:** Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg **ARAC dosing:** Age (yrs) Dose 1 – 1.99 16 mg 2 – 2.99 20 mg 3 – 8.99 24 mg ≥ 9 30 mg	Day 1	**Note age-based dosing** **Delivery within 6 hrs of IV MTX infusion**	
Filgrastim (G-CSF)	SubQ	5 mcg/kg/dose	Daily beginning on Day 7	Continue until WBC > 3000/µL	

Intensification Block (2) -Arm A-VHR

This course is only for patients randomized to treatment on Arm A-VHR .See Section 4.12 for details.

_____ _____
Patient name or initials DOB

Enter Cycle #_____ Ht_____cm Wt_____kg BSA____m²

Date Due	Date Given	Day	DEX ___mg	IV MTX ____mg	LCV ___mg$	VCR ____mg	MESNA	IFOS ____mg	DAUN ____mg	PEG-ASP ____IU	IT MTX ____mg	IT HC ____mg	IT ARAC ____mg	G-CSF ____mcg	Studies	Comments
			Enter calculated dose above and actual dose administered below													
		1	___mg ___mg	____mg		____mg					____mg	____mg	____mg		a,b,c,d	
		2	___mg ___mg				____mg ___mg ____mg ____mg ___mg ____mg	____mg ___mg								
		3	___mg ___mg		____mg$		____mg ___mg ____mg ____mg ___mg ____mg	____mg ___mg								
		4	___mg ___mg				____mg ___mg ____mg	____mg								
		5	___mg ___mg						____mg							
		6				____mg				____IU						
		7												____mcg	b*	
		21	**Start next course (Intensification Block 3 Appendix I-J) on Day 22 or when blood count parameters are met (whichever occurs later).**													

[1] Obtain with each IT administration *Every 2 days after completion of chemotherapy until count recovery

$Please document the number of doses of leucovorin administered

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

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APPENDIX I-J

Intensification Block (3) Arm A-VHR

This course is only for patients randomized to treatment on Arm A-VHR. See Section 4.13 for details.

_____ Patient name or initials

_____ DOB

Start Day 1 when ANC ≥ 750/µL and platelets ≥ 75,000/µL. HR3 lasts 21 days. This Cycle lasts 21 days and this Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (May be given IV)	10 mg/m^2/dose BID	Days 1-5	Total daily dose: 20 mg/m^2/day, divided BID	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine, **T-ALL ONLY** e. BM MRD **T-LLy ONLY:** f. Chest CT/CXR[2] g. Abdomen/pelvis CT (or MRI)[2] h. Bone scan[2] i. Diagnostic biopsy/ cytology **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High dose cytarabine (ARAC)	IV over 3 hours	2000 mg/m^2/dose Q12 hours x 4 doses	Days 1-2		
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose Q12 hours x5 doses	Days 3-5	See Section 4.13 for administration guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 6	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	**MTX and HC dosing:** Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg **ARAC dosing:** Age (yrs) Dose 1 – 1.99 16 mg 2 – 2.99 20 mg 3 – 8.99 24 mg ≥ 9 30 mg	Day 5	**Note age-based dosing**	
Filgrastim (G-CSF)	SubQ	5 mcg/kg/dose	Daily beginning on Day 7	Continue until WBC > 3000/µL	

Enter Cycle # _____ **Ht**_____**cm** **Wt**_____**kg** **BSA**____**m^2**

Date Due	Date Given	Day	DEX ___mg	ARAC ____mg	ETOP ____mg	PEG-ASP ___IU	IT MTX ___mg	IT HC ___mg	IT ARAC ___mg	G-CSF ___mcg	Studies	Comments
			Enter calculated dose above and actual dose administered below									
		1	___mg ___mg	____mg ____mg							a,b,d	
		2	___mg ___mg	____mg ____mg								
		3	___mg ___mg		____mg ___mg							
		4	___mg ___mg		____mg ___mg							
		5	___mg ___mg		____mg		___mg	___mg	___mg		c	
		6				____IU						
		7								___mcg		
		21									**T-ALL:** b*, e **T-LLy:** b*, i, (f,g,h)[2]	
Start next course (Delayed Intensification Appendix I-K) on Day 22 or when blood count parameters are met (whichever occurs later).												

[1] Obtain with each IT administration [2] See Section 7.0 for details

*Every 2 days after completion of chemotherapy until count recovery

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX I-K

DELAYED INTENSIFICATION- Arm A-VHR (without bortezomib)

This Delayed Intensification course is for patients randomized to treatment on Arm A-VHR (no bortezomib). See Section 4.8 for details.

Patient name or initials _____

DOB _____

Patients receive this block immediately after HR Intensification 3 and must meet all of the following criteria: **VHR T-ALL** Post-HR Intensification Block 3 MRD was completed and demonstrated undetectable MRD as described in Section 4.13 Start 7 days after collection of HR Intensification Block 3 bone marrow for MRD or when ANC ≥750/µL and platelets ≥75,000/µl, whichever occurs later. **VHR T-LLy:** Post-HR Intensification Block 3 disease evaluation was completed and demonstrated a radiographic CR OR a radiographic PR and a biopsy showing no residual disease as described in Section 10.4 Start when ANC ≥750/µL and platelets ≥75,000/µl **All patients:** Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (May be given IV)	5 mg/m²/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m²/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 1-15 min	25 mg/m²/dose	Days 1, 8, & 15		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	PEG-ASP ____IU	IT MTX _____mg	Studies	Comments
				Enter calculated dose above and actual dose administered below					
		1	____mg	____mg ____mg	____mg		_____mg	a,b,c,d	
		2							
		3							
		4				____IU			
		5							
		6							
		7							
		8	____mg		____mg			b	
		15	____mg	____mg ____mg	____mg			b	
		16							
		17							
		18				____IU			
		19							
		20							
		21							
		22						b	
			This therapy delivery map continues on the next page with Day 29.						

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

DELAYED INTENSIFICATION- Arm A-VHR (without bortezomib)

This Delayed Intensification course is for patients randomized to treatment on Arm A-VHR (no bortezomib). See Section 4.8 for details.

Patient name or initials

DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15,43, & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	**Note age-based dosing**	
Cyclophosphamide (CPM)	IV over 30-60 minutes	1000 mg/m²/dose	Day 29	See Section 4.8 for administration guidelines	
Cytarabine (ARAC)	IV over 1-30 minutes or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42	See Section 4.8, Section 5.13 & Appendix VII for administration guidelines	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ___mg	PEG-ASP ___IU	IT MTX ____mg	CPM ____mg	ARAC ____mg	TG ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29			____mg	____mg	____mg	____mg	b,d,c	
		30								
		31								
		32								
		33								

		36			____mg		____mg		b,c	
		37								
		38								
		39								
		40								
		41								
		42								
		43	___mg	___IU					b	
		44								
		45								
		46								
		47								
		48								
		49								
		50	___mg						b	

		57							b	

		63							b	
		64	**Start next course (IM CMTX, APPENDIX I-L) on Day 64 or when blood count parameters are met (whichever occurs later)**							

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX I-L

INTERIM MAINTENANCE (CMTX) – Arm A-VHR This IM course is for patients randomized to Arm A-VHR. See Section 4.7 for details.	_____ Patient name or initials _____ DOB

Begin IM when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.10 This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (CMTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m² **escalate by 50 mg/m²/dose**	Days 1, 11, 21, 31 & 41	See Section 4.7 and Section 5.10 for details	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1 – 1.99 — 8 mg 2 – 2.99 — 10 mg 3 – 8.99 — 12 mg ≥ 9 — 15 mg	Days 1 & 31	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	IV MTX *(escalating dose)*	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg		____mg	a,b*,c	
		2			____IU			

		11	____mg	____mg			b*	

		21	____mg	____mg			b*	
		22			____IU			

		31	____mg	____mg		____mg	b*,c	

		41	____mg	____mg			b*	

		56						
		57	**Start next course (Maintenance, Appendix I-M) on Day 57 or when blood count parameters are met (whichever occurs later).**					

[1] Obtain with each IT administration

*To be performed prior to each dose of methotrexate

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

THERAPY DELIVERY MAP – MAINTENANCE ARM A
(T-ALL and T-LLy)

APPENDIX I-M

MAINTENANCE- Arm A

This Maintenance course is for Arm A. See Section 4.14 for details

_____ Patient name or initials _____ DOB

Maintenance begins when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. Only Mercaptopurine and PO Methotrexate will be interrupted for myelosuppression as outlined in Section 5.11. This Cycle lasts 12 weeks (84 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Thiopurine metabolites- as clinically indicated f. Optional Banking/Biology **T-LLy ONLY:** g. Chest CT/CXR h. Abdomen/pelvis CT (or MRI) i. Bone scan **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (May be given IV)	3 mg/m²/dose	Days 1-5, 29-33 & 57-61	Total daily dose: 6 mg/m²/day, divided BID	
Mercaptopurine (MP)	PO	75 mg/m²/dose	Days 1-84	See Section 4.14, Section 5.11 and Appendix VI for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m²/dose weekly	Days 8, 15, 22, **29@**, 36, 43, 50, 57, 64, 71 & 78 @**NOTE:** Omit Day 29 of Cycles 1- 4 for SR T-ALL and T-LLy patients and cycles 1- 2 for IR T-ALL and T-LLy patients	See Section 5.11 for suggested starting dose based on TPMT and NUDT15 status (if available) **Please note Day 29**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Day 1 &Day 29 of Cycles 1- 4 for **SR T-ALL and T-LLy patients ONLY.** Day 29 of Cycles 1-2 **IR T-ALL and T-LLy patients ONLY**	**Note age-based dosing** **Please note Day 29**	

Enter Cycle # _____ Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR ___mg	DEX ___mg ___mg	MP ___mg	PO MTX ___mg	IT MTX ___mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1$	_____mg	___mg ___mg	____mg		____mg	a,b,c,d	
		5							
		8				____mg			
		15				____mg			
		22				____mg			
		29	_____mg	___mg ___mg		____mg@	____mg&	a,b,c	
		33							
		36				____mg			
		43				____mg			
		50				____mg			
		57	_____mg	___mg ___mg		____mg		a,b	
		61							
		64				____mg			
		71				____mg			
		78				____mg			
		84					f[5] (g[4],h[3],i[3])[2#]		
		85	**Begin next cycle on Day 85 regardless of counts and repeat until two years (for T-ALL girls and all T-LLy pts, regardless of gender) and three years (for T-ALL boys) from the start of Interim Maintenance (see Section 4.14). Only MP & PO MTX will be interrupted for myelosuppression during subsequent Maintenance cycles as outlined in Section 5.11.**						

[1] Obtain with each IT administration [2] T-LLy ONLY [3] If baseline is negative, no repeat scans are required.

[4] If CR at end-Consolidation perform a CXR; If PR or NR at end-Consolidation perform chest CT

[5] Collect ONLY if the patient relapses. **T-ALL**: as a part of AALL08B1 (or APEC14B1 if available to ALL patients) **T-LLy**: submit via APEC14B1 (if enrolled).

[$]RADIATION THERAPY (T-ALL:IR CNS3 and all VHR patients, T-LLy:CNS3 only) See Section 16.0

[#] Only collect at the completion of therapy.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II: THERAPY DELIVERY MAPS – ARM B (T-ALL and T-LLy)

APPENDIX II-A

INDUCTION- Arm B (with bortezomib) This induction is for all patients randomized to treatment on Arm B (with bortezomib). See Section 4.5 for details.	Patient name or initials _____ DOB _____

Patients must complete and sign the appropriate informed consent and undergo bortezomib randomization before starting Induction therapy. This Course lasts 5 weeks (35 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Bortezomib (BOR) *IND#58443*	IV push over 3-5 seconds	1.3 mg/m^2/dose	Days 1, 4, 8 & 11	At least 72 hours must have elapsed between doses.	a. Hx/PE with VS/Wt (BSA) CBC/diff/plts b. Bilirubin (total and direct), ALT, AST creatinine c. CSF cell count & cytospin[2] d. Electrolytes including PO_4 e. TPMT and NUDT15 genotype (if available) f. BM MRD g. Performance status h. Pregnancy test i. BM cytomorphology j. CXR k. Pulse oximetry & Chest CXR [7] l. Cell banking **T-LLy only** m. Chest CT n. Abdomen/pelvis CT (or MRI) o. Bone scan p. Diagnostic biopsy/ cytology q. PET scan **Optional Studies T-ALL ONLY** Bortezomib Response Study (open to Arms A and B): See Section 15.1 for details r. PB sample (optional) s. BM sample (optional) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Cytarabine (IT ARAC)	IT	Age (yrs) / Dose 1 – 1.99 / 30 mg 2 – 2.99 / 50 mg ≥ 3 / 70 mg	Given at time of diagnostic lumbar puncture (LP)* **OR** Day 1	May give prior to randomization **Note age-based dosing**	
VinCRIStine (VCR)	IV Push Over 1 min$^+$	1.5 mg/m^2/dose	Days 1, 8, 15 & 22	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Dexamethasone (DEX)	PO (May be given IV)	3 mg/m^2/dose BID	Days 1-28 (no taper)	Total daily dose: 6 mg/m^2/day, divided BID	
DAUNOrubicin (DAUN)	IV Push/infusion Over 1-15 min	25 mg/m^2/dose	Days 1, 8, 15 & 22		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/**dose**	Day 4 and 18	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 8 & 29 (Days 15 & 22 **for CNS3 ONLY)**	**Note age-based doing** **Please note CNS3**	

Page 1 of 2

INDUCTION- Arm B (with bortezomib)

This induction is for all patients randomized to treatment on Arm B (with bortezomib). See Section 4.5 for details.

Patient name or initials _____ DOB _____

Therapy Delivery Map **Ht** ____ **cm** **Wt** ____ **kg** **BSA** ____ **m²**

Date Due	Date Given	Day	BOR ____mg	IT ARAC ____mg	VCR ____mg	DEX ____mg ____mg	DAUN ____mg	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
				Enter calculated dose above and actual dose administered below							
		-2/-1/0/LP*								(a,b,d,g,h,i,j, m, n, o, p)[4@] (r)[5,^] (f, l)[$]	
		1	____mg	____mg	____mg	____mg ____mg	____mg			a,b,c*,d, e[11],k[7],q[4]	
		4	____mg					____IU **(1 dose)**		k[7]	
		8	____mg		____mg		____mg		____mg	a,c, k[7]	
		11	____mg							k[7]	
		15			____mg		____mg		____mg#	a,c#,	
		18						____IU **(1 dose)**			
		22			____mg		____mg		____mg#	a,c#	
		29							____mg	a,b,c,f[8],i[1], (j,m,n[9],o[10], q[12])[4] (r, s)[5]	
		36	**Start next course (Consolidation, Appendix II-B) on Day 36 or when blood count parameters are met (whichever occurs later). Patients with Day 29 marrow M2 or M3 or MRD >5% should start as soon as possible (not wait for Day 36 or count recovery to occur.)**								

*On Day 1 **OR** at the time of diagnostic lumbar puncture (LP) if < than 72 hours from the start of protocol therapy.

^Pre –treatment

$ **T-ALL:** Done as part of AALL08B1 or APEC14B1 **T-LLy**: If enrolled on APEC14B1, submit as a part of APEC14B1. If not enrolled on APEC14B1, submit as part of this protocol (see Section 13.6 for details)

#CNS3 patients ONLY @Baseline

1 **T-LLy:** only if positive at diagnosis

[2] Obtain with each IT administration

[3] Optional for T-LLy. Required for T-ALL

[4] T-LLy ONLY

[5] T-ALL ONLY

[6] To be collected at hours 0, 6 and 24 relative to the first dose of bortezomib. See Section 15.1 for details

[7] Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

[8] follow-up exams only if baseline demonstrates disease

[9] Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at Baseline are negative, no repeat scans are required.

[10] Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease.

[11] To be performed any time during Induction

[12] PET scan is recommended but not required at baseline. If a PET is obtained at baseline, PET imaging should be continued with subsequent response assessments until patient no longer has PET-avid disease.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II-B

CONSOLIDATION Arm-B This Consolidation course is for patients on Arm B. See Section 4.6 for details.	_____ _____ Patient name or initials DOB

Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). Patients with Day 29 marrow M2 or M3 or MRD >5% should start as soon as possible (not wait for Day 36 or count recovery to occur.) Once Consolidation therapy has begun, interruptions for myelosuppression should occur only at Day 29. Patients with T-ALL and persistent testicular disease at end-Induction will receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Within the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (See Section 16.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 8, 15, 22 **Omit Days 15 & 22 for CNS3 patients ONLY**	**Note age-based dosing** **Please note CNS3**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[2] d. Bilirubin (total and direct), ALT, AST creatinine e. Performance Status f. BM MRD[1,4] g. Bone Marrow cytomorphology T-LLy Only h. Chest CT/CXR i. Abdomen/pelvis CT (or MRI), Bone scan, PET scan **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 30-60 minutes	1000 mg/m^2/dose	Days 1 & 29	See Section 4.6 for admin guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m^2/dose	Days 1-4, 8-11, 29-32 & 36-39		
Mercaptopurine (MP)	PO	60 mg/m^2/dose	Days 1-14 & 29-42	See Section 4.6 and Appendix VI for administration guidelines	
VinCRIStine (VCR)	IV Push over 1 min$^+$	1.5 mg/m^2/dose	Days 15, 22, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Days 15 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
T-ALL patients with biopsy proven testicular disease at end-Induction will receive testicular XRT. See Section 4.4 & Section 16.0 for additional details.					

CONSOLIDATION Arm-B This Consolidation course is for patients on Arm B. See Section 4.6 for details.	_____ _____ Patient name or initials DOB

Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). Patients with Day 29 marrow M2 or M3 or MRD >5% should start as soon as possible (not wait for Day 36 or count recovery to occur.) Once Consolidation therapy has begun, interruptions for myelosuppression should occur only at Day 29. Patients with T-ALL and persistent testicular disease at end-Induction will receive XRT to the testes during Consolidation (a testicular biopsy is required if there is any uncertainty regarding the clinical response). Within the first two weeks of Consolidation, testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (See Section 16.2). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (2)** pages.

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	IT MTX ____mg		CPM ____mg	ARAC ____mg	MP ____mg	VCR ____mg	PEG-ASP ____IU	Studies	Comments
			CNS3 T-ALL	**All other patients**							
			Enter calculated dose above and actual dose administered below								
		1$	____mg	____mg	____mg	____mg	____mg			a,b,c,d,e[5]	
		2				____mg					
		3				____mg					
		4				____mg					
		8	____mg	____mg		____mg				b,c	
		9				____mg					
		10				____mg					
		11				____mg					
		15		____mg				____mg	____IU	b,c	
		22		____mg				____mg		b,c	
		29			____mg	____mg	____mg			b	
		30				____mg					
		31				____mg					
		32				____mg					
		36				____mg				b	
		37				____mg					
		38				____mg					
		39				____mg					
		42									
		43						____mg	____IU	b	
		50						____mg		b	
		56								b, g[6], (h[7],i[8])[3]	
		57								f[1,4]	

Start next course (Based on Risk Assignment. See Section 4.1.2) on Day 57 or when blood count parameters are met (whichever occurs later).

1 End of Consolidation bone marrow is not performed on SR T-ALL patients. It is REQUIRED for T-ALL patients with end Induction BM MRD ≥ 0.01% ONLY

2 Obtain with each IT administration 3 T-LLy ONLY 4 T-ALL only 5 Prior to Day 1 therapy

6 T-LLy: Only if positive at end Induction.

7If patient has CR at end-Induction perform a CXR. If PR or NR at end-Induction perform a chest CT

8 If baseline is negative, no repeat scans are required.

$ T-ALL and T-LLy patients with persistent testicular disease at end-Induction should receive radiation to the testes during Consolidation. See Section 16.2 for details.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Page 2 of 2

THERAPY DELIVERY MAPS – ARM B-SR (T-ALL and T-LLy)

APPENDIX II-C

INTERIM MAINTENANCE with CMTX- Arm B-SR This IM course is for patients or assigned to Arm B-SR. See Section 4.7 for details	Patient name or initials DOB

Begin IM when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.10. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (CMTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m² **escalate by 50 mg/m²/dose**	Days 1, 11, 21, 31 & 41	See Section 4.7 and Section 5.10 for details	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) – Dose 1 – 1.99 – 8 mg 2 – 2.99 – 10 mg 3 – 8.99 – 12 mg ≥ 9 – 15 mg	Days 1 & 31	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	IV MTX *(escalating dose)*	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg		____mg	a,b*,c	
		2			____IU			

		11	____mg	____mg			b*	

		21	____mg	____mg			b*	
		22			____IU			

		31	____mg	____mg		____mg	b*,c	

		41	____mg	____mg			b*	

		56						
		57	**Start next course (Delayed Intensification, Appendix II-D) on Day 57 or when blood count parameters are met (whichever occurs later).**					

[1] Obtain with each IT administration

*To be performed prior to each dose of methotrexate

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II-D

DELAYED INTENSIFICATION Arm B-SR (with bortezomib) This Delayed Intensification (DI) course is for patients randomized to treatment on Arm B-SR (with bortezomib). See Section 4.9 for details	_____ Patient name or initials _____ DOB

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy. Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Bortezomib (BOR) *IND#58443*	IV push over 3-5 seconds	1.3 mg/m^2/dose	Days 1, 4, 15 & 18	At least 72 hours must have elapsed between doses.	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Electrolytes including PO_4 f. Pulse Oximetry (O2 saturation) and CXR- Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Dexamethasone (DEX)	PO (May be given IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 1-15 min	25 mg/m^2/dose	Days 1, 8, & 15		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1,29 & 36	**Note age-based dosing**	

Therapy Delivery Map **Ht cm** **Wt kg** **BSA m^2**

Date Due	Date Given	Day	BOR ____mg	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	PEG-ASP ____IU	IT MTX _____mg	Studies	Comments
					Enter calculated dose above and actual dose administered below					
		1	____mg	____mg	____mg ____mg	____mg		_____mg	a,b,c,d,e, f*	
		2								
		3								
		4	____mg				____IU		f*	
		5								
		6								
		7								
		8		____mg		____mg			b	
		15	____mg	____mg	____mg ____mg	____mg			b, f*	
		16								
		17								
		18	____mg				____IU		f*	
		19								
		20								
		21								
		22							b	
				This therapy delivery map continues on the next page with Day 29.						

* Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

DELAYED INTENSIFICATION Arm B-SR (with bortezomib)

This Delayed Intensification (DI) course is for patients randomized to treatment on Arm B-SR (with bortezomib). See Section 4.9 for details

Patient name or initials

DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Electrolytes including PO_4 f. Pulse Oximetry (O2 saturation) and CXR- Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 [1] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	**Note age-based dosing**	
Cyclophosphamide (CPM)	IV over 30-60 minutes	1000 mg/m²/dose	Day 29	See Section 4.9 for administration guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42	See Section 4.9, Section 5.13 & Appendix VII for administration guidelines	

Therapy Delivery Map **Ht____ cm** **Wt____ kg** **BSA____ m²**

Date Due	Date Given	Day	VCR ____mg	PEG-ASP ____IU	IT MTX ____mg	CPM ____mg	ARAC ____mg	TG ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29			____mg	____mg	____mg	____mg	b,d,c	
		30								
		31								
		32								
		33								
		36			____mg		____mg		b,c	
		37								
		38								
		39								
		40								
		41								
		42								
		43	____mg	____IU					b	
		44								
		45								
		46								
		47								
		48								
		49								
		50	____mg						b	
		57							b	
		63							b	
		64	**Start next course (Maintenance, Appendix II-M) on Day 64 or when blood count parameters are met (whichever occurs later)**							

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

THERAPY DELIVERY MAPS – ARM B-IR (T-ALL and T-LLy)

APPENDIX II-E

INTERIM MAINTENANCE #1 with HDMTX- Arm B-IR

This IM course is only for patients randomized to Arm B-IR. See Section 4.10 for details.

_____ Patient name or initials

_____ DOB

Patients receive this block immediately after consolidation and must meet all of the following criteria: Post-consolidation risk assignment must have been completed as described in Section 4.1. Start when ANC ≥750/µL and platelets ≥75,000/µl. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.9.1, Section 5.9.2, and Section 5.9.3 This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
High-Dose Methotrexate (HD MTX)	IV over 24 hours	5000 mg/m^2/dose	Days 1, 15, 29 & 43	See Section 5.9 & Appendix IV for administration guidelines **Note: 2 stage administration**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	42, 48, and 54 hours after the start of the HD MTX infusion	See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.	
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1, 15, 29 & 43	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Mercaptopurine (MP)	PO	25 mg/m^2/dose	Days 1-56	See Section 4.10, Section 5.11 and Appendix VI for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 1 & 29	Deliver within 6 hours of the start of IV MTX (hr -6 to +6) **Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m^2**

Date Due	Date Given	Day	HD MTX ____mg	LCV	VCR ____mg	MP ____mg	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	____mg		____mg	____mg	____mg	a,b*,c	
		2							
		3		____mg$					
		4							
		5							

		15	____mg		____mg			b*	
		16							
		17		____mg$					
		18							
		19							

		29	____mg		____mg		____mg	b*,c	
		30							
		31		____mg$					
		32							
		33							
		34							

		43	____mg		____mg			b*	
		44							
		45		____mg$					
		46							
		47							

		56							
		57	**Start next course (Delayed Intensification, Appendix II-F) on Day 57 or when blood count parameters are met (whichever occurs later).**						

[1] Obtain with each IT administration *To be performed prior to each dose of methotrexate

$Please document the number of doses of leucovorin administered

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II-F

DELAYED INTENSIFICATION Arm B-IR (with bortezomib)
This Delayed Intensification (DI) course is for patients randomized to treatment on Arm B-IR (with bortezomib). See Section 4.9 for details

_____ Patient name or initials

_____ DOB

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to starting therapy. Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Bortezomib (BOR) *IND#58443*	IV push over 3-5 seconds	1.3 mg/m^2/dose	Days 1, 4, 15 & 18	At least 72 hours must have elapsed between doses.	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Electrolytes including PO_4 f. Pulse Oximetry (O2 saturation) and CXR- Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Dexamethasone (DEX)	PO (May be given IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 1-15 min	25 mg/m^2/dose	Days 1, 8, & 15		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Days 1, 29 & 36	**Note age-based dosing**	

Therapy Delivery Map **Ht** cm **Wt** kg **BSA** m^2

Date Due	Date Given	Day	BOR ____mg	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	PEG-ASP ____IU	IT MTX _____mg	Studies	Comments
					Enter calculated dose above and actual dose administered below					
		1	____mg	____mg	____mg ____mg	____mg		_____mg	a,b,c,d,e, f*	
		2								
		3								
		4	____mg				____IU		f*	
		5								
		6								
		7								
		8		____mg		____mg			b	

		15	____mg	____mg	____mg ____mg	____mg			b, f*	
		16								
		17								
		18	____mg				____IU		f*	
		19								
		20								
		21								
		22							b	
				This therapy delivery map continues on the next page with Day 29.						

[1] Obtain with each IT administration ^ To be performed prior to first dose of bortezomib

*Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

DELAYED INTENSIFICATION Arm B-IR (with bortezomib)

This Delayed Intensification (DI) course is for patients randomized to treatment on Arm B-IR (with bortezomib). See Section 4.9 for details

Patient name or initials

DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Electrolytes including PO_4 f. Pulse Oximetry (O2 saturation) and CXR- Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	**Note age-based dosing**	
Cyclophosphamide (CPM)	IV over 30-60 minutes	1000 mg/m^2/dose	Day 29	See Section 4.9 for administration guidelines	
Cytarabine (ARAC)	IV or SubQ	75 mg/m^2/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m^2/dose	Days 29-42	See Section 4.9, Section 5.13 & Appendix VII for administration guidelines	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m^2**

Date Due	Date Given	Day	VCR ____mg	PEG-ASP ____IU	IT MTX ____mg	CPM ____mg	ARAC ____mg	TG ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29			____mg	____mg	____mg	____mg	b, c,d,e	
		30								
		31								
		32								
		33								

		36			____mg		____mg		b,c,e	
		37								
		38								
		39								
		40								
		41								
		42								
		43	____mg	____IU					b,e	
		44								
		45								
		46								
		47								
		48								
		49								
		50	____mg						b,e	

		57							b,e	

		63							b,e	
		64	**Start next course (IM#2 , APPENDIX II-G) on Day 64 or when blood count parameters are met (whichever occurs later)**							

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II-G

INTERIM MAINTENANCE #2 with CMTX- Arm B-IR This IM course is for patients randomized to Arm B-IR. See Section 4.7 for details	Patient name or initials DOB

Begin IM when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.10. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (CMTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m² **escalate by 50 mg/m²/dose**	Days 1, 11, 21, 31 & 41	See Section 4.7 and Section 5.10 for details	
Pegaspargase (PEG-ASP)	IV over1-2 hours	2500 International units/m²/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) — Dose 1 – 1.99 — 8 mg 2 – 2.99 — 10 mg 3 – 8.99 — 12 mg ≥ 9 — 15 mg	Days 1 & 31	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m²**

Date Due	Date Given	Day	VCR ____mg	IV MTX *(escalating dose)*	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg		____mg	a,b*,c	
		2			____IU			
		11	____mg	____mg			b*	
		21	____mg	____mg			b*	
		22			____IU			
		31	____mg	____mg		____mg	b*,c	
		41	____mg	____mg			b*	
		56						
		57	**Start next course (Maintenance Appendix II-M) on Day 57 or when blood count parameters are met (whichever occurs later).**					

[1] Obtain with each IT administration

*To be performed prior to each dose of methotrexate

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

THERAPY DELIVERY MAPS – ARM B-VHR (T-ALL and T-LLy)

APPENDIX II-H

Intensification Block (1) - Arm B-VHR This course is only for patients randomized to treatment on Arm B-VHR. See Section 4.11 for details	_____ Patient name or initials _____ DOB

T-ALL patients who are M2 or M3 at the end of Consolidation should proceed directly to Intensification Block 1 without waiting for count recovery or MRD results to proceed. Patients receive this block immediately after consolidation and must meet all of the following criteria: Post-consolidation risk assignment must have been completed as described in Section 4.1. **T-ALL only:** Begin Intenstification Block #1 after collection of end of consolidation bone marrow for MRD. when ANC ≥750/µL and platelets ≥75,000/µl, and organ function requirements are met as defined in Sections 5.9.1, 5.9.2, and 5.9.3, or whichever occurs later. **T-LLy only:** Start when ANC ≥750/µL and platelets ≥75,000/µl. This Cycle lasts 21 days and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (May be given IV)	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day, divided BID	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High dose methotrexate (HD-MTX)	IV	5000 mg/m^2/dose	Day 1	See Section 5.9 & Appendix IV for administration guidelines	
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	Days 3-4	Minimum of 3 doses given at 42, 48, and 54 hours after the start of the HD MTX infusion See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.	
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1 & 6	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Cyclophosphamide (CPM)	IV over 1-6 hours	200 mg/m^2/dose Q12 hrs x5 doses	Days 2-4	See Section 4.11 for administration guidelines	
High dose cytarabine (ARAC)	IV over 3 hours	2000 mg/m^2/dose Q12 hours x 2 doses	Day 5		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 6	Administer 3 hours after completion of the second HD-AraC infusion through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	**MTX and HC dosing:** Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg **ARAC dosing:** Age (yrs) Dose 1 – 1.99 16 mg 2 – 2.99 20 mg 3 – 8.99 24 mg ≥ 9 30 mg	Day 1	**Note age-based dosing** **Delivery within 6 hrs of IV MTX infusion**	
Filgrastim (G-CSF)	SubQ	5 mcg/kg/dose	Daily beginning on Day 7	Continue until WBC > 3000/µL	

Intensification Block (1) - Arm B-VHR

This course is only for patients randomized to treatment on Arm B-VHR. See Section 4.11 for details

_____
Patient name or initials

_____
DOB

Enter Cycle # _____ Ht_____cm Wt_____kg BSA____m^2

Date Due	Date Given	Day	DEX ___mg	IV MTX ____mg	LCV	VCR ____mg	CPM ____mg	ARAC ____mg	PEG-ASP ____IU	ITT ____mg (MTX) ____mg (HC) ____mg (ARAC)	G-CSF ____mcg	Studies	Comments
			Enter calculated dose above and actual dose administered below										
		1	___mg ___mg	____mg		____mg				____mg (MTX) ____mg (HC) ____mg (ARAC)		a,b,c,d	
		2	___mg ___mg				____mg ___mg						
		3	___mg ___mg		____mg$		____mg ___mg						
		4	___mg ___mg				____mg						
		5	___mg ___mg					____mg ___mg					
		6				____mg			____IU				
		7									____mcg	b*	
		21	**Start next course (Intensification Block 2 Appendix II-I) on Day 22 or when blood count parameters are met (whichever occurs later).**										

*Every 2 days after completion of chemotherapy until count recovery

$Please document the number of doses of leucovorin administered

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II-I

Intensification Block (2) Arm B-VHR

This course is only for patients randomized to treatment on Arm B-VHR. See Section 4.12 for details.

_____
Patient name or initials

_____
DOB

Start Day 1 when ANC ≥750/µL and platelets ≥75,000/µL. This Cycle lasts 21 days and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (May be given IV)	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day, divided BID	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High dose methotrexate (HD-MTX)	IV	5000 mg/m^2/dose	Day 1	See Section 5.9 & Appendix IV for administration guidelines	
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	Days 3-4	Minimum of 3 doses given at 42, 48, and 54 hours after the start of the HD MTX infusion See Section 5.9 and Appendix IV for HD MTX Infusion and Leucovorin rescue guidelines.	
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1 & 6	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Mesna	IV	300 mg/m^2/dose Hour 0, 4, and 8 from start of each ifosfamide infusion	Days 2-4	Hydration following ifosfamide administration: If patient stops methotrexate hydration for whatever reason, need to continue until 12 hours post ifosfamide infusion.	
Ifosfamide (IFOS)	IV over 1 hr	800 mg/m^2/dose Q12 hours x5 doses	Days 2-4	Suggested hydration: Administer 3000 mL/m^2/day (125 mL/m^2/hr) using fluid containing 0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity < 1.010 and urine output > 3 mL/kg/hr prior to start of ifosfamide **Start immediately after HD-MTX**	
DAUNOrubicin (DAUN)	IV Push/infusion Over 1-15 min	30 mg/m^2/dose	Day 5		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 6	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	**MTX and HC dosing:** Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg **ARAC dosing:** Age (yrs) Dose 1 – 1.99 16 mg 2 – 2.99 20 mg 3 – 8.99 24 mg ≥ 9 30 mg	Day 1	**Note age-based dosing** **Delivery within 6 hrs of IV MTX infusion**	
Filgrastim (G-CSF)	SubQ	5 mcg/kg/dose	Daily beginning on Day 7	Continue until WBC > 3000/µL	

Intensification Block (2) Arm B-VHR

This course is only for patients randomized to treatment on Arm B-VHR. See Section 4.12 for details.

_____
Patient name or initials

_____
DOB

Enter Cycle #_____ Ht_____cm Wt_____kg BSA____m^2

Date Due	Date Given	Day	DEX ___mg	IV MTX ____mg	LCV	VCR ____mg	MESNA ____mg	IFOS ____mg	DAUN ____mg	PEG-ASP ____IU	ITT ____mg (MTX) ____mg (HC) ____mg (ARAC)	G-CSF ____mcg	Studies	Comments
			Enter calculated dose above and actual dose administered below											
		1	___mg ____mg	____mg		____mg					____mg (MTX) ____mg (HC) ____mg (ARAC)		a,b,c,d	
		2	___mg ____mg				____mg ____mg ____mg ____mg ____mg ____mg	____mg ____mg						
		3	___mg ____mg		____mg$		____mg ____mg ____mg ____mg ____mg ____mg	____mg ____mg						
		4	___mg ____mg				____mg ____mg ____mg	____mg						
		5	___mg ____mg						____mg					
		6				____mg				____IU				
		7										____mcg	b*	
		21	**Start next course (Intensification Block 3 Appendix II-J) on Day 22 or when blood count parameters are met (whichever occurs later).**											

*every 2 days after completion of chemotherapy until count recovery

$Please document the number of doses of leucovorin administered

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

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APPENDIX II-J

Intensification Block (3) Arm B-VHR This course is only for patients randomized to treatment on Arm B-VHR. See Section 4.13 for details.	_____ Patient name or initials _____ DOB

This Cycle lasts 21 days and this Therapy Delivery Map is on one (1) page. Start Day 1 when ANC ≥ 750/µL and platelets ≥ 75,000/µL. HR3 lasts 21 days.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO (May be given IV)	10 mg/m^2/dose BID	1-5	Total daily dose: 20 mg/m^2/day, divided BID	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine **T-ALL ONLY** e. BM MRD **T-LLy ONLY:** f. Chest CT/CXR[2] g. Abdomen/pelvis CT (or MRI)[2] h. Bone scan[2] i. Diagnostic biopsy/cytology[4] [2] See Section 7.0 for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High dose cytarabine (ARAC)	IV	2000 mg/m^2/dose Q12 hours x 4 doses	Days 1-2		
Etoposide (ETOP)	IV over 2 hrs	100 mg/m^2/dose Q12 hours x5 doses	Days 3-5	See Section 4.13 for administration guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 6	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Triple Intrathecal Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	**MTX and HC dosing:** Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg **ARAC dosing:** Age (yrs) Dose 1 – 1.99 16 mg 2 – 2.99 20 mg 3 – 8.99 24 mg ≥ 9 30 mg	Day 5	**Note age-based dosing**	
Filgrastim (G-CSF)	SubQ	5 mcg /kg/dose	Daily beginning on Day 7	Continue until WBC > 3000/µL	

Enter Cycle #_____ Ht_____cm Wt_____kg BSA____m^2

Date Due	Date Given	Day	DEX ___mg	ARAC ____mg	ETOP ____mg	PEG-ASP ____IU	ITT ____mg (MTX) ____mg (HC) ____mg (ARAC)	G-CSF ___mcg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		1	___mg ___mg	____mg ____mg					a,b,d	
		2	___mg ____mg	____mg ____mg						
		3	___mg ____mg		____mg ____mg					
		4	___mg ____mg		____mg ____mg					
		5	___mg ____mg		____mg		____mg (MTX) ____mg (HC) ____mg (ARAC)		c	
		6				____IU				
		7						___mcg		
		21							**T-ALL:** b*e **T-LLy:** b*,i, (f,g,h)[2]	
			Start next course (Delayed Intensification Appendix II-K) on Day 22 or when blood count parameters are met (whichever occurs later).							

[1] Obtain with each IT administration

*every 2 days after completion of chemotherapy until count recovery

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II-K

DELAYED INTENSIFICATION- Arm B-VHR (with bortezomib)

This Delayed Intensification (DI) course is for patients randomized to treatment on Arm B-VHR (with bortezomib). See Section 4.9 for details

_____ Patient name or initials

_____ DOB

Patients receive this block immediately after HR Intensification 3 and must meet all of the following criteria: **VHR T-ALL** Post-HR Intensification Block 3 MRD was completed and demonstrated undetectable MRD as described in Section 4.13 Start 7 days after collection of HR Intensification Block 3 bone marrow for MRD or when ANC ≥750/µL and platelets ≥75,000/µl, whichever occurs later. **VHR T-LLy:** Post-HR Intensification Block 3 disease evaluation was completed and demonstrated a radiographic CR OR a radiographic PR and a biopsy showing no residual disease as described in Section 10.4 Start when ANC ≥750/µL and platelets ≥75,000/µl **All patients:** Once Delayed Intensification has begun, it may be interrupted for myelosuppression (ANC ≤ 750/µL and platelets ≤ 75,000/µL) on Day 29 ONLY. Once the Day 1 therapy or Day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL. This Course lasts 9 weeks (63 days) and this Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Bortezomib (BOR) *IND#58443*	IV push over 3-5 seconds	1.3 mg/m^2/dose	Days 1, 4, 15 & 18	At least 72 hours must have elapsed between doses.	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Electrolytes including PO_4 f. Pulse Oximetry (O2 saturation) and CXR- Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 min$^+$	1.5 mg/m^2/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
Dexamethasone (DEX)	PO (May be given IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID	
DOXOrubicin (DOXO)	IV Push Over 1-15 min	25 mg/m^2/dose	Days 1, 8, & 15		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	**Note age-based dosing**	

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA___m^2**

Date Due	Date Given	Day	BOR ____mg	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	PEG-ASP ____IU	IT MTX _____mg	Studies	Comments
					Enter calculated dose above and actual dose administered below					
		1	____mg	____mg	____mg ____mg	____mg		_____mg	a,b,c,d,e, f*	
		2								
		3								
		4	____mg				____IU		f*	
		5								
		6								
		7								
		8		____mg		____mg			b	
		15	____mg	____mg	____mg ____mg	____mg			b, f*	
		16								
		17								
		18	____mg				____IU		f*	
		19								
		20								
		21								
		22							b	

This therapy delivery map continues on the next page with Day 29.

[1] Obtain with each IT administration

* Patients who develop respiratory signs or symptoms as defined in Section 5.2.2 should have pulse oximetry (02 saturation) and Chest x-ray documented within 12 hours prior to each dose of bortezomib.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

DELAYED INTENSIFICATION- Arm B-VHR (with bortezomib)

This Delayed Intensification (DI) course is for patients randomized to treatment on Arm B-VHR (with bortezomib). See Section 4.9 for details

Patient name or initials

DOB

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Electrolytes including PO_4 f. Pulse Oximetry (O2 saturation) and CXR- Patients who develop respiratory signs or symptoms as defined in Section 5.2.2
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	Day 4, 18, & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1 – 1.99 8 mg 2 – 2.99 10 mg 3 – 8.99 12 mg ≥ 9 15 mg	Days 1, 29 &36	**Note age-based dosing**	
Cyclophosphamide (CPM)	IV over 30-60 minutes	1000 mg/m^2/dose	Day 29	See Section 4.9 for administration guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m^2/dose	Days 29-42	See Section 4.9, Section 5.13 & Appendix VII for administration guidelines	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Therapy Delivery Map **Ht_____cm** **Wt_____kg** **BSA____m^2**

Date Due	Date Given	Day	VCR ____mg	PEG-ASP ____IU	IT MTX _____mg	CPM ____mg	ARAC _____mg	TG _____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29			_____mg	____mg	_____mg	_____mg	b,d,c	
		30								
		31								
		32								
		33								
		36			_____mg		_____mg		b,c	
		37								
		38								
		39								
		40								
		41								
		42								
		43	____mg	____IU					b	
		44								
		45								
		46								
		47								
		48								
		49								
		50	____mg						b	
		57							b	
		63							b	
		64	**Start next course (IM CMTX, APPENDIX II-L) on Day 64 or when blood count parameters are met (whichever occurs later)**							

[1] Obtain with each IT administration

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

APPENDIX II-L

INTERIM MAINTENANCE (CMTX) – Arm B-VHR This IM course is for patients randomized to Arm B-VHR. See Section 4.7 for details	_____ Patient name or initials _____ DOB

Begin IM when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL. Patients need to meet renal and hepatic function requirements to initiate methotrexate as described in Section 5.10. This Course lasts 8 weeks (56 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts Bilirubin, ALT, creatinine c. CSF cell count & cytospin[1] **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (CMTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m² **escalate by 50 mg/m²/dose**	Days 1, 11, 21, 31 & 41	See Section 4.7 & Section 5.10 for details	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) – Dose 1 – 1.99 – 8 mg 2 – 2.99 – 10 mg 3 – 8.99 – 12 mg ≥ 9 – 15 mg	Days 1 & 31	**Note age-based dosing**	

Therapy Delivery Map **Ht____ cm** **Wt____ kg** **BSA____ m²**

Date Due	Date Given	Day	VCR ____mg	IV MTX *(escalating dose)*	PEG-ASP ____IU	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg		____mg	a,b*,c	
		2			____IU			
		11	____mg	____mg			b*	
		21	____mg	____mg			b*	
		22			____IU			
		31	____mg	____mg		____mg	b*,c	
		41	____mg	____mg			b*	
		56						
		57	**Start next course (Maintenance Appendix II-M) on Day 57 or when blood count parameters are met (whichever occurs later).**					

[1] Obtain with each IT administration

*To be performed prior to each dose of methotrexate

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES.

Page 1 of 1

THERAPY DELIVERY MAP – MAINTENANCE ARM B
(T-ALL and T-LLy)

APPENDIX II-M

MAINTENANCE- Arm B
This Maintenance course is for Arm B. See Section 4.14 for details

_____ Patient name or initials _____ DOB

Maintenance begins when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL. Only Mercaptopurine and PO Methotrexate will be interrupted for myelosuppression as outlined in Section 5.11. This Cycle lasts 12 weeks (84 days) and this Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	a. Hx/PE with VS/Wt (BSA) b. CBC/diff/plts c. CSF cell count & cytospin[1] d. Bilirubin, ALT, creatinine e. Thiopurine metabolites- as clinically indicated f. Optional Banking/Biology **T-LLy ONLY:** g. Chest CT/CXR h. Abdomen/pelvis CT i. Bone scan **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (May be given IV)	3 mg/m²/dose	Days 1-5, 29-33 & 57-61	Total daily dose: 6 mg/m²/day, divided BID	
Mercaptopurine (MP)	PO	75 mg/m²/dose	Days 1-84	See Section 4.14, Section 5.11 and Appendix VI for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m²/dose weekly	Days 8, 15, 22, **29@**, 36, 43, 50, 57, 64, 71 & 78 @**NOTE:** Omit Day 29 of Cycles 1- 4 for SR T-ALL and T-LLy patients and cycles 1- 2 for IR T-ALL and T-LLy patients	see Section 5.11 for suggested starting dose based on TPMT and NUDT15 status (if available) **Please note Day 29**	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1 – 1.99 / 8 mg 2 – 2.99 / 10 mg 3 – 8.99 / 12 mg ≥ 9 / 15 mg	Day 1 &Day 29 of Cycles 1- 4 for **SR T-ALL and T-LLy patients ONLY.** Day 29 of Cycles 1-2 **IR T-ALL and T-LLy patients ONLY**	**Note age-based dosing** **Please note Day 29**	

Enter Cycle #_____ Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR _____mg	DEX ___mg ___mg	MP ____mg	PO MTX ____mg	IT MTX ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1$	_____mg	___mg ___mg	____mg		____mg	a,b,c,d	
		5							
		8				____mg			
		15				____mg			
		22				____mg			
		29	_____mg	___mg ___mg		____mg@	____mg&	a,b,c	
		33							
		36				____mg			
		43				____mg			
		50				____mg			
		57	_____mg	___mg ___mg		____mg		a,b	
		61							
		64				____mg			
		71				____mg			
		78				____mg			
		84						f[5] (g[4],h[3],i[3])[2#]	
		85	**Begin next cycle on Day 85 regardless of counts and repeat until two years (for T-ALL girls and all T-LLy pts, regardless of gender) and three years (for T-ALL boys) from the start of Interim Maintenance (see Section 4.14). Only MP & PO MTX will be interrupted for myelosuppression during subsequent Maintenance cycles as outlined in Section 5.11**						

[1] Obtain with each IT administration [2] T-LLy ONLY [3] If baseline is negative, no repeat scans are required.
[4] If CR at end-Consolidation perform a CXR; If PR or NR at end-Consolidation perform chest CT at completion of Maintenance therapy.
[5] Collect ONLY if the patient relapses. **T-ALL**: as a part of AALL08B1 (or APEC14B1 if available to ALL patients) **T-LLy**: submit via APEC14B1 (if enrolled).

[$]RADIATION THERAPY (T-ALL:IR CNS3 and all VHR patients, T-LLy:CNS3 only) See Section 16.0

[#] Only collect at the completion of therapy.

SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE THE COG MEMBER WEBSITE FOR SUPPORTIVE CARE GUIDELINES

APPENDIX III: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY AALL1231 FOR PATIENTS WITH T-ALL
(for children from 7 through 12 years of age)

A Study of Bortezomib in Children with Newly Diagnosed T-Lymphoblastic Leukemia (T-ALL)

1. We have been talking with you about a type of cancer called T-lymphoblastic leukemia or T-ALL. T-ALL is a type of cancer that only affects T-cells (a special kind of cell of your immune system). T-cell ALL grows in the bone marrow. The bone marrow is inside your bones. It is where your blood is made. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-ALL. We will do this by comparing 2 ways to treat T-ALL. Some of the children and teens in this study will get the usual treatment for T-ALL. Some of the children and teens will get the usual treatment plus a drug called bortezomib. In this study bortezomib is experimental, but is approved by the FDA to treat other conditions. The chemotherapy you get will be decided by chance, like flipping a coin for “heads” or “tails”. We don’t know which way is better. That is why we are doing this study.

3. Children and teens that are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. You will also have scans performed to make sure the T-ALL is responding to treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called ‘benefits’. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called ‘risks’. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. It is also possible that your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer for as long as possible.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. Almost all of these samples will be taken when other standard blood tests and bone marrow tests are done. If there is any blood or bone marrow left over from tests done for this study, we would like to save them for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra blood or bone marrow samples or save the leftover samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY AALL1231 FOR PATIENTS WITH T-ALL
(for teens from 13 through 17 years of age)

A Study of Bortezomib in Children with Newly Diagnosed T-Lymphoblastic Leukemia (T-ALL)

1. We have been talking with you about a type of cancer called T-lymphoblastic leukemia or T-ALL. T-ALL is a type of cancer that only affects T-cells (a special kind of cell of your immune system). T-cell ALL grows in the bone marrow. The bone marrow is inside your bones. It is where your blood is made. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-ALL. We will do this by comparing 2 ways to treat T-ALL. Some of the children and teens in this study will get the usual treatment for T-ALL. Some of the children and teens will get the usual treatment plus a drug called bortezomib. In this study bortezomib is experimental, but is approved by the FDA to treat other conditions. The chemotherapy you get will be decided by chance, like flipping a coin for “heads” or “tails”. We don’t know which way is better. That is why we are doing this study.

3. Children and teens that are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. You will also have scans performed to make sure the T-ALL is responding to treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called ‘benefits’. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called ‘risks’. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. It is also possible that adding bortezomib to your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer for as long as possible. Adding bortezomib to your treatment plan could also reduce how well your treatment works.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. Almost all of these samples will be taken when other standard blood tests and bone marrow tests are done. If there is any blood or bone marrow left over from tests done for this study, we would like to save them for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra blood or bone marrow samples or save the leftover samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY AALL1231 FOR PATIENTS WITH T-LLy
(for children from 7 through 12 years of age)

A Study of Bortezomib in Children with Newly Diagnosed T-Lymphoblastic Lymphoma (T-LLy)

1. We have been talking with you about a type of cancer called T-lymphoblastic lymphoma or T-LLy. T-LLy is a type of cancer that occurs in the lymph system, which is made up of the lymph nodes and other lymph tissue throughout the body. Lymph tissue makes and stores infection-fighting white blood cells called lymphocytes. These cells become cancerous when a subject has lymphoma. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-LLy. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-LLy. We will do this by comparing 2 ways to treat T-LLy. Some of the children and teens in this study will get the usual treatment for T-LLy. Some of the children and teens will get the usual treatment plus a drug called bortezomib. In this study bortezomib is experimental, but is approved by the FDA to treat other conditions. The chemotherapy you get will be decided by chance, like flipping a coin for “heads” or “tails”. We don’t know which way is better. That is why we are doing this study.

3. Children and teens that are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. You will also have scans performed to make sure the T-LLy is responding to treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

4. Sometimes good things can happen to people when they are in a research study. These good things are called ‘benefits’. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called ‘risks’. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. It is also possible that your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer for as long as possible.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. Almost all of these samples will be taken when other standard blood tests and bone marrow tests are done. If there is any blood or bone marrow left over from tests done for this study, we would like to save them for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra blood or bone marrow samples or save the leftover samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY AALL1231 FOR PATIENTS WITH T- LLy
(for teens from 13 through 17 years of age)

A Study of Bortezomib in Children with Newly Diagnosed T-Lymphoblastic Lymphoma (T-LLy)

1. We have been talking with you about a type of cancer called T-lymphoblastic lymphoma or T-LLy. T-LLy is a type of cancer that occurs in the lymph system, which is made up of the lymph nodes and other lymph tissue throughout the body. Lymph tissue makes and stores infection-fighting white blood cells called lymphocytes. These cells become cancerous when a subject has lymphoma. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have T-LLy. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat T-LLy. We will do this by comparing 2 ways to treat T-LLy. Some of the children and teens in this study will get the usual treatment for T-LLy. Some of the children and teens will get the usual treatment plus a drug called bortezomib. In this study, bortezomib is experimental, but is approved by the FDA to treat other conditions. The chemotherapy you get will be decided by chance, like flipping a coin for “heads” or “tails”. We don’t know which way is better. That is why we are doing this study.

3. Children and teens that are part of this study will be treated with chemotherapy. Chemotherapy is a type of medicine that destroys cancer cells. You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. You will also have scans performed to make sure the T-LLy is responding to treatment. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.

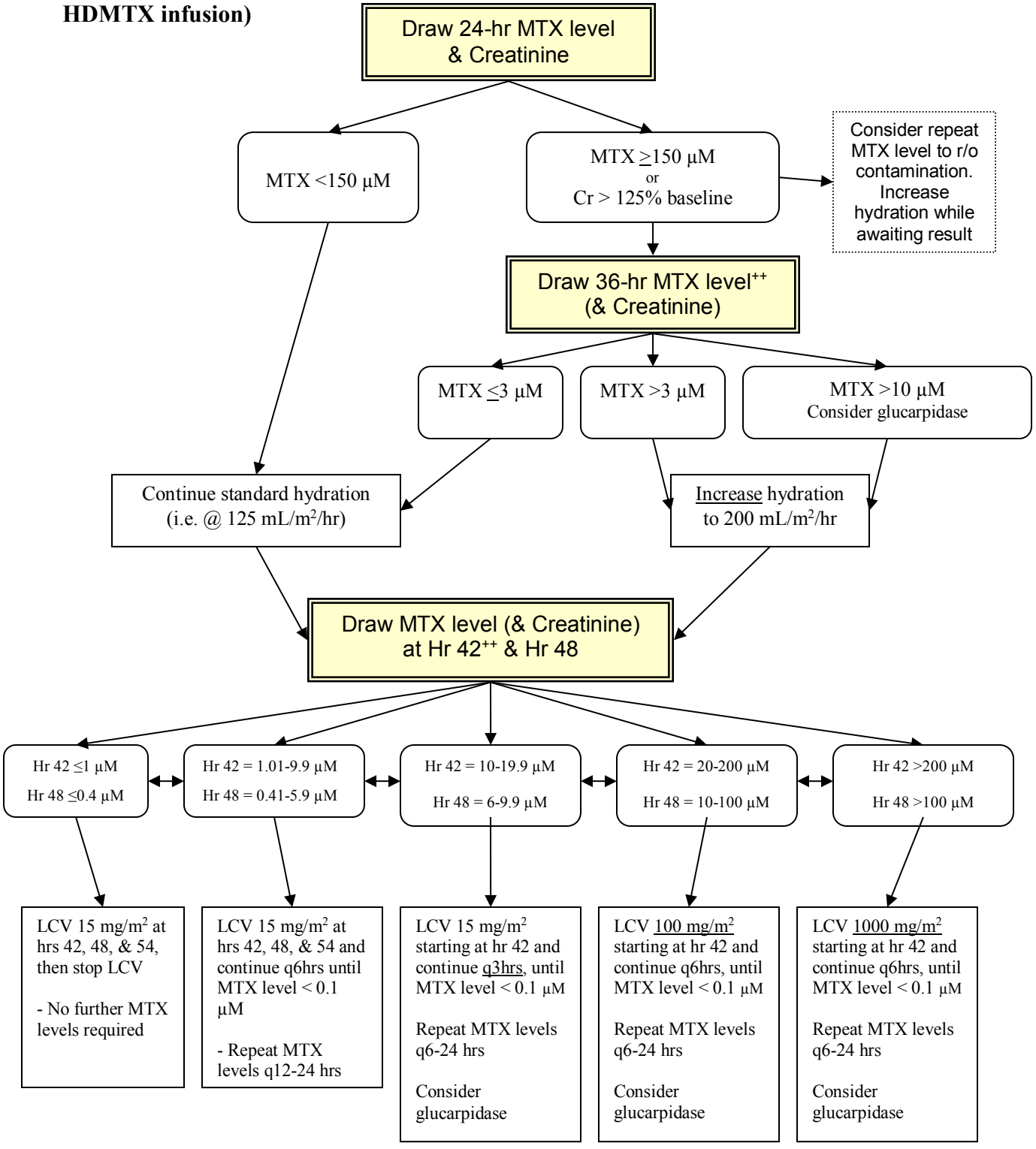
4. Sometimes good things can happen to people when they are in a research study. These good things are called ‘benefits’. We hope that a benefit to you of being part of this study is keeping the cancer away for as long as possible, but we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called ‘risks’. The risks to you from this study are increased toxicities that can cause infections or make it harder for a patient to fight off infections, loss of healthy blood cells and damage to bones or joints. It is also possible that adding bortezomib to your treatment plan may increase the side effects of treatment without improving the chances of getting rid of the cancer for as long as possible. Adding bortezomib to your treatment plan could also reduce how well your treatment works.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. Almost all of these samples will be taken when other standard blood tests and bone marrow tests are done. If there is any blood or bone marrow left over from tests done for this study, we would like to save them for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra blood or bone marrow samples or save the leftover samples for research.

APPENDIX IV: HIGH-DOSE METHOTREXATE FLOWCHART
(Please refer to Section 5.9 for complete details; all levels are timed from the start of the HDMTX infusion)



++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤1 and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

APPENDIX V: CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Weak Inhibitors	Inducers
alfentanil[4,5]	atazanavir	aprepitant	alprazolam	armodafinil
amiodarone[4]	boceprevir	atazanavir	amiodarone	barbiturates
aprepitant/fosaprepitant[5]	clarithromycin	cimetidine	atorvastatin	bosentan
benzodiazepines	cobicistat	conivaptan	bicalutamide	carbamazepine
bortezomib	darunavir	crizotinib	cilostazol	deferasirox
brentuximab	conivaptan	cyclosporine	cimetidine	echinacea
budesonide[5]	delavirdine	diltiazem	ciprofloxacin	efavirenz
calcium channel blockers	grapefruit[3]	dronedarone	cyclosporine	etravirine
cisapride	grapefruit juice[3]	erythromycin	fluvoxamine	fosphenytoin
citalopram/escitalopram	indinavir	fluconazole	isoniazid	glucocorticoids[2]
glucocorticoids[2]	itraconazole	fluvoxamine	nicardipine	modafinil
conivaptan[5]	ketoconazole	fosamprenavir	propofol	nafcillin
crizotinib	lopinavir/ritonavir	fosaprepitant	quinidine	nevirapine
cyclosporine[4]	nefazodone	grapefruit[3]	sertraline	oxcarbazepine
cyclophosphamide	nelfinavir	grapefruit	tacrolimus	phenobarbital
dapsone	posaconazole	juice[3]	ranolazine	phenytoin
darifenacin[5]	ritonavir	imatinib		pioglitazone
darunavir	saquinavir	mifepristone		primidone
dasatinib[5]	telaprevir	nilotinib		rifabutin
dihydroergotamine	telithromycin	verapamil		rifampin
docetaxel	voriconazole			rifapentin
doxorubicin				ritonavir
dronedarone[5]				St. John's wort
eletriptan[5]				topiramate
ergotamine[4]				
erlotinib				
esomeprazole				
estrogens				
etoposide				
everolimus[5]				
felodipine[5]				
fentanyl[4]				
fosaprepitant				
gefitinib				
haloperidol				
HIV antiretrovirals				
HMG Co-A inhibitors[5]				
ifosfamide				
imatinib				
indinavir[5]				
irinotecan				
itraconazole				

ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam modafinil monteleukast nefazodone nilotinib nisoldipine[5] omeprazole ondansetron paclitaxel pazopanib quetiapine[5] quinidine saquinavir[5] sildenafil simvastatin[5] sirolimus[4,5] sunitinib tacrolimus[4,5] telaprevir tamoxifen temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vinca alkaloids zolpidem				

[1]Certain fruits and fruit juices (star fruit, Seville oranges, pomegranate, ginko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 6.5 and 6.9 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates

APPENDIX VI: MERCAPTOPURINE DOSING TABLE

Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

MERCAPTOPURINE 25 mg/m^2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.49	½ tab / d x 3	75 mg/wk
0.50 - 0.64	½ tab / d x 4	100 mg/wk
0.65 - 0.78	½ tab / d x 5	125 mg/wk
0.79 - 0.92	½ tab / d x 6	150 mg/wk
0.93 – 1.07	½ tab / d x 7	175 mg/wk
1.08 – 1.21	1 tab / d x 1; ½ tab / d x 6	200 mg/wk
1.22 – 1.35	1 tab / d x 2; ½ tab / d x 5	225 mg/wk
1.36 – 1.49	1 tab / d x 3; ½ tab / d x 4	250 mg/wk
1.50 – 1.64	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
1.65 – 1.78	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
1.79 – 1.92	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
1.93 – 2.07	1 tab / d x 7	350 mg/wk
2.08 – 2.21	1½ tab / d x 1; 1 tab / d x 6	375 mg/wk
2.22 - 2.35	1½ tab / d x 2; 1 tab / d x 5	400 mg/wk
2.36 – 2.49	1½ tab / d x 3; 1 tab / d x 4	425 mg/wk
2.50 – 2.64	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
2.65 – 2.78	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
2.79 – 2.92	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
2.93 – 3.00*	1½ tab / d x 7	525 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

MERCAPTOPURINE 60 mg/m^2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.33 - 0.38	½ tab / d x 6	150 mg/wk
0.39 - 0.44	½ tab / d x 7	175 mg/wk
0.45 - 0.50	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.51 - 0.56	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.57 - 0.62	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.63 - 0.68	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.69 - 0.74	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.75 - 0.80	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.81 - 0.86	1 tab / d x 7	350 mg/wk
0.87 - 0.92	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.93 - 0.98	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.99 - 1.04	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
1.05 - 1.10	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.11 - 1.16	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.17 - 1.22	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.23 - 1.27	1½ tab / d x 7	525 mg/wk
1.28 - 1.33	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.34 - 1.39	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.40 - 1.45	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.46 - 1.51	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.52 - 1.57	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.58 - 1.63	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.64 - 1.69	2 tab / d x 7	700 mg/wk
1.70 - 1.75	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk

1.76 - 1.81	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.82 - 1.87	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.88 - 1.93	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.94 - 1.99	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
2.00 - 2.05	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
2.06 - 2.11	2½ tab/ d x 7	875 mg/wk
2.12 - 2.17	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
2.18 - 2.23	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
2.24 - 2.29	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
2.30 - 2.35	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
2.36 - 2.41	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
2.42 - 2.47	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
2.48 - 2.52	3 tab/ d x 7	1050 mg/wk
2.53 - 2.58	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.59 - 2.64	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.65 - 2.70	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.71 - 2.76	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.77 - 2.82	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.83 - 2.88	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.89 - 2.94	3½ tab/ d x 7	1225 mg/wk
2.95 - 3.00	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

MERCAPTOPURINE 75 mg/m^2

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk
2.41 – 2.45	3½ tab/ d x 5; 4 tab / d x 2	1275 mg/wk

2.46 – 2.49	3½ tab/ d x 4; 4 tab / d x 3	1300 mg/wk
2.50 – 2.54	4 tab/ d x 4; 3½ tab / d x 3	1325 mg/wk
2.55 – 2.59	4 tab/ d x 5; 3½ tab / d x 2	1350 mg/wk
2.60 – 2.64	4 tab/ d x 6; 3½ tab / d x 1	1375 mg/wk
2.65 – 2.69	4 tab/ d x 7	1400 mg/wk
2.70 – 2.73	4 tab/ d x 6; 4½ tab / d x 1	1425 mg/wk
2.74 – 2.78	4 tab/ d x 5; 4½ tab / d x 2	1450 mg/wk
2.79 – 2.83	4 tab/ d x 4; 4½ tab / d x 3	1475 mg/wk
2.84 – 2.88	4½ tab/ d x 4; 4 tab / d x 3	1500 mg/wk
2.89 – 2.92	4½ tab/ d x 5; 4 tab / d x 2	1525 mg/wk
2.93 – 2.97	4½ tab/ d x 6; 4 tab / d x 1	1550 mg/wk
2.98 – 3.00	4½ tab/ d x 7	1575 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.*

APPENDIX VII: THIOGUANINE DOSING TABLE

THIOGUANINE 60 mg/m^2

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 40 mg)	Cumulative Weekly Dose
0.31 - 0.35	½ tab / d x 7	140 mg/wk
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.60 - 0.64	1 tab/ d x 6; ½ tab / d x 1	260 mg/wk
0.65 - 0.69	1 tab / day	280 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
0.79 - 0.83	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
0.98 - 1.02	1½ tab /day	420 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.31 - 1.35	2 tab / day	560 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
1.46 - 1.49	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
1.50 - 1.54	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
1.55 - 1.59	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
1.60 - 1.64	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
1.65 - 1.69	2½ tab / d	700 mg/wk
1.70 - 1.73	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
1.74 - 1.78	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
1.79 - 1.83	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
1.84 - 1.88	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
1.89 - 1.92	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
1.93 - 1.97	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk
1.98 - 2.02	3 tab / d x 7	840 mg/wk
2.03 - 2.07	3 tab / d x 6; 3½ tab / d x 1	860 mg/wk
2.08 - 2.11	3 tab / d x 5; 3½ tab / d x 2	880 mg/wk
2.12 - 2.16	3 tab / d x 4; 3½ tab / d x 3	900 mg/wk
2.17 - 2.21	3½ tab / d x 4; 3 tab / d x 3	920 mg/wk
2.22 - 2.26	3½ tab / d x 5; 3 tab / d x 2	940 mg/wk
2.27 – 2.30	3½ tab / d x 6; 3 tab / d x 1	960 mg/wk

2.31 – 2.35	3½ tab / d x 7	980 mg/wk
2.36 – 2.40	3½ tab / d x 6; 4 tab / d x 1	1000 mg/wk
2.41 – 2.45	3½ tab / d x 5; 4 tab / d x 2	1020 mg/wk
2.46 – 2.49	3½ tab / d x 4; 4 tab / d x 3	1040 mg/wk
2.50 – 2.54	4 tab / d x 4; 3½ tab / d x 3	1060 mg/wk
2.55 – 2.59	4 tab / d x 5; 3½ tab / d x 2	1080 mg/wk
2.60 – 2.64	4 tab / d x 6; 3½ tab / d x 1	1100 mg/wk
2.65 – 2.69	4 tab / d x 7	1120 mg/wk
2.70 – 2.73	4 tab / d x 6; 4½ tab / d x 1	1140 mg/wk
2.74 – 2.78	4 tab / d x 5; 4½ tab / d x 2	1160 mg/wk
2.79 – 2.83	4 tab / d x 4; 4½ tab / d x 3	1180 mg/wk
2.84 – 2.88	4½ tab / d x 4; 4 tab / d x 3	1200 mg/wk
2.89 – 2.92	4½ tab / d x 5; 4 tab / d x 2	1220 mg/wk
2.93 – 2.97	4½ tab / d x 6; 4 tab / d x 1	1240 mg/wk
2.98 – 3.00	4½ tab / d x 7	1260 mg/wk

**Patients exceeding a BSA of 3.00 m^2 should have their TG doses calculated on actual BSA with no maximum dose.*

APPENDIX VIII: STAGING CLASSIFICATION OF CHILDHOOD NON-HODGKIN LYMPHOMA

Modified from Murphy [Seminars in Oncology (1980) 7; 332-339]

Stage	Criteria for Extent of Disease
Localized	
I	A single tumor (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement
Disseminated	
III	Two single tumors (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intra-thoracic tumors (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease. All paraspinal or epidural tumors, regardless of other tumor site(s)
IV	Any of the above with initial CNS and/or bone marrow involvement

Enumeration of Number of Regions of Nodal Involvement

Each of these twenty regions is counted separately for purposes of determining number of sites of involvement.

Peripheral Regions

Right neck; cervical, supraclavicular, occipital, and pre-auricular
Left neck; cervical, supraclavicular, occipital, and pre-auricular
Right infraclavicular
Left infraclavicular
Right axilla and pectoral
Left axilla and pectoral
Right epitrochlear and brachial
Left epitrochlear and brachial

APPENDIX IX: MINIMAL RESIDUAL DISEASE-SAMPLE SHIPPING REQUIREMENTS

MRD samples will be shipped to the COG ALL Reference Flow Cytometry Lab using the shipping and handling requirements below.

Samples are to be shipped to Dr. Brent Wood at the University of Washington, Flow Cytometry Laboratory. The AALL1231 Specimen Transmittal Form is to be submitted with each sample submitted to the COG Reference Laboratory. The specimen transmittal form information should always include the name and telephone number of a person designated by the PI to receive calls from the Reference Laboratory directors. The PI's FAX number must also be noted on each sample inclusion form. Because clinical recommendations will be made on these samples, **always** include the patient's name, birth date and COG number on any sample submitted. This is a CLIA requirement. COG ALL Reference Laboratories may be unable to analyze specimens if adequate patient identifiers are not provided.

Samples for the Reference Laboratories are to be collected in special 15 mL conical tubes (SM) containing EDTA/RPMI as the anticoagulant and media diluent. These tubes will be prepared in the Reference Laboratories and mailed in batches to each participating institution, where they can be stored frozen at -20°C until use. Tubes are stable for 3 months if refrigerated and stable for 1 year if frozen.

To request prepared and pre-packaged sample shipping tubes, click on the following link:

https://ricapps.nationwidechildrens.org/KitManagement/

Select 'AALL08B1' from the protocol list to order the shipping tubes required for MRD samples.

Bone Marrow Collection Procedures for Reference Laboratories:

a. Collect 1-2 ml of BM from the 1st pull into a syringe and transfer the specimen immediately into the 15 mL shipping media conical tube with RPMI/EDTA. Collection of marrow volumes beyond 2 ml or use of marrow other than the 1st pull will result in hemodilution and may effect quantitation of MRD.
b. Mix well. Up to 5 mL of BM can be placed in one 15 mL tube with RPMI/EDTA. If you don't have shipping media tubes, you can place the BM into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is enhanced in the shipping media tubes.
c. 1-2 mL of BM will be sufficient for analysis either at diagnosis or following therapy.

16.1.2 Sample Shipping

Bone marrow samples for MRD studies will be shipped to one place:

Western Flow Cytometry Reference Laboratory
Brent Wood, MD, PhD
Seattle Cancer Care Alliance
Hematopathology Laboratory, Room G7-800
825 Eastlake Ave. E.
Seattle, WA 98109-1028
Phone: 206-288-7060
FAX: 206-288-7127

SAMPLES THAT ARE EXPECTED TO BE DELAYED FOR MORE THAN 48 HOURS—PLACE A COLD PACK (NOT ICE PACK) IN SHIPMENT. ALL TUBES SHOULD BE LABELED WITH AT LEAST TWO PATIENT IDENTIFIERS, INCLUDING THE NAME AND THE COG

NUMBER. IN ADDITION, AN AALL1231 SPECIMEN TRANSMITTAL FORM AVAILABLE IN RAVE SHOULD ALWAYS BE SUBMITTED WITH EACH SAMPLE.

Call Reference Laboratories only when shipping a sample to be delivered on Saturday.

Samples for the Flow Cytometry Reference Laboratory should be mailed by FEDERAL EXPRESS PRIORITY (DELIVERY BEFORE 10 AM) using the COG Federal Express account number available at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

APPENDIX X: EVALUATING MECHANISMS OF BORTEZOMIB RESPONSE AND RESISTANCE IN T-ALL AND IDENTIFYING BIOMARKERS AND MECHANISMS OF CHEMOTHERAPY RESISTANCE AND RESPONSE IN T-ALL, FOCUSING ON ETP ALL

Eligible samples:

All pre-treatment bone marrow samples from both arms of the study (Arm A and Arm B) are eligible. Peripheral blood samples should be sent to the Horton lab only if the patient samples meet the following criteria:

Eligible patients must have an initial absolute blast count of **at least 1000 lymphoblasts/µL**. To calculate the absolute blast percentage, multiply the total WBC by the % peripheral blasts:

(WBC)(% blast)(1000) = absolute blast count/µL

As an example, if the patient has a WBC of 10 and 50% blasts, the absolute blast count is:
(10)(.5)(1000) = 5000/µL

If the initial % blasts is unknown, send peripheral blood samples only if the total WBC is more than 10,000 cell/µL and notify the Horton lab of the % blast as soon as available (contact information provided below).

Samples must be received by the Horton lab **no later than 72h after collection.** Bone marrow and peripheral blood samples can be batched if they will arrive within 72h. If samples will not arrive within 72h, please send the bone marrow separately from peripheral blood samples. Day 1 peripheral blood samples should be shipped together. The Horton lab can accept Saturday shipments if we are contacted ahead of time. Please contact Gaye Jenkins or other Horton lab representative (832-824-4676) for alternative address and shipping information for Saturday delivery.

Sample collection time points:

	On -study	Day 1, Hour 0	Day 1, Hour 6	Day 1, Hour 24	End of Induction
Bone Marrow (Induction only)	5 mL* (peripheral blood can be substituted if >80% blasts) #				5 ml* (peripheral blood can be substituted if >30% blasts)
Peripheral Blood (Induction only)		5 mL* (before start of systemic chemotherapy)	5 mL* (6h following the start of systemic chemotherapy)	5 mL* (24h following the start of systemic chemotherapy)	5 mL* (same day as end of induction bone marrow)

 # If the blast count is <80% and bone marrow is not available, please call Dr. Horton or Gaye Jenkins to discuss on a case-by-case basis.

***Sample Collection:**

1. **Bone marrow**: send in heparin or ACDA tube (ACDA preferred). Can also be sent diluted 1:1 in shipping media. Do not send bone marrow samples in Cell Save tubes.

2. **Peripheral blood: For all Day 1 samples,** Collect 5 mL sample into the CellSave tubes (3 mL) and heparin tubes (2 mL). Collect sample into collection tubes directly, do not transfer a heparinized sample into the Cell Save tube; the Cell Save fixative will not work if the sample has already been heparinized. Either lithium heparin or sodium heparin is acceptable. **Do not use lithium heparin PST (plasma separator tubes).** End-of Induction samples should be sent in heparin tubes only.

Shipping Note: Samples collected on Saturday and Sunday can be shipped Monday for Tuesday arrival. See below for information on obtaining and shipping samples in ThermoSafe containers.

Specimen Requirements:
Store samples in refrigerator until shipment.
CellSave tubes will be provided by the Horton lab to each institution.
To obtain more CellSave tubes, contact the Horton lab at the numbers provided below.
If the CellSave tubes are not available, submit entire 5 mL sample in heparin tubes. Note that the **sample integrity is greatly enhanced by the use of CellSave tubes.**

- Each sample should be clearly labeled to include the 6 digit COG number as well as the 4 digit treatment accession number; study number (AALL1231), date and time sample was drawn.

On the AALL1231 Specimen Transmittal Form in the Medidata/Rave system record the exact time and date that the sample is drawn along with the exact start time for administration of systemic chemotherapy. Please note the WBC and % blasts on the specimen transmittal form.
Please include a copy of the AALL1231 specimen transmittal form and institutional immunophenotype report with the sample submission to the laboratory. Please also fax a copy of the institutional immunophenotype report to FAX #: (832) 825-1206.

Note: it is acceptable for blood to be collected from a central line.

Shipping Requirements:
Prior to sample collection, please contact Dr. Horton at (832) 824-4269 or Gaye Jenkins/Horton lab at (832) 824-4676 for ThermoSafe shipping containers. These containers maintain biology samples at a constant temperature and are recommended, but not required, for biology sample shipment. Shipment of peripheral blood samples should not be delayed for receipt of shipping containers.

If Thermo-Safe shipping container is not available:
- Place collection tubes in a primary container. Wrap each collection tube separately to protect from breakage during shipment. Place the container in a Styrofoam box.
- Please place an **ice pack** in the primary container. During the non-winter months (April-October) add additional ice packs to the Styrofoam box to assure the samples stays cold during shipment.
- Package sample as appropriate for biologic material.

For all samples, including those in ThermoSafe containers:
Include a large ice pack in the ThermoSafe containers.
- Include a copy of the submitted (in Rave) AALL1231 Specimen Transmittal Form with each shipment.
- **If possible, please** send a copy of the **bone marrow immunophenotype report with the first peripheral blood sample.** If this is not possible, please send the report that day via fax (832-825-1206) or email to Dr. Horton at tmhorton@txccc.org and Gaye Jenkins at gnjenkin@txccc.org (Please strip unnecessary identifiers)

- **Ship the sample by Federal Express Priority Overnight delivery to:**

  Dr. Terzah Horton c/o Gaye Jenkins
  Feigin Center, Suite 760.01
  1102 Bates St.
  Baylor College of Medicine
  Houston, TX 77030
  832-824-4676

  FedEx account # 296621072
  Add air bill comment: TCH CC# 3332

- Notify Gaye Jenkins or Horton lab representative **prior** to shipment of the sample. Phone: (832) 824-4676. Please email the Fed-Ex tracking number to the email addresses above if prior notification is not possible.
- If possible, do not ship samples for delivery on a weekend or holiday. Please contact the Horton lab for special instructions if samples are collected on a Friday.

Appendix XI: Minimal Residual Disease (MRD): Description and Characterization of Assay

Description of populations for testing

Patients with newly diagnosed T-ALL will have MRD measured in the bone marrow (BM) at the end of the first block of Induction therapy (Day 29). Those patients (~50%) with MRD levels < 0.01% in BM at Day 29 will be considered Standard Risk and assigned to the least intensive cytotoxic therapy. For the remaining patients (~50%), MRD will be assessed in BM at the end of Consolidation (EOC) therapy. Those with MRD < 0.1% (~40%) will be considered Intermediate Risk and receive intermediate intensity therapy. The remainder (~10%) will be considered Very High Risk and receive intensified therapy followed by an additional MRD assessment with those positive for MRD taken off study. Specimens from all patients will also be assayed at study entry in order to define an abnormal phenotype that will facilitate detection of MRD.

Part of the diagnostic immunophenotyping at study entry will include the marginal cost for early thymic precursor (ETP) subclassification, a subset having a poor outcome[70] and whose outcome is an important secondary endpoint of the study. Data from AIEOP-BFM 2000 suggest that while ETP ALL is often associated with poor prognosis, it may not be an independent risk factor for poor outcome, as most patients with ETP ALL who do poorly are identifiable by poor response to chemotherapy (PPR, Induction failure, or MRD positivity).[38] It is critical to understand whether or not ETP phenotype independently predicts outcome in T-ALL as these patients may need alternative therapy or HSCT for cure. Multivariate analysis will be performed to determine if ETP ALL is an independent predictor of poor outcome based on MRD rates at end Induction and end of Consolidation. Preliminary data suggest ETP represents 12.4% of T-ALL in AALL0434, yielding 118 ETP patients of the 952 T-ALL anticipated on AALL1231. There are few data available to predict the proportion of ETP+ patients that will have MRD < 0.1% at EOC. Overall, we expect that ~10% of T-ALL patients will have MRD ≥ 0.1% at EOC, while ~90% will have MRD <0.1%. Given the known higher percentage of end of Induction MRD+ patients among the ETP+ subset, we hypothesize that ~50% of ETP+ patients (n=59) will have MRD ≥ 0.1% at EOC (5-fold higher rate than MRD-negative), while ~50% (n=59) will have MRD <0.1%. If the 4-year EFS of these ETP+, EOC MRD <0.1% patients is ~50% or better, it would suggest that ETP patients can be risk stratified based on MRD alone (unless there is a specific therapy available for ETP patients). However, if this assumption is incorrect and ETP+ patients with MRD < 0.1% at EOC have an EFS < 50%, it would suggest that MRD alone cannot be used to risk stratify these patients and alternative strategies (stem cell transplant in CR1 or other novel therapies) should be pursued for all ETP patients. Hence, we will see if the lower limit of the 95% confidence interval for the 4-year EFS estimate for ETP+, EOC MRD < 0.1% patients exceeds 50%.

Patients with T-LLy will have the level of marrow involvement assessed at diagnosis to facilitate risk stratification into Standard and Intermediate risk groups. All T-LLy patients will also be assessed for MRD at Day 29, as this study will enroll more T-LLy patients than any to date and offers a unique opportunity to establish risk factors for this understudied patient population. We hypothesize that T-LLy patients with <0.01% MRD at end of Induction will have the best outcome, consistent with existing data in T-ALL. No data exist on the frequency of marrow MRD following therapy for T-LLy, although the frequency of marrow involvement at diagnosis > 0.01% is 66% in AALL0434. Assuming that about 80% of T-LLy patients will have MRD < 0.01% at end of Induction, this yields roughly 198 T-LLy patients on AALL1231. This will enable us to estimate the 4-year EFS for MRD negative T-LLy patients with a maximum standard error of 3.6%.

Laboratory for MRD Testing

The MRD studies will be performed solely in the flow cytometry laboratory located in the Hematopathology Laboratory at the University of Washington in Seattle directed by Dr. Brent Wood. This laboratory has more than 5 years of experience performing this assay on nearly 1,400 pediatric patients enrolled on the

ongoing COG T-ALL trial AALL0434. In addition, for the past 8 years this laboratory has generated MRD results used for risk assignment on COG frontline B-lineage ALL trials for more than 10,000 pediatric patients.

Technical description of the assay
Analyte and platform: The assay detects leukemic cells at high sensitivity against a background of normal peripheral blood or marrow cells using multiparameter flow cytometry. It is based on the principle that leukemic cells express cellular antigens at levels that differ from those seen in normal cells.[196-198] Cells are stained with antibodies that have been previously shown to be informative for this purpose, and that have been conjugated to different fluorochromes designed to maximize the resolution between normal and abnormal cells. Specifically, the antibody combinations used are: CD16 PB/cCD3 FITC/CD7 PE/CD56 PE-Cy5/CD5 PE-Cy7/CD38 A594/sCD3 FITC/CD45 APC-H7 and CD8 BV421/CD48 FITC/CD5 PE/CD34 PE-TR/CD16+56 PE-Cy5/CD3 PE-Cy7/CD4 A594/CD7 APC/CD45 APC-H7 are used to identify leukemic cells. Evaluation for ETP type will be performed by using the following antibody combination in a single tube for pretreatment samples only: HLA-DR PB, CD7 FITC, CD13+CD33 PE, CD117 PE-Cy5, CD34 PE-Cy7, CD38 A594, CD1a APC, CD45 APC-H7. Stained cells are analyzed on a LSRII flow cytometer (Becton Dickinson, San Jose, CA). The proportion of leukemic MRD cells is expressed as a percentage of T/NK cells in each of the two tubes. An additional tube containing the DNA binding dye Syto16 along with CD7 and CD45 is used to calculate the proportion of T/NK cells as a percentage of total nucleated cells, which, when combined with results from the other two tubes allows computation of MRD as a percent of all nucleated cells. Finally, CD45 and side scatter is used to exclude granulocytes from the denominator so that the final value for MRD is expressed as a percent of mononuclear cells. By acquiring at least 750,000 events, it is possible to detect leukemic cells with a routine sensitivity of 0.01%, better in a subset of cases. This assay is currently used to determine prognostically significant thresholds for the on-going AALL0434 clinical trial.

Specimens and processing: Either PB or BM is used for the assays described here. Samples are drawn at local institutional sites and sent in anticoagulated tissue culture medium provided to the local institutions and processed in most cases within 24 hours of collection. Aliquots of whole PB or BM are stained with the combinations of antibodies noted above followed by simultaneous red blood cell lysis with ammonium chloride and fixation using a small amount of formaldehyde. Finally the sample is washed once and listmode data acquired on the flow cytometry.

Scoring procedures/criteria for positive/cut-points: Listmode data are analyzed in third party software using a hierarchical gating strategy with visual interpretation of multiple bivariate dot plots performed by Dr. Wood. Leukemic populations identified are analytically isolated from background normal cells using Boolean logic and based on the principle that leukemic cells express antigens in a pattern different from that seen during normal maturation of that lineage. For patients with T-ALL, the combination of a cut-point of < 0.01% leukemic cells in BM at Day 29 after initiation of chemotherapy and <0.1% leukemic cells in BM at end of Consolidation will be used to identify patients with a standard risk of relapse. For the remaining patients a cut-point of ≥ 0.1% leukemic cells at the end of Consolidation therapy will be used to identify patients at very high risk of relapse. Very high-risk patients that remain MRD positive ≥ 0.01% after intensification of therapy will be removed from the trial for additional therapy. For patients with T-LLy, patients with < 1% BM involvement at diagnosis will be considered Standard Risk and those with ≥ 1% BM involvement at diagnosis will be considered Intermediate or Very High risk depending on CT scan at Day 29. Blasts will be scored for ETP type using the published definition,[70] i.e. lack of expression of CD1a and CD8, expression of one or more of CD13, CD33, CD34, CD117 or HLA-DR, and CD5 expression 1 log lower than the mature T cells or < 75% positive.

Background: Minimal Residual Disease (MRD) is known to be a powerful prognostic factor in childhood B lineage ALL.[36,37,199-205] Only limited data is available for T-ALL, most of it based on relatively small numbers of patients using PCR methodology.[206-210] The largest and most comprehensive study to date of 484 pediatric patients[38] demonstrates that MRD negativity (< 0.01%) by PCR at end of Induction is the most favorable prognostic factor followed by negativity at end of Consolidation (< 0.01%) regardless of MRD positivity at end of Induction. The presence of MRD ≥ 0.1% at end of Consolidation is associated with an increased risk of relapse. Moreover, patients with T-lymphoblastic lymphoma (T-LLy) who have minimal disseminated disease detected by flow cytometry at the time of diagnosis have an adverse outcome.[211] These studies clearly demonstrate that MRD is prognostically important in T-ALL/T-LLy, although confirmation by other large clinical trials is needed.

Flow cytometric approaches to MRD detection in T-ALL have the potential advantage that they are informative in the vast majority of cases, including those where T–cell receptor rearrangements are not present or not detected by PCR.[212] The studies published involve small patient cohorts and largely rely either on the expression of immature antigens, e.g. TdT, CD99, CD1a, or CD34, on T cells outside of the thymus[213-219] or on the absence of surface CD3 expression in the presence of cytoplasmic CD3, an aberrant T cell immunophenotype provided NK cells are effectively excluded.[215] Although the use of TdT and/or CD99 positivity in conjunction with cCD3 is a common strategy, we have shown that following Induction chemotherapy down-regulation of both is very common[220] and can lead to either underestimation or false negative results. The studies that have examined the correlation between MRD detection by Flow cytometry or PCR in T-ALL involve small patient cohorts but show a positive correlation between the techniques, although to a somewhat lesser degree than for B-ALL[41,214,219] perhaps reflecting the reliance of the flow cytometric methods used in those studies on inconsistently expressed immature antigens. Taken together, the data suggest that MRD in T-ALL can be detected by flow cytometry and that it correlates with PCR assays that have been shown to correlate with clinical outcome.

The assay to be employed on AALL1231 is the same as that currently in use on AALL0434 and does not rely on the immature antigens TdT or CD99. The assay uses a combination of more broadly expressed T cell antigens known to be both differentially expressed and more stable in T-ALL,[220] discordant expression of surface and cytoplasmic CD3 with NK cell exclusion,[215] and decreased to absent expression of CD48. The latter has been identified by our group (ASH abstract 2011) as a consistent finding in T-ALL at diagnosis that is relatively stable after Induction chemotherapy. This approach improves upon the published assays and employs a novel antigen in a high level (8-9 color) context that should improve both sensitivity and specificity through exclusion of non-leukemic populations via improved antigenic correlation.
Reference methods for minimal residual disease assays are not available, consequently determination of assay performance characteristics is problematic. Nevertheless, correlation of this flow cytometric assay with a PCR-based high-throughput sequencing assay (HTS) shows a high degree of correlation to a level of roughly 0.01%, suggesting a sensitivity of 0.01%. Those samples positive at any level by flow cytometry show no false positives in comparison with HTS, while flow cytometry negative samples show a single false negative just above 0.01% by HTS, suggesting a high degree of specificity above the level of 0.01%. Independent enumeration from the two tubes of the flow cytometric assay also shows a high degree of correlation without false positives or negatives in either direction, further suggesting a high degree of specificity. Given the absence of proficiency testing programs for this assay, blinded samples will be exchanged with another laboratory 3 times per year and concordance demonstrated.

Expected population distribution: On AALL0434, this assay has identified that roughly 50% of T-ALL patients lack detectable MRD (< 0.01%) at Day 29 in BM, suggesting a group at standard risk for relapse. Similarly, on AALL0434 roughly 10% of patients are estimated to have detectable MRD (≥ 0.1%) at the end of Consolidation, the only caveat being that on AALL0434 only patients with MRD ≥ 1% at Day 29 were assessed for MRD at end of Consolidation. The remaining roughly 40% of patients are considered to have an intermediate risk of relapse. On AALL0434, ETP patients represent 12.4% of the cohort. For T-

LLy, roughly 65% are estimated to have BM involvement <1% at diagnosis and are considered Standard Risk with the remaining roughly 35% of patients being Intermediate or Very High risk.
Cut-point rationale: The Day 29 (0.01%) and end of Consolidation (0.1%) cut-points are the same as those that have been shown to be prognostically important at their respective time points in a prior BFM study[38] and are confirmed to be prognostically important in T-ALL in a preliminary review of outcome data from AALL0434. For T-LLy, the cut-point of 1% is the same as that currently in use in AALL0434.

Result Access: Results from these analyses will be provided to investigators via the Children's Oncology Group clinical data system, using the identical established procedure already developed to communicate results in our frontline trials

Analytical performance: Our flow cytometric assay for minimal residual disease has been used in nearly 1,000 children with T-ALL enrolled in the on-going AALL0434 COG clinical trial for which outcome is not yet available. Consequently, we are not yet able to demonstrate the relationship of MRD to clinical outcome using this assay, but will do so when the outcome data is made available. Given our experience with a B-ALL MRD assay of similar design that has been shown to be highly prognostically significant (unpublished from AALL0232), the published data with assays of this type to date and the correlation of those assays with prognostically significant PCR assays, we are confident the assay will stratify patients for relapse risk. Comparison of this assay with PCR as a surrogate for outcome is not easily done, as the PCR assays are very labor and resource intensive and the group does not have access. However, we have done a limited correlation of this assay with a next-generation sequencing MRD assay (see attached Integrated Assay application) showing good correlation down to the range of 0.01% to 0.1% without false positives,[221] shown in Figure 1.

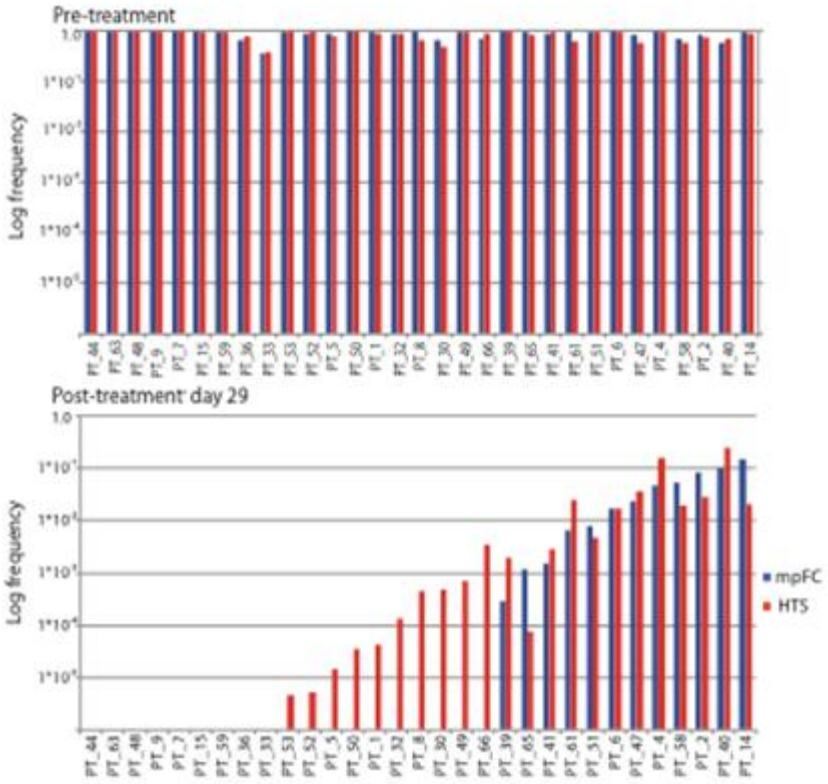


Figure 1. Identification of leukemic populations prior to and following therapy by the flow cytometric assay (mpFC) and next generation sequencing (HTS). Sequence data are reported as the frequency of the clonal sequence of total rearranged T cell sequences; Flow cytometry data are reported as the T-ALL frequency of total T cells including all CD7+ T/NK events.

We are unable to assess the precision of this assay in the usual fashion of having multiple replicates because the amount of sample available for repeat testing is limited. However, we have taken advantage of the fact that we use two different antibody combinations to calculate MRD, and can demonstrate a high degree of concordance between the two measurements, as shown in Figure 2. The small subset of mildly discordant samples is due the inability of one antibody combination to completely define the MRD population, which is evident at the time of analysis and would not lead to errors in reporting.

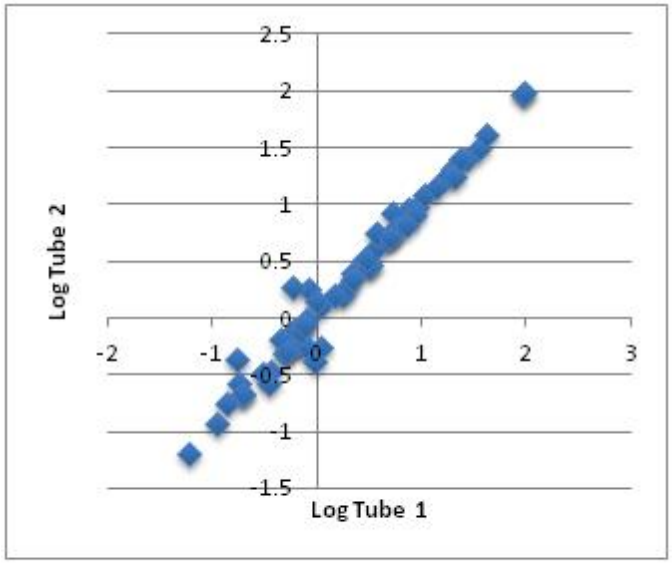


Figure 2. Correlation of MRD levels between two tubes used for MRD detection

The success rate of this assay in our hands is excellent. Less than 1% of samples received give indeterminate results in our assay. We do not have any extensive data on any critical preanalytical variables that have an impact on the performance characteristics of this test. Obviously, quality of the marrow initially obtained could have an impact if the specimen is significantly hemodiluted. While we do not have any direct means to measure hemodilution, we can use the proportion of nucleated red cells recovered in our sample as a surrogate for marrow quality. In preliminary analyses for a conceptually similar assay used for B-lineage ALL MRD monitoring we were unable to demonstrate an outcome difference between patients who lacked MRD but had low levels of nRBCs compared to those with high levels, suggesting that hemodilution in routinely obtained samples does not cause a significant underestimate of the MRD-positive patient population.

To standardize our ability to define ETP T-ALL, a cohort of cases of possible ETP T-ALL were independently reviewed by Dr. Dario Campana, who published the description of the ETP immunophenotype, and Dr. Wood. Discordant cases were reviewed and interpretive criteria refined. Applying these criteria to 790 cases of ETP from AALL0434 provided a frequency of ETP of 12.4%, which agrees very well with published frequency of 12.6%.[70]

APPENDIX XII: ADDITIONAL INFORMATION FOR PROPOSED BIOLOGY STUDIES: STUDIES OF PROTEASOME ACTIVITY, PROTEOMICS, AND SIGNAL TRANSDUCTION

Biology Objectives 1.3.2 and 1.3.3

I. HYPOTHESIS AND BACKGROUND:

The cornerstone of therapy in acute lymphoblastic leukemia (ALL) is risk stratification of patients based upon genetic alterations and minimal residual disease (MRD). While this strategy has proven beneficial in pre-B ALL, prognostic associations with genetic aberrations in T-ALL are not sufficiently compelling to contribute to risk-adapted therapy, likely due to the significant heterogeneity of mutations in this disease[222]. The AALL1231 clinical trial is testing the novel hypothesis that the addition of proteasome inhibitor therapy to an augmented BFM (ABFM) backbone will improve T-ALL event free survival (EFS). Recent data suggests that the many genetic subtypes of T-ALL, including the early thymic progenitor (ETP) phenotype, may converge on a more limited set of deregulated signaling pathways and cellular processes.[223] However, the frequencies with which signaling pathways are deregulated, how they impact prognosis, or how they modulate chemotherapy responses, are poorly understood. With better understanding and validation, these biochemical aberrations could be used clinically to identify patients with a "high risk" molecular signature that would benefit from more intensive chemotherapy.

Because DNA mutation analysis and gene expression profiling (GEP) have to date resulted in only modest gains in predictive power in T- ALL, we propose using protein analysis methods to understand the biochemical underpinnings of T- ALL. Our **long-term goal** is to identify and validate protein cell stress and/or signaling alterations that can be used alone or incorporated with GEP into a single, simple, and robust molecular classification system to aid in risk stratification and inform the design of future clinical trials incorporating targeted agents. If successful, the results of this research will move the study forward from an **integrated study to an integral study** that can be incorporated into future T-ALL clinical trials. The **overall objective** of this study is to determine whether proteasome and/or altered signal transduction patterns can identify protein expression profiles that predict response to bortezomib-containing therapy or are prognostic of clinical outcome. Based on our strong preliminary data, our **central hypothesis** is that proteasome alterations, protein cell stress activation, and/or the pattern of signaling networks will predict therapy response and allow us to identify patients with a "high-risk" protein expression pattern that could benefit from more intense chemotherapy. The **rationale** for this work is that a better understanding of the role of biochemical alterations in T-ALL will result in the optimization of simple, robust assays that will aid in pediatric ALL risk stratification and personalization of chemotherapy, ultimately improving clinical outcome. We will test our central hypothesis with the following **specific aims**:

Specific Aim 1: To determine if changes in proteasome function or cell stress protein expression patterns can predict bortezomib response and drug resistance in T-ALL.

a) To delineate the mechanisms of bortezomib action and resistance in T-ALL to determine if proteasome alterations correlate with clinical response (as measured by minimal residual disease (MRD) or outcome (EFS).
b) To determine if reverse phase protein lysate arrays (RPPA) predict chemotherapy response or resistance.
    1. To determine if protein cell stress pathways, such as the unfolded protein response, are active at baseline and how activity changes in response to chemotherapy +/- bortezomib,
    2. To define a putative "high risk" protein expression profile that identifies patients receiving either standard or intermediate risk therapy that would benefit from the more intense chemotherapy.
    3. To determine if RPPA protein expression profiles correlate with treatment group or T-ALL subtypes.

Specific Aim 2: To identify biomarkers and mechanisms of chemotherapy resistance and response in T-ALL, focusing on ETP-ALL.

a) To use single cell phosphoflow cytometry (SCPFC) to determine if differences in constitutive activation of the MAPK, PI3K/AKT/mTOR, and/or JAK/Stat pathways between ETP and non-ETP T cell subtypes will serve as a biomarker of chemotherapy response or resistance.
b) To determine if augmented NFκB signaling predicts response to induction chemotherapy with or without bortezomib in ETP and non-ETP T-ALL.
c) To use RPPA and SCPFC to build and validate multivariate classifiers to predict patient response to chemotherapy and determine risk of relapse.

II. SIGNIFICANCE: Previous research for prognostic risk factors in pediatric ALL have mostly focused on the characterization of genetic abnormalities.[224] Many of the new biologic agents being introduced into T-ALL therapy, however, directly target protein activation. We expect that the results of this research work will enable us to determine if cell stress pathways such as the UPR or altered signaling networks can identify protein biomarkers that predict response to induction therapy with Vincristine, Dexamethasone, Asparaginase, doxorubicin (VXAD) +/- the proteasome inhibitor (PI) bortezomib. Specifically, our goal is to develop a "high-risk" protein classifier that identifies patients with a higher risk of relapse in the standard and intermediate risk group. If these patients can be identified with a valid molecular classifier, this could directly result in improved therapy and outcome, as higher risk patients would be assigned to more intensive therapy. There are also significant gaps in our understanding of the role of the UPR and other cell stress pathways in response to T-ALL treatment. Successful completion of the aims described will better define the role of these biochemical pathways in response to chemotherapy. Although the primary objective of the clinical trial is to determine if bortezomib-containing therapy increases long-term survival, the objective of this work is to develop protein expression classifiers that provide useful predictive and prognostic information whether or not bortezomib is found to be an effective agent. This contribution will be significant because it will add the predictive power of protein alterations to the armamentarium of genetic mutations currently used to assess relapse risk, increasing the power of risk stratification and identifying patients most likely to benefit from therapies that target deregulated cell signaling pathways in T-ALL.

This research will also have a significant positive impact on future research for three reasons. First, successful completion of this application will define the contribution of alterations in signaling and cell stress proteins to treatment outcomes, an objective within the NIH mission to improve the diagnosis and treatment of cancer. Second, markers of protein cell stress pathway activation could be used to determine the mechanism of action of biologic agents that directly alter protein homeostasis such as proteasome inhibitors (PI) and tyrosine kinase inhibitors (TKI) in appropriate T-ALL subgroups. Third, the results of this study could enable the future development of simple, robust diagnostic assays testing specific proteins or protein clusters that predict response to (VXAD) induction. This will allow for further refinements in risk stratification and, by predicting response to VXAD alone or to PI-containing therapy, will lead to the further development of personalized T-ALL treatment.

III. INNOVATION: Prior research has demonstrated that mRNA abundance does not always correlate with protein expression,[225] highlighting a need for new approaches to assess protein signal transduction in multi-institution trials. There is precedence for this approach. Previous proteomic studies in ALL have utilized prospective cohorts to show that proteasome activity is prognostic of clinical outcome (Horton AACR abstract 2014) and that SCPFC can predict response to therapy in both ALL[226,227] and AML[228-230]. RPPA is also predictive of response duration in adult ALL.[231] *The proposed research is innovative because, with the successful completion of these aims, we will demonstrate that RPPA and SCPFC can transition into simple robust assays that can be applied to large sample sets in multi-institution clinical trials. The data generated from this application will also provide prospective validation of clinical usefulness of the RPPA and SCPFC techniques in the setting of a phase 3 clinical trial.*

Our preliminary data (see below) indicates that RPPA and SCPFC are both feasible and informative in the setting of a multi-institutional clinical trial. Proteomic data from either static (RPPA) or dynamic (SCPFC) molecular diagnostics, in combination with genomic data, could become key assays for response prediction and risk stratification in T-cell ALL where utility of genetic classifiers has been limited. Since gene-expression profiling (GEP) data can be combined with protein array data, there also is the potential to develop more in-depth and robust models of therapy response and relapse risk.[232,233] *The innovation of this study will be in creating the foundation for combined proteome and transcriptome analyses in future trials*.

IV. JUSTIFICATION FOR PROSPECTIVE COLLECTION OF FRESH SAMPLES

Shipping and handling delays are commonplace in multi-institutional clinical trials. Although most samples can be shipped overnight, samples are frequently delayed up to 72h over weekends. Although DNA mutation analysis and gene expression profiling (GEP) can be performed on frozen samples after shipping, GEP and mutation analyses have (to date) limited predictive power in T-ALL. We propose a broader approach using protein analysis methods to understand the biochemical underpinnings of T-ALL. Our long-term goal is to develop a simple, robust protein analysis that could either be incorporated with GEP/ mutation analysis, or used alone as a complementary tool for risk stratification.

Both of the aims of this study will require prospective collection of *fresh* lymphoblasts. This has been demonstrated for RPPA (see below) prior to the initiation of a similar study in AAML1031. A very similar set of experiments was reviewed by both the COG AML Biology committee and by the NCI, which is currently providing R01 funding for the project. Although SCPFC can theoretically be performed on banked specimens, multiple laboratories (C. Mullighan, J. Dick, D. Teachey, R. Lock, M. Hermiston, and A. Fernando, personal communications) have found that T-ALL samples, particularly those of the ETP phenotype, have extremely poor viability and yields upon thawing relative to pre-B ALL samples. For example, the yield upon thawing of 10 AALL0434 T-ALL samples from the COG tissue bank ranged from 3.8-17.8% (mean 6.94% viable cells, equivalent to 0.44 to $2.9x10^6$ cells/vial) (Shimano and Hermiston, unpublished observations; Fig 2A). This is in contrast to adequate viability (>70% of samples have >90% viability) when B-ALL are cells thawed from the COG tissue bank. Similarly, the Teachey laboratory found that only 30% of banked ETP-ALL cells had viability greater than 90% post thaw. While all of these high post-thaw viability samples engrafted successfully in Nod Scid Gamma (NSG) mice, none of the remaining 70% of samples with poor post-thaw viability engrafted.

Based on these observations and our belief that understanding the biology of ETP and high-risk T-ALL at a functional level is critical for identification of protein pathways resulting in chemotherapy resistance, we propose to perform these analyses on fresh samples. Since RPPA and SCPFC both require fresh cells, it will also provide a unique opportunity to compare these methods and to determine if 1) one of the two is more robust in a Phase 3 clinical trial, and 2) if the assays provide complementary information. Use of fresh cells will also enable us to achieve our long-term goal of developing a simple, robust protein classifier that can be combined with mutation analysis and GEP to aid in risk stratification. The objective of the classifier is to identify patients with a "high-risk" molecular signature that have been placed in either the SR or IR risk group, thus improving risk stratification and increasing EFS in these groups. Because sample availability has greatly limited our ability to study T-ALL biology to date, the use of fresh tissue will enable a comprehensive biochemical analysis in both non-ETP and ETP-ALL subtypes.

A. Feasibility of collecting pre-treatment bone marrow samples from multiple sites for SCPFC analysis:

To evaluate the feasibility of shipping fresh T-ALL cells for SCPFC, Dr. Brent Wood shipped 10 pairs of fresh ETP and non-ETP ALL samples (left-over after diagnostic flow cytometric phenotyping and MRD analyses) to the Hermiston Lab at UCSF over a six-month period. Even with delays of 72 hours, viability remained uniformly good (range 81-98%) and robust signaling responses could be obtained on all samples (Figure 1B). Moreover, preliminary data indicates that engraftment rates in NSG mice are quite high (data not shown).

Together, these data indicate that it is feasible to collect pre-treatment samples in the setting of samples shipped from multiple sites.

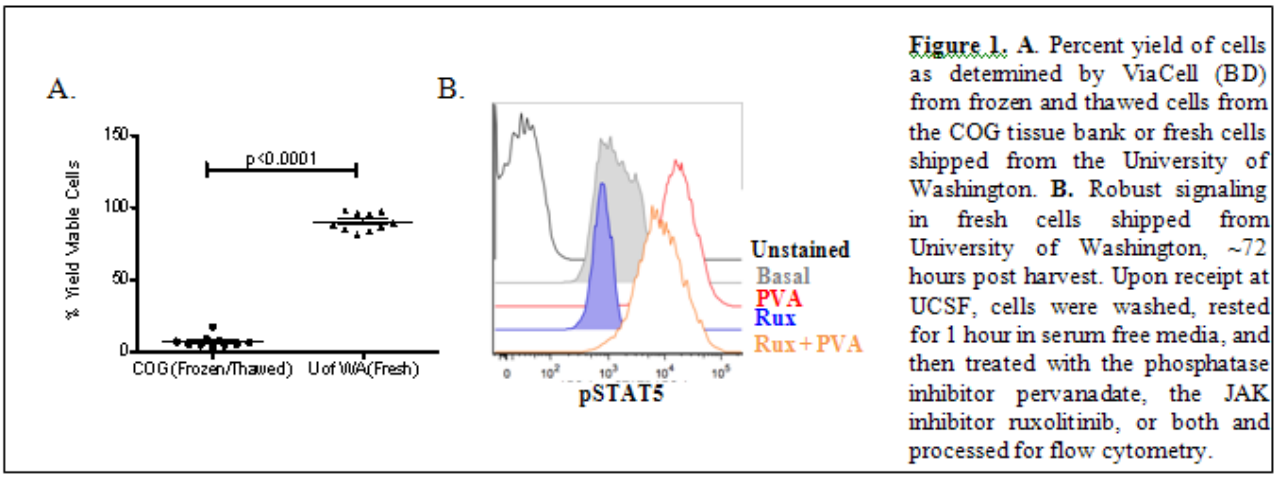
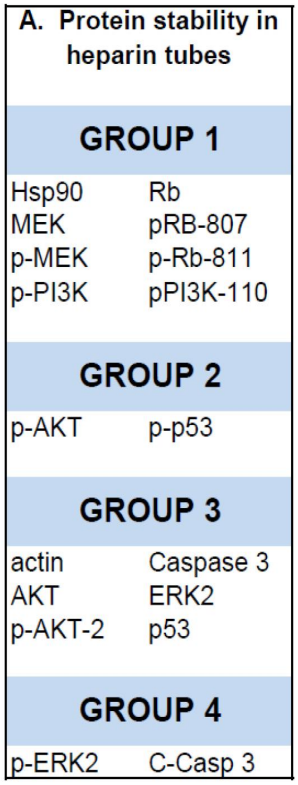


Figure 1. A. Percent yield of cells as determined by ViaCell (BD) from frozen and thawed cells from the COG tissue bank or fresh cells shipped from the University of Washington. **B.** Robust signaling in fresh cells shipped from University of Washington, ~72 hours post harvest. Upon receipt at UCSF, cells were washed, rested for 1 hour in serum free media, and then treated with the phosphatase inhibitor pervanadate, the JAK inhibitor ruxolitinib, or both and processed for flow cytometry.

B. Feasibility of collecting pre-treatment peripheral blood and bone marrow samples from multiple sites for RPPA analysis: To test the magnitude of the effect of shipping and handling delays on protein expression, we generated two custom protein arrays, one to test the stability of protein expression in heparin tubes (Table 1 and figure 2A) and a second to test protein stability in CellSave (CS) preservative tubes (Veridex) following treatment (Figure 2B). In the first analysis, 7 pediatric AML samples were processed either on site or after shipment by air courier from New York University (Horton, manuscript in preparation). Shipping was done with peripheral blood in heparin tubes and lysates were prepared under 5 conditions as shown in Table 1. We found that 16 of 18 proteins (Groups 1-3) (Fig. 2A) showed either no change or a decrease in protein concentration that could be calibrated if samples were processed within <72h. These data indicate that reliable signaling information can be obtained from shipped cells.

Table 1: AML Sample: Test of Shipping Conditions

Sample Treatment / Sample	Tx:1 Same day processing	Tx 2: Held at 4° C	Tx 3: Held at room temp	Tx 4: Shipped at 4° C	Tx 5: Shipped at room temp
Sample 2-PB[1]	X	24h	24h	24h	24h
Sample 3-BM	X	72h	72h	72h	72h
Sample 4-PB	X	72h	72h	72h	72h
Sample 5-BM	X	24h	24h	24h	24h
Sample 5-PB	X	48h	48h	48h	48h
Sample 6-BM	X	24h	24h	24h	24h
Sample 7-PB	X	24h	24h	24h	24h



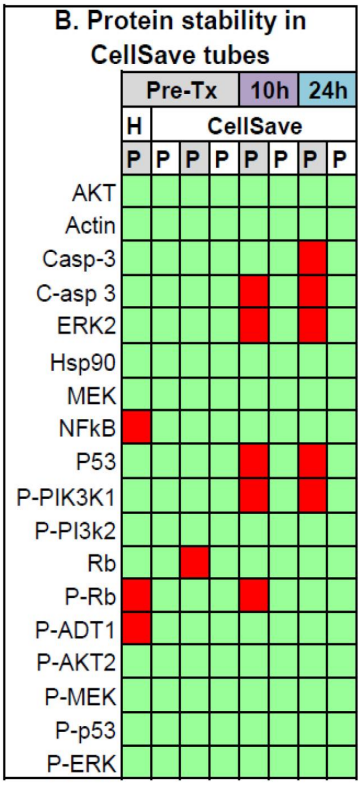


Figure 2:

A. Protein stability in pediatric AML. Samples were collected in heparin tubes and shipped over 24-72h. Changes in mean protein concentration were normalized and compared to the range of each protein expression in 544 adults with AML (normalization from -3 to +3). **Group 1:** Minimal/no change (<0.5 normalized log2 protein concentration) with shipping. **Group 2:** Predictable change (0.5-1 unit decrease) with shipping. **Group 3:** Time sensitive: Minimal change if process <72h from collection. **Group 4:** Unpredictable changes (>0.5 units) independent of shipment time.

B. Protein stability in CellSave preservation tubes: Control lanes (ln) 1-2: Normalized protein conc. - heparin (H) vs. CellSave in pre-tx samples. Significant differences noted in red; no significant difference in green. Ln 3-8: Comparison of protein concentration before, and at 10h and 24h after ADE therapy. Ln3-4: pre-treatment; Ln 5-6: 10h after treatment; Ln 7-8: 24h post-treatment. Gray P= unadjusted p value by Student's t test; White P= adjusted p value after correction for multiple comparisons using false discovery rate method.

C. <u>Justification for prospective collection of non-frozen samples in Cell Save preservation tubes for RPPA analysis</u>. Using a second patient cohort, the second array compared protein quality of lysates prepared from fresh cells versus frozen pellets (Tables 2 and 3). This array was done based on preliminary data in the Kornblau lab, using heparin tubes for pre-treatment samples, that demonstrating that frozen samples underwent significant sample degradation (Figure 3). **This data indicated that RPPA lysates must be made with fresh T-ALL samples,** and that the use of cryopreserved samples would result in sample degradation and potentially misleading results**.**

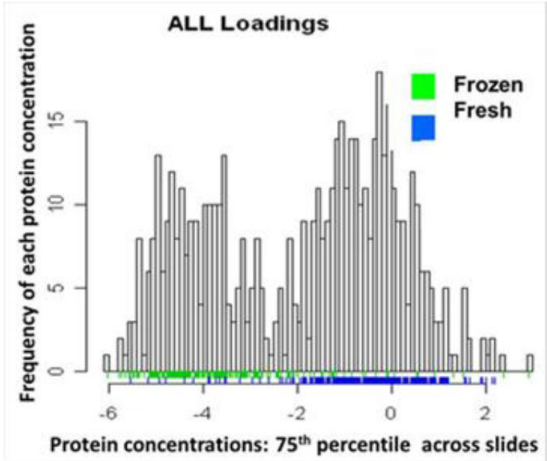


Figure 3: Protein degradation with freezing prior to RPPA lysate preparation: Protein expression of freshly made protein lysates (blue) vs. Proteins lysates made from cyropreserved cells (green). The 75th percentile of all proteins across the slide are compared between slides made from lysates prepared from fresh samples. vs. lysates made after samples had been cryopreserved and used at a later time. Each bar represents the frequency of the relative concentration for each protein from the 2 arrays

To determine if collection of fresh material in CS tubes alone would be sufficient for sample preservation in shipped samples, our second custom RPPA (Tables 2 and 3) compared CS tubes with immediate processing to those collected before treatment, 6h and 24h after treatment (n=23) with and without freezing. Protein expression between groups was compared using Student's t tests analyzing 17 validated RPPA antibodies. Although pre-treatment samples showed little difference in protein expression after shipping (Table 2, left panel) post-treatment samples demonstrated highly significant differences (Table 2, right panel). We then compared protein expression shipped in CS tubes without freezing (Table 3) where there are only a few significant differences between CS samples processed immediately and those processed with non-frozen samples (Table 3, right panel). A summary of the statistically post-treatment using fresh lysates are shown in Figure 2B. Based on

these analyses, we concluded that 1) the effects of shipping and time delays <72h should be minimal and should not confound protein expression analysis, and 2) CS preservation tubes processed within 72h can protect protein expression from changes during shipping. **Taken together, these data indicate that RPPA, SCPFC, the UPR and other cell stress proteins is both feasible and reliable as long as samples are collected prospectively and lysates prepared prior to cryopreservation.**

Table 2: Differences between protein expression using frozen lysates: CS immediate processing vs. CS processed after a 24-72h delay.

	Pre-tx		6h Post		24h Post	
Protein	p	adjusted p	p	adjusted p	p	adjusted p
AKT	0.24	0.38	0.000233	0.00035	0.000523	0.00086
Actin	0.16	0.33	0.000433	0.0006	0.000275	0.00071
Caspase_3	0.40	0.51	0.000135	0.0003	0.000036	0.00036
Caspase_3_cl	0.14	0.32	0.000008	0.00007	0.000121	0.00051
ERK2_	0.32	0.45	0.000571	0.00073	0.000399	0.00086
Hsp90	0.20	0.36	0.000103	0.00026	0.000506	0.00086
MEK	0.13	0.32	0.000197	0.00035	0.000040	0.00036
NF_kB	0.33	0.45	0.000653	0.00078	0.001630	0.00244
P53	0.10	0.32	0.000229	0.00035	0.000141	0.00051
pPI3K110	0.07	0.32	0.000065	0.00023	0.000195	0.00059
pPI3K85	0.14	0.32	0.001386	0.00156	0.002756	0.00331
Rb	0.04	0.32	0.000028	0.00013	0.000096	0.00051
pRb	0.02	0.32	0.000021	0.00013	0.000512	0.00086
p_AKT308	0.14	0.32	0.000217	0.00035	0.002068	0.00286
p_AKT	0.50	0.56	0.000087	0.00026	0.003824	0.00430
p_MEK	0.97	0.97	0.020626	0.02184	0.133027	0.14085
p_P5	0.74	0.78	0.000006	0.00007	0.002342	0.00301
p_erk	0.49	0.56	0.103560	0.10356	0.514352	0.51435
	n=23	n=17	n=23	n=17	n=22	n=16

Significant differences (<0.05) are highlighted "Normalizedmean protein concentrations for each protein comparedusing Student'st test." Adjustedp determinedby false discovery rate method to adjust for multiple comparisons.

Table 3: Differences between protein expression using non-frozen lysates: CS processed immediate processing vs. CS processed after a 24-72h delay.

CellSave tubes					
pretreatment		6h post-treatment		24h post-treatment	
imm	delay	imm	delay	imm	delay
raw data		raw data		raw data	
p	adjusted p	p	adjusted p	p	adjusted p
0.35	0.58	0.10	0.14	0.06	0.13
0.34	0.58	0.07	0.14	0.03	0.11
0.27	0.54	0.09	0.14	0.04	0.11
0.68	0.77	0.09	0.14	0.15	0.21
0.25	0.54	0.10	0.14	0.04	0.11
0.16	0.49	0.04	0.14	0.02	0.11
0.15	0.49	0.05	0.14	0.03	0.11
0.46	0.59	0.10	0.14	0.08	0.13
0.40	0.59	0.20	0.23	0.10	0.15
0.16	0.49	0.04	0.14	0.01	0.11
0.23	0.54	0.03	0.14	0.03	0.11
0.14	0.49	0.08	0.14	0.06	0.13
0.04	0.49	0.03	0.14	0.08	0.13
0.15	0.49	0.08	0.14	0.35	0.43
0.46	0.59	0.12	0.15	0.18	0.23
0.97	0.99	0.67	0.67	0.65	0.68
0.99	0.99	0.14	0.17	0.43	0.48
0.63	0.76	0.53	0.56	0.73	0.73
23	22	23	22	23	22

Significant differences (<0.05) are highlighted "Normalizedmean protein concentrations for each protein comparedusing Student'st test." Adjustedp determinedby false discovery rate method to adjust for multiple comparisons.

V. APPROACH

A. Sample collection, sample size and prioritization: The COG AALL1231 study will be a Phase 3 study which will randomize pediatric and adolescent/young adult (AYA) T-cell ALL and T-cell lymphoblastic lymphoma (T-LL) patients to receive either standard chemotherapy (modified BFM=VXAD) or standard therapy with bortezomib (VXAD-B), with the goal of obtaining 952 eligible, evaluable patients with T-ALL. T-LL patients will be excluded from this biology study.

Bone marrow (5cc at start of study and 5cc at end of Induction (Day 29) in heparinized tubes) will be collected for proteasome and SCPFC analysis. Peripheral blood (PB, 3mL in CS tube, 2 ml in a heparinized tube) will be collected for each eligible patient prior to the start of therapy and at 6 hours (h) and 24h following start of treatment. One requirement for eligibility for biology studies will be to have an absolute blast count (ABC) of at least 1000 cells/µL to have sufficient lymphoblasts for RPPA, SCPFC and proteasome analysis. We estimate that approximately 80% of patients will have sufficient PB lymphoblasts based on the historical control trial AALL0434.Based on bone marrow collection in AALL07P1 and AAML07P1, we estimate that we will receive at least 50% of pretreatment marrows. Based on the Horton lab collection of similar samples on the COG phase 3 AML trial AAML1031, eligible, evaluable and usable peripheral blood were obtained from 36% of enrolled patients. *Based on the percentage of patients with eligible blasts in PB and collection rates from the COG AML study AAML1031, we estimate that we will receive 476 eligible, evaluable, and usable bone marrow samples (238/tx group), and 342 PB samples from T-ALL patients (171/treatment (tx) group).* This will be the sample size for comparing cellular signaling pathways in treatment groups (VXAD +/-B) and in ETP vs. non-ETP patients.

SCPFC will be done from both bone marrow and peripheral blood. Assuming ETP will occur in 12.4% of patients, the samples size for ETP and non-ETP will be quite different. If marrow is received from 50% of eligible patients (estimate from AAML1031 and AALL07P1) we will have 476 marrow samples (238/tx group) with 59 ETP/417 non-ETP patients (30 ETP/tx group, 208 non ETP/tx group). Although the sample size will be smaller, we will also plan to examine changes in PB protein expression in both ETP and non-ETP groups. For peripheral blood we will have 342 patients, 42 of which will be ETP and 300 non-ETP.

Table 4: Prioritization of experiments for peripheral blood and bone marrow collection

Experiment	Aim	Lymphoblast # required/[a]	Sorting	Est blood volume	Tube type[b]	Timepoint (s)	Priority
RPPA	1	$8x10^5$	yes	1-2 mL	CS	0h, 6h, 24h	1
SCPFC	1&2	$1x10^7$	no	1-2 mL	Hep	0h, 6h, 24h	1
Proteasome expression[c]	1a	$5x10^6$	yes	1mL	CS	0h, Day 29[d]	2
Proteasome activity[c]	1a	$3x10^6$	yes	1 mL	Hep	0h, Day 29[d]	2
UPR-qRT-PCR	1	$2x10^6$	yes	0.5 mL	Hep	0h, 6h, 24h	3
UPR protein	1a	$1x10^7$	yes	1mL	CS	0h, 6h, 24h	3

a: #= number, sx = sample; b: CS =CellSave preservation tubes (Veridex), c. proteasome assays will be done with bone marrow prior to treatment and with bone marrow at the end of Induction (Day 29).

For assessment of proteasome activity/expression (Priority 2), we will use BM (pre-treatment and End of Induction (Day 29). Proteasome activity will be compared to response to therapy (as determined by End of Induction (Day 29) MRD with a cutoff at 0.01%) and EFS at 4 year. For bone marrow samples, the sample size is estimated to be 476 (238 Day 29 MRD >=0.01% /238 MRD <0.01%). Changes over time (pre-treatment vs. Day 29 bone marrow) will have a sample size of 238 (119/MRD status), accounting for the 50% drop-out rate of Day 29 bone marrow compared to pre-treatment bone marrow. It is likely that we will have sufficient sample size to compare baseline proteasome activity by ETP status (59 ETP/ 417 non-ETP).

UPR studies will be done with peripheral blood, and bone marrow if extra remains (Priority 3). For UPR protein analysis, we estimate that 25% of the "UPR patients" will have sufficient material for analysis,[234] resulting in a sample size of 86 patients (43 patients/tx group).

For ease of collection and processing at individual sites, all samples will be sent to the Horton lab where the will be divided and subsequently sent to the Hermiston laboratory (Figure 4). The estimate of lymphoblasts per samples will vary significantly depending on the absolute blast count of the sample and the processing required for analysis (e.g., requirement for cell sorting). As in previous studies, we have limited our blood collection volume to 5 mL (2mL heparin, 3mL CS preservation tubes).

B. Workflow. Figure 4 demonstrates the workflow for sample analysis. WBC number and viability will be determined upon receipt of shipped samples using an automated fluorescence cell counter. Cells will then be processed as previously described [235] with the addition of non-T cell depletion using magnetic separation prior to processing for RPPA lysates proteasome, and UPR analysis. Depletion will not be performed on heparin samples for SCPFC analysis or (if excess sample) for xenograft engraftment. Protein pellets and protein lysates will be prepared on day of receipt. Because sample availability has greatly limited our ability to study ETP biology to date, xenografts will be established in NSG mice from any leftover cells not required for these assays. Any samples emerging from these xenografts will be deposited in the BioPathology Center to be banked for future use.

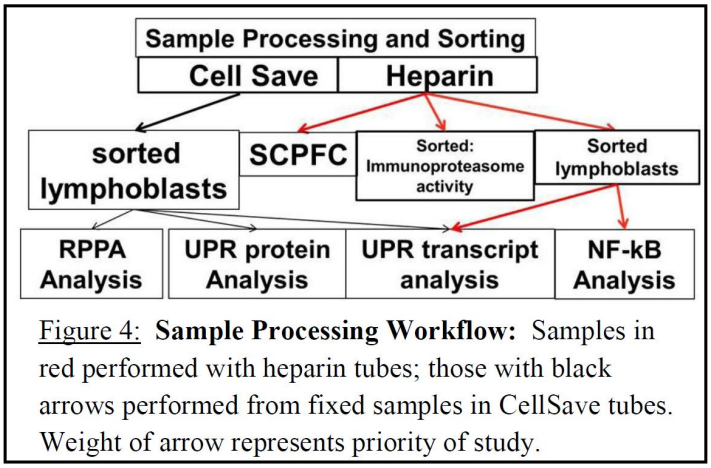


Figure 4: **Sample Processing Workflow:** Samples in red performed with heparin tubes; those with black arrows performed from fixed samples in CellSave tubes. Weight of arrow represents priority of study.

C. Study Team: We have developed a very experienced team of experts with expertise in the areas of focus in these correlative studies: David Teachey (T-cell biology), R. Sifers (UPR), S. Kornblau (RPPA), M. Hermiston (biochemical analysis in T-ALL) and T. Horton, (protein homeostatis). Dr. Horton has conducted several COG clinical trials with bortezomib in relapsed leukemia and lymphoma.[235-240] She will combine her expertise with specialists in the UPR, RPPA and SCPFC that, as a team, are uniquely placed to evaluate protein cell stress pathways within a multi-site clinical trial. We have assembled a statistical team that will be led by M. Devidas, head of the COG statistical core. Protein array analysis and UPR will be done by A. Tsimelzon and C. Ahern (Baylor College of Medicine) and K. Coombes (MD Anderson); SCPFC analysis will be done by C. Delgado-Martin, M. Hermiston and A. Olshen at UCSF; proteasome analysis will be performed by the laboratory of Jacqueline Cloos (VU Medical Center, Amsterdam). Dr. Devidas will review all statistics and aid in the correlation of array results with clinical outcome.

D. Specific Aim 1: **To determine if changes in proteasome function or cell stress protein expression patterns can predict bortezomib response and drug resistance in T- ALL**

1.) Subaim 1a. To delineate the mechanisms of bortezomib action and resistance in T-ALL to determine if proteasome alterations correlate with clinical response (Day 29 MRD) or outcome (EFS).

a. **Overview**

Baseline UPR activation is associated with improved 5y-EFS in adults with AML.[241] There is also evidence that response to PI therapy correlates with UPR activation.[242] However, while *in vitro* studies have shown that UPR activation can induce T-ALL cell apoptosis,[243-245] UPR activation following T-ALL chemotherapy has not been examined in patients. This aim will examine whether baseline UPR activation, or changes that occur in the first hours of VXAD +/- bortezomib can determine if induction of UPR effectors can predicts response to VXAD +/- bortezomib chemotherapy in T-ALL. As part of our goal of identifying prognostic and predictive protein cell stress biomarkers, the objective of this aim will specifically focus on defining the role of the UPR in pediatric T-ALL cell apoptosis and the utility of UPR activation as a indicator of chemotherapy response. We will test the working hypothesis that activation of the UPR pathway will enhance VXAD-mediated apoptosis. Such findings would be of importance, because it will allow, for the first time, the use of UPR proteins as predictors of chemotherapy response.

Several prior studies have examined mechanisms of bortezomib action and resistance in pediatric leukemia. Three signal transduction pathways are of interest based on preliminary data and feasibility from our lab and others: 1) the response of the proteasome to proteasome inhibitor (PI) therapy,[239,246] 2) the activation of the endoplasmic reticulum (ER)-mediated unfolded protein response (UPR), and 3) the activation of the NF-κB pathway.

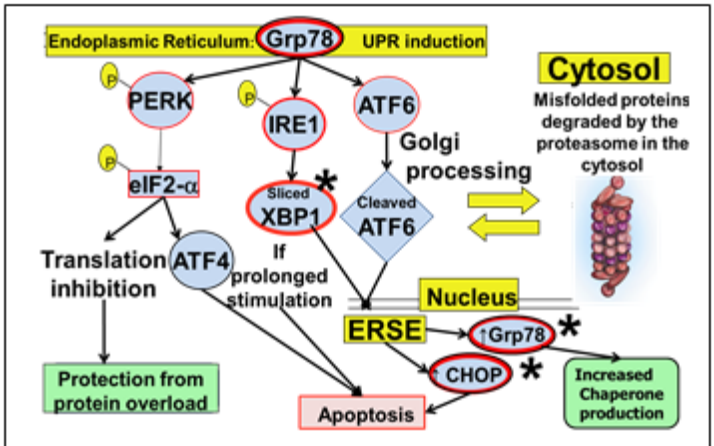


Figure 5: Activation of the UPR: The UPR sensor Grp78 activates three UPR paths, all of which can trigger apoptosis if protein folding capacity if overwhelmed. Proteins with asterisks: UPR transcripts that will be tested on all samples. Methods: UPR transcripts (red circles) will be quantified by qRT-PCR and UPR proteins (black circles) by immunoblots. Antibodies have been optimized for use with clinical samples. ERSE = endoplasmic reticulum response element.

1) Overview of proteasome expression and activity in pediatric leukemia: Although PI therapy has had encouraging results in multiple myeloma and follicular large B cell lymhoma, its efficacy is often limited by the development of proteasome resistance. Although proteasome resistance in T-ALL can result from proteasome mutations,[247] they can also correlate with change in proteasome capacity.[248] The Cloos laboratory has recently shown that

immunoproteasome activity is higher in T-ALL lymphoblasts than in pre-B cells and AML, both in cell lines and in primary patient samples.[239] In a recent collaboration between the Cloos and Horton laboratories, we discovered that patients having higher immunoproteasome expression were more likely to respond to bortezomib, as measured by CR2 after cycle 1 of therapy (see preliminary data below).[246]

2) Overview of the unfolded protein response (UPR): Studies have shown that pathways regulating cell stress, the ubiquitin-proteasome pathway, and the UPR are integrally linked. Damaged proteins awaiting proteasome degradation accumulate in the ER and induce expression of the UPR sensor protein Grp78 (Fig 5).[249,250] Grp78 activates three effector branches of the UPR (Figure 5): the pancreatic kinase like ER kinase (PERK)/eIF2-α pathway (left), the IRE1/XBP1 pathway (middle), and the AFT6 pathway (right).[243] Phospho (P)-eIF2α inhibits global translation, while spliced (s)XBP1 and cleaved (c) AFT6 induce the transcription of chaperone proteins that assist with protein folding.[251] However, if cellular damage is too extensive for repair, UPR effectors (Grp78, IRE1, sXBP1 and CHOP) trigger apoptosis.[245,252]

3. The role of NF-κB activation: NF-κB activity was shown to be inhibited in early trials of bortezomib in pediatric leukemia.[235] Recent data with a larger sample sample size (n=61) collected from patients enrolled on both Phase 2 trials of bortezomib in pediatric leukemia (AAML07P1 and AALL07P1) have shown that, although NF-κB is decreased in many patients, the decrease does not correlate with clinical response. However, whether this holds true in T-ALL has not been adressed. Due to the analytic limitations of the NF-κB ELISA in prior studies, NF-κB analysis will be performed using SCPFC in Aim 2b.

b. **Rationale and preliminary data**

1) Immunoproteasome preliminary data: Results from Jacqueline Cloos (VU Medical Center, Amsterdam, the Netherlands) and the Horton lab have shown that the ratio of immunoproteasome to proteasomes vary widely in pediatric leukemia patients and that increased proteasome activity correlated with increased sensitivity to PI inhibitors including bortezomib.[239] We have expanded this analysis to determine if proteasome activity correlated with response to bortezomib-containing chemotherapy (Figure 6). Samples collected on the Phase 2 clinical trials AALL07P1 and AAML07P1 were assessed for proteasome activity and expression. This study showed, for the first time, that the **baseline ratio of immunoproteasome to proteasome expression correlated with response to therapy** (post-induction CR).[246] Patients that reached a complete remission (CR) following induction, had 2-fold higher ratios of both β5i/β5 and β1i/β1subunit expression compared to patients who did not (p=0.019 and p=0.022). We also observed increased ratios of pre-treatment subunit-

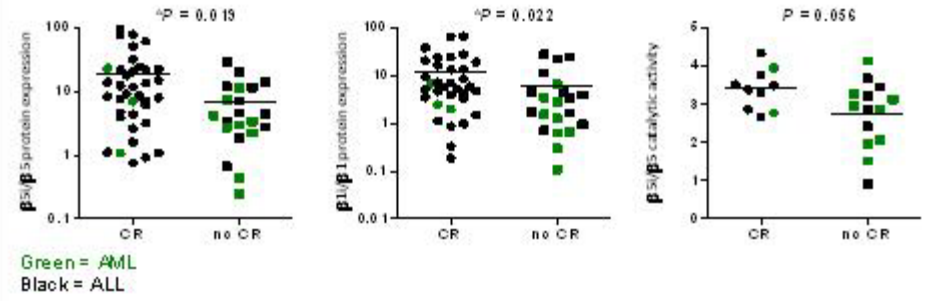


Figure 6: Ratio of immunoproteasome to proteasome protein subunit expression and catalytic activity in patients with CR after induction.

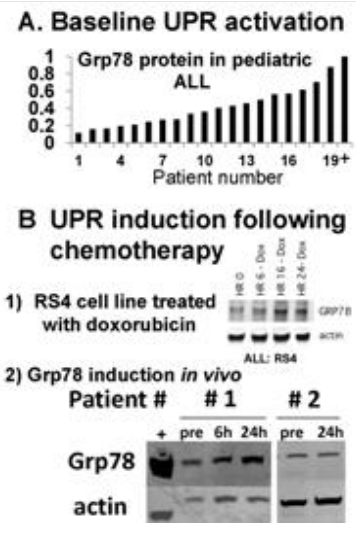


Figure 7: UPR activation in ALL: **A.** The UPR chaperone Grp78 protein is variably expressed at baseline in pediatric ALL patients. **B.** UPR activation (as measured by increases in the UPR sensor Grp78) is seen in both cell lines and in some (but not all) primary ALL patients following VPAD. + control: RAW cell.

specific catalytic activity of β5i/β5 were observed in patients that reached CR (n=10) compared to those who did not (n=14).

2) UPR activation: Similar to adult AML, we **hypothesize** that patients with an intact UPR pathway will have a better response to VXAD +/- B,[241,253] and that patients sensitive to bortezomib will have robust UPR activation following chemotherapy. Preliminary data from the Horton lab shows that baseline UPR activation, as determined by Grp78 protein expression, varies widely between ALL samples (Fig 7A) (Horton et. al., manuscript in preparation). UPR activation after chemotherapy (VPAD; P = prednisone) was also seen in 1/7 pediatric ALL patients (Fig 7B).

c. **Experimental Design**

Subaim 1a will focus on known candidate signal transduction pathways involved with the response to bortezomib. We will evaluate UPR activation using both transcript analysis (qRT-PCR) and protein analysis (immunoblots). Although UPR qRT-PCR does not equate with protein expression, it does reflect UPR pathway activation and activation of proteins that can trigger apoptosis. It also requires limited cell numbers ($2x10^6$) and will be done on most eligible patients (in the context of being Priority 3). Also, qRT-PCR for most UPR transcripts can be performed using CS tubes. Although the yield is decreased by approximately 50%, the results are similar (Horton, unpublished results). Based on data from AAML1031, we estimate that 25% of patients will have sufficient sample for UPR protein analysis by immunoblot.

1) Determine if there is evidence of baseline UPR activation: Since an overwhelmed UPR can trigger apoptosis,[252] we hypothesize that baseline induction of the UPR could indicate cell stress and correlate with therapy response (MRD) and clinical outcome (EFS).[241] We will assess baseline UPR activation by quantitating sXBP1 (an early event in UPR activation), the UPR sensor GRP78, and the UPR terminal effector CHOP. Initial assessment will be by qRT-PCR, as this requires the fewest number of cells and can be done on all eligible, evaluable, and usable patients (n=342). Baseline GRP78 and CHOP will be compared to normal lymphocytes and ALL cell lines. sXBP1 will be the primary measure of baseline UPR activation. Transcript expression will be compared by response (MRD) and and outcome (EFS). We expect that baseline UPR expression will be more common in treatment responders based on our preliminary data; however, groups will also be compared over the first day of treatment to determine if changes over time are more predictive of response.

2) Determine if chemotherapy (VXAD+/-B) induces the UPR. In addition to baseline UPR activation, we will also assess UPR activation following treatment, allowing us to correlate both baseline and induced UPR activation with clinical outcome. UPR effectors (sXBP1,GRP78, CHOP) will be assessed during day 1 of therapy (0h, 6h, and 24h). Our working hypothesis is that chemotherapy will activate the UPR(i.e. increase over time from 0h to 6h or 24h) in some, but not all, patients and that UPR activation will be more pronounced in the patients receiving bortezomib-containing chemotherapy. This is based on our preliminary data (Fig 7) a In patients that have evidence of UPR activation following treatment, we will determine which of the three UPR pathways is activated. We have optimized 7 antibodies for detection of UPR immunoblots (Grp78, PERK, p-eIF2-α, IRE-1, XBP1, CHOP and ATF4) and 11 primer sets for qRT-PCR quantitation of UPR transcripts (above +spliced Xbp1, p-PERK, ATF6, and calreticulin) (Fig 5). We expect that chemotherapy will induce UPR transcripts and effector proteins and result in increased spliced (s)Xbp1, an indicator of UPR activation and an apoptosis trigger.

3) Assess the prevalence of UPR activation in ETP-ALL: Prior work indicates that baseline UPR activation in adult AML is more frequent in high-risk cytogenetic phenotypes such as monosomy 7 and del5q.[241] However, the extent of UPR activation is unknown in ETP-ALL. We expect that UPR activation will be more pronounced in ETP-ALL; however it is possible that only the non-apoptotic pathways (p-eIF2α down-reguation and chaperone induction) will be common and that effector molecules may not be triggered, as seen in Waldenstroms macroglobulinemia.[254] This will be assessed by qRT-PCR and (in patients with sufficient material) immunoblots.

4) Assess UPR activation by treatment and response groups: Baseline UPR activation, as well as UPR induction following chemotherapy, will be stratified by treatment groups. Our working hypothesis is that VXAD+B treated patients will have more sustained activation of protein cell stress pathways, including terminal UPR proteins that trigger apoptosis such as Grp78 (through caspase 7), CHOP (through caspase 4), and sXbp1 (via JNK).[244] We also expect to find that patients responding to therapy (VXAD+/-B) will have evidence of increased sXBP1 transcripts, sustained IRE1 activation, and increased Grp78 and CHOP.[244,245,251] These proteins will be more fully evaluated in the context of other protein cell stress pathways in SA1b. Our goal is to develop a protein expression classifier that can predict response to VXAD+/-B, and to determine if protein classifiers can also identify SR and IR patients likely to benefit from more intense chemotherapy based on their 'high-risk" protein signature.

d.) **Statistical methods and justification**

1) Sample size- Please see Section V for sample size assumptions and justification.

In addition to determining the effect sizes of assays between treatment groups, we will also compare with early response to treatment (MRD) and T-ALL phenotype (ETP vs non-ETP). For the analysis of data across time (0h, 6h and 24h) we do not know *a priori* the most relevant time points to compare. Short-term differences could have returned to baseline by 24h, and may be most accurately estimated by changes between 0h and 6h. Long-term reactions would be best measured by 0h-24h comparison. Complex changes, such as increase at 6h and decreases by 24h (NF-κB) are best measured using all three time points as descriptors. However, for simplicity we have provided the affect sizes for changes from 0h to 24h in Table 5.

Table 5: Effect-size (detectable differences) based on sample size for proteasome activity and UPR*

1. Proteasome studies (done with BM)	**Samples size (max)**	**Effect size ***	**2. UPR studies**	**Sx. Size (max)**	**Effect size ***
Baseline and change (pretx to Day 29) in proteasome activity by treatment arm (VXLD vs VXLD+B)	476 (238/tx group) 238 (119/tx group)	0.257 0.365	Baseline PCR-(BM) by ETP	476 (59 ETP/ 417 non-ETP	0.391
Baseline and change (pretx to Day 29) in proteasome activity by response (MRD status)	476 (238/MRD grp 238 (119/MRD grp	0.257 0.365	PCR-D1change-(PB) by ETP	342 (42 ETP/ 300 non-ETP	0.463
Baseline and change (pretx to Day 29) in proteasome activity by ETP status (12.4% ETP/ 87.6% non ETP)	476 (59 ETP/417 non-ETP 238 (30 ETP/208 non ETP)	0.391 0.549	Baseline UPR protein (PB) UPR Protein change D1 PB	86 (43/tx grp) 70 (35/tx grp	0.611 0.679

Assumptions: alpha = 0.05, beta = 0.2.Abbreviations: tx = treatment, w= with, Day 29 = End induction, PCR = qRT-PCR. grp= group

* Effect size = standardized mean difference of either 1) the measurement at baseline, or 2) the change in measurement over time as noted. With this effect size, the study will have at least 80% power at 2-sided significance level of 0.05 to detect such difference given the corresponding sample size.

Effect sizes in previous studies of the proteasome, the UPR and RPPA have demonstrated that the effect sizes listed in Table 5 and Table 6 (below) are smaller than those needed to detect statistically significant differences in prior leukemia studies.

- Proteasome expression measurements from pediatric patients enrolled in either AALL07P1 (n=46) or AAML07P1 (n-12) showed a 2-fold difference in proteasome subunit expression in those that had reached a complete remission (CR) following induction vs. those that had not, for both β5i/β5 and β1i/β1 subunit expression (p=0.019 and p=0.022).

- A previous UPR study (n=105)[238] in adult AML determined that the activation of the UPR, as measured by the presence of spliced XPB1, correlated with relapse after CR1 (n=88 sXPB1+, n=17 sXBP1 neg, p=0.0182)
- Work with RPPA in adult AML have been able to detect $\log_2$ differences of 0.03 and greater (p=0.041, n=205). Differences as small as $\log_2$ 0.01 have been shown to be statistically different in larger data sets (n=511).[231]

2. SubAim 1b. To determine if reverse phase protein lysate arrays (RPPA) predict chemotherapy response or resistance.

1. To determine if protein cell stress pathways, such as the unfolded protein response, are active at baseline and how activity changes in response to ABFM chemotherapy +/- bortezomib,
2. To define a putative "high risk" protein expression profile that identifies patients receiving either standard or intermediate risk therapy that would benefit from the more intense chemotherapy.
3. To determine if RPPA protein expression profiles correlate with treatment group or T-ALL subtypes.

a) Rationale: In Sub-aim 1b, we will use a biochemical approach to identify protein combinations that are prognostic in T-ALL. This subaim is more comprehensive than Specific aim 1a, and will use a "candidate biomarker approach" to examine proteins previously identified as prognostic in either adult or pediatric acute leukemia.

b) Preliminary data:

1. RPPA feasibility: The Kornblau lab has analyzed one cohort of adult ALL and two cohorts of adult AML using RPPA. The first, with 539 samples from 258 patients, was probed with 51 antibodies;[255] the second, with 747 samples from 539 patients, was probed with 231 antibodies.[234] A subsequent array for adult ALL used 194 sampes with 131 antibodies. These studies demonstrated that there were recurrent patterns of protein expression that correlated with outcome (Fig. 6). In the AML, RPPAs proteins constellations correlated with cytogenetic subtype and EFS. In ALL, RPPA protein clusters correlated with CR duration. Prelminary analysis of pediatric ALL and AML samples is ongoing.

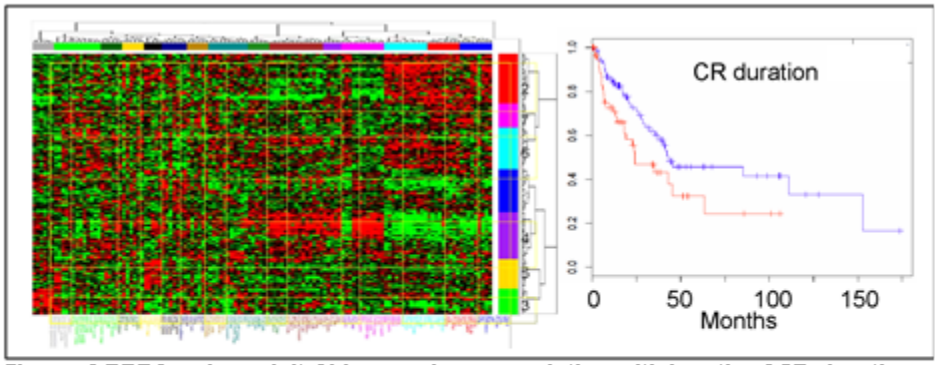


Figure 6 RPPA using adult ALL samples: correlation with length of CR duration: Heat map and outcomes for protein expression profiles from 194 adults with ALL. Left: Protein expression profiles from 194 adults formed 7 protein expression clusters that correlate with cytogenetic subtypes. Right: Protein expression profiles and outcome: Patients divide into 2 groups, those with better complete response (CR) duration (blue line, median 45 months) and those with a shorter CR duration (red line, median 22 months) (p=0.034).

The Kornblau lab recently published an analysis of proteins expression clusters with 180 antibodies, using only 150,000 CD34+CD38- AML cells per sample.[240] **No other currently available technology can analyze as many proteins with as little material.** RPPA analysis for this patient cohort consisted of 260 validated antibodies for the proteins involved in 25 different protein functional groups (i.e. PI3K/AKT, JAK/STAT, WNT/β-catenin, UPR, apoptosis, autophagy, cell cycle regulation integrins and adhesion proteins) that are known to be deregulated in acute leukemia, or are involved in DNA damage repair.[240] The Kornblau lab, in collaboration with the K Coombes (MDACC statistics) and the Qutub laboratory (Rice University) have recently developed statistical methodology to generate interaction networks from the RPPA datasets in combination with known networks from the literature, and can map differences in expression onto these interactome maps, thereby revealing the variations in expression that are present between different types of leukemia, or alternatively, between different treatment or response groups.

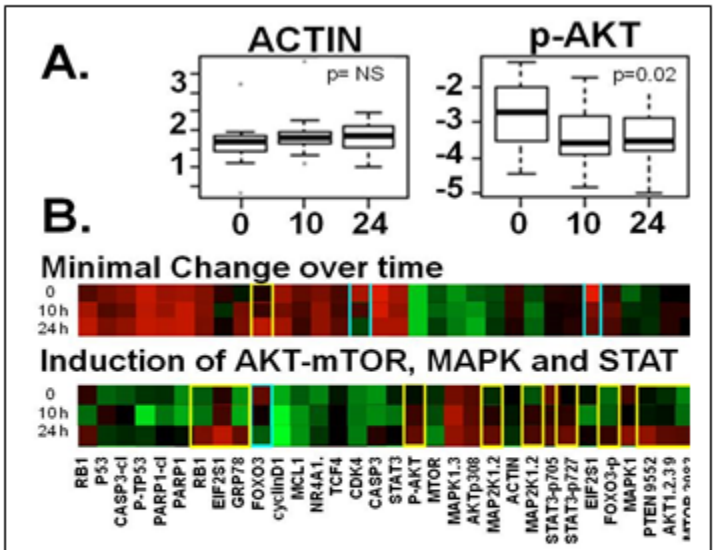


Figure 7: Results from feasibility test set using AAML1031 samples. **A.** Mean protein concentrations from 17 patients were compared for 32 proteins. There were minimal changes in in actin over time, whereas there was a significant decrease in phospho-AKT following treatment (one-way ANOVA). **B:** Heat map of the heterogeneity of protein expression between samples. The top panel shows minimal change in protein expression, whereas the patient in the bottom panel shows both increases (yellow boxes) and decreases

2) **Antibody validation:** RPPA antibodies have gone through extensive testing prior to inclusion on the array,[234,241,255] including both analytic validation and assay validation with clinically relevant samples.[256,257] Antibodies validated for RPPA use demonstrate specificity of signal and, in the case of phosphorylation or cleavage sensitive antibodies, context-specific validation has been performed in baseline and stimulated samples.[255] Validation steps have included: 1) antibody specificity as determined by immunoblot, 2) appropriate induction of phosphorylation/cleavage in response to known inducing agents, 3) correlation of RPPA signal with immunoblot expression ($R \geq 0.5$), 4) acceptable sigmoidal curve fit of signal with sample dilution (analyzed using SuperCurve),[255] 5) variable slope normalization[258] and, in cases of high background, 6) topographical normalization. Slides with unacceptable variances are redone. RPPA has acceptable intra-assay and interassay variability, with intra-assay coefficients of variation (COV) of 6-15% and established interassay reproducibility. We have established standard operating procedures (SOPs) for sample processing, cell sorting and RPPA, and laboratory staff in both the Horton and Kornblau labs are experienced with the procedure.

3) Clinical trial feasibility test set**:** Our preliminary data shows that we can reliably assess post-chemotherapy protein activation by analyzing samples collected during Day 1 of therapy. Seventeen patients from the AAML1031 clinical trial were tested by RPPA (Fig 7) using both heparin and CS tubes. Using a test set of 32 validated RPPA antibodies, we assessed protein activation following ADE therapy. We have determined that 1) CellSave tubes preserve protein expression profiles post-treatment, as shown by the relative stability of actin expression, but a decrease in p-AKT (Fig 7A); and 2) that we can detect the heterogeneous patterns of changes in protein expression over time, with some patients having minimal changes over time (Figure 7B, top panel), whereas other patients have induction of several key regulatory proteins, including AKT, m-TOR, MAPkinase and the FOXO3 pathway (Figure 7B, bottom panel) following treatment.

RPPA analysis for this patient cohort will consist of 260 validated antibodies for proteins involved in 25 -protein functional groups including PI3K-AKT, JAK-STAT, Wnt-β-catenin, apoptosis, autophagy, cell

cycle regulation, DNA damage response, integrins and adhesion proteins.[259] The Kornblau lab and K Coombes (MDACC) along with the Qutub lab (Rice University) have recently developed statistical methodology to generate interaction networks from RPPA datasets in combination with known networks from the literature and can map differences in expression onto interactome maps, thereby revealing the variations in expression that are present between different leukemia response groups, subtypes, or treatment regimens. [260]

c. Experimental design

1) Assessment of dynamic changes in lymphoblast protein activation following chemotherapy: Peripheral blood will be collected in CellSave tubes at three time points on the first day of therapy (0h, 6h, and 24h) and lysates prepared from 200,000 cells for RPPA analysis. Samples will be divided into a training set and test set of roughly equal size. For training set evaluation 171 patient samples (85/treatment group) will undergo serial dilutions and will be spotted onto a single array in duplicate with appropriate controls (cell lines, cell lines treated with chemotherapy, normal PBMC). Replicate slides will be probed with 260 validated antibodies (1 antibody/slide) and normalized protein concentrations determined using SuperCurve.[255]

Our statistical analysis will involve three complementary approaches to examine the dynamic changes that occur in the T-ALL blasts in response to therapy over time. The first will use unsupervised hierarchical clustering ("class discovery") methods to look for protein expression clustering in the training set. We will determine what signatures, or signature components, are static and which are dynamic in response to therapy, and the time course of these changes. Next we will apply the thresher method to limit the dataset to those proteins that are changing dynamically and to define the dynamic principal components from the relevant functionally related protein groups.[260] Finally we will map the observed dynamic changes onto interaction networks, derived from the static data and the known literature, to graphically visualize how each functionally related protein group, and it's direct and indirectly connected members, are being modulated.

By comparing the analysis seen between the different therapies we can discriminate what pathways are differentially modulated by bortezomib, compared to the standard therapy arm, and what are the critical components of each of dynamically modulated protein functional group. Correlation of these protein expression patterns with therapy outcome can reveal which are defensive responses being engaged by the leukemic blasts to evade therapy. Identification of these resistance associated defensive adaptations will suggest further therapies to employ to block bortezomib resistance and improve efficacy. Both static changes (pre-treatment) and dynamic changes over time will be assessed for each protein as well as for each protein functional group. Baseline protein activation, as well as changes over time, will be compared based on 4 year EFS as the primary response endpoint. We expect that chemotherapy responsiveness will differ between protein expression clusters. We will also determine if protein expression varies within T-ALL subgroups. As in adults, we expect that pediatric RPPA profiles will correctly identify T-ALL subgroups[234] as well as identify defensive resistance mechanisms not only for bortezomib-containing therapy, but for VXAD therapy as well, showing that **this body of work will lead to integral studies whether or not bortezomib is an effective agent.** . The training set will be used to develop a protein expression classifier to predict VXAD +/- bortezomib response in the test set.

d. **Statistical methods**

1) Sample size adjustment for drop-outs

We are requesting sample (BM (n=476) and PB (n=342)) for RPPA (BM) and SCPFC analysis (BM and PB). Additional samples will account for two potential sources of sample drop-out. First, we anticipate that approximately 20% of samples identified will have insufficient or unusable sample for RPPA and SCPFC analysis (non-viable samples, collected in wrong tubes, only partially collected sample set, damaged material, etc) Second, during RPPA and SCPFC construction, there will be additional samples that are inevaluable, either due to loss of tissue spots on the RPPA array, inadequate T-ALL cells for UPR analysis, or inadequate sample using quality control criteria (5%). The drop-out rate in our prior RPPA studies using local samples for the same analyses was approximately 5% (Horton lab, unpublished data). An historical drop-out rate of

approximately 5% is also supported by the leukemia RPPA literature.[261] UPR qRT-PCR dropout rate will depend on the quality of the RNA.

The sample size will be drawn from the same samples set for both RPPA and SCPFC. As concluded by Simon et al.,[243] "genes that have low variation across the entire set of samples would be difficult to use for prognostic prediction in clinical situations". Therefore, we will demonstrate statistical power in cell signaling node identification using the median and 90% percentile. We will adjust for multiple comparisons (total 6 signal transduction nodes) using the Holm's method.[262]

2) RPPA analysis

As discussed in SA 1a, there are multiple comparisons of interest. We predict that there will be sufficient power to detect at significant differences between groups as shown below (Table 6). Methods for RPPA and SCPFC analysis have been previously described,[255] Both unsupervised and supervised clustering analyses of the data sets will be completed as outlined below.

a) Unsupervised hierarchical clustering analysis

Unsupervised clustering of all RPPA and SCPFC data will be performed to identify biologically-defined subgroups that will be correlated with clinical outcomes (MRD and EFS). Independent of potential outcome correlations of clusters, this approach will also identify biologically-defined T-ALL subgroups, aiding in a development of biologically-based (i.e. targeted) therapies for these patient populations. Unsupervised clustering analysis will be performed as previously described.[234,263]

b) Stratification of RPPA protein expression profiles by treatment group

A similar clustering analysis as delineated above will be applied to training sets stratified by treatment group. The training set will include 171 patients. With a 1:1 randomization between treatment groups, it is expected that 85 patients will have received each treatment. compare protein expression patterns in VXAD responders (4yr EFS-no event) to responders in the VXAD-B group (4yr EFS-no event). We will specifically look for protein patterns in VXAD non-responders that are also found in VXAD-B responders, suggesting proteins that predict patients likely to respond to bortezomib-containing chemotherapy. Analysis of protein expression clusters by treatment group will also determine if there are protein classifiers that can differentiate response between treatments.

Table 6: Effect-size (detectable differences) based on sample size for each experiment (two-sample 2-sided t-test, alpha=5%, power=80%)

1. RPPA studies	**Samples size (max)**	**Effect-Size**
Baseline RPPA by tx group	342 (171/ tx group)	0.304
Changes in RPPA at D1 by tx group	280 (140/ tx group)	0.336
Baseline RPPA by response groups (4-yr EFS)	342 (291 non-event/51event)	0.426
Changes in RPPA at D1 by response groups (4 yr EFS)	280 (238 non-event/42 event)	0.471
Baseline RPPA by response groups (Day 29 MRD)	342 (171 >=0.01%/ 171 <0.01%)	0.304
Changes in RPPA at D1 by response groups (Day 29 MRD)	280 (140 >=0.01%/ 140 <0.01%)	0.336
Baseline RPPA by **ETP** vs. non-ETP	342 (42 ETP/300 not)	0.463
Changes in RPPA by ETP vs. non-ETP	280 (35 ETP/245 not)	0.508

Tx = treatment, D1 = Day 1, Day 29 MRD: < or >0.01% at end of induction.

One of the advantages of this study is the ability to analyze protein expression patterns over time during the first day of treatment. By comparison of patients that receive VXAD to VXAD-B, we expect be able to 1) determine if there are proteins induced in VXAD responders that are not present in VXAD responders; these proteins might be putative predictors of bortezomib response. The expression of baseline UPR proteins has been linked to bortezomib response in similar tumor types[242,254] however, this study is unique in its ability to assess UPR activation over time in patients randomly assigned to VXAD+/-B therapy. We will also look for

changes in the protein expression patterns of VXAD non-responders that are no longer present in VXAD-B non-responders, indicating another set of proteins that could potentially identify markers of response to bortezomib. Based on accrual in the AAML1031 study, we estimate that we will have Day 1 samples on 82% of patients (approximately 280 samples, 140 samples/tx group), allowing for sufficient samples to make comparisons of protein expression over time between treatment groups.

c) Supervised gene expression analysis by response (1y-EFS)

We will analyze pediatric T-ALL patients as a group to determine if RPPA provides prognostic/predictive information independent of known prognostic variables and information that is complementary to existing prognostic markers. To determine the effect of current disease risk group stratification on the prognostic value of the RPPA and SCPFC protein profiles, EFS data will be analyzed adjusted for treatment arm and ETP status.

d) Building an outcome predictor

Prior data from the Kornblau lab[234,264] and others suggest that protein expression profiles between VXAD responders and VXAD-B responders will differ; RPPA and SCPFC (see aim 2) will likely identify specific biochemical pathways that predict response to bortezomib-containing chemotherapy, such as the UPR[265] and other cell stress pathways, including autophagy,[265,266] and DNA damage response.[267] Based on preliminary data from the Hermiston lab and others we also will likely identify changes in specific signal transduction pathways (NF-κB, JAK/STAT and NOTCH) that will track with clinical outcome. We will build candidate classifiers in a stepwise fashion:

i. We will first look at dynamic changes in protein activations following chemotherapy in sorted lymphoblasts. The purpose is to discover natural groupings based on proteomic data only, without any information about outcome, to compare those groups with other known classifications and then to perform bioinformatics analysis to identify pathways active in each of the newly identified clusters

ii. Once clinical outcomes become available, we will analyze the difference in protein profiles between VXAD and VXAD-B treatment groups as they relate to clinical outcome. This part will include different unsupervised methods, group comparisons and will search for differentially expressed proteins and pathways.

iii. Finally, we will create a classifier(s) to predict clinical outcome. We will use outcome variables MRD status (Day 29, 0.01% cutoff) and 4-year EFS) We may have different classifiers for different outcome variables as well as for different risk groups and T-ALL subtypes.

As with other high-dimensional data, RPPA data analysis will include low-level and high-level analysis:

iv. Low-level analysis, relative protein levels will be determined by interpolation of dilution curves from the global "standard curve" using the R package "SuperCurve".[268] (http://bioinformatics. mdanderon.org/Software/OOMPA/ Current/SuperCurve-manual.pdf). After normalization for protein loading and appropriate transformation, assessments of quality will be performed.[234,255] To the maximum extent possible, samples that will be directly compared to each other will be printed on the same slide to avoid possible batch effects.

v. High-level analysis: To determine clusters (classes) with potentially different outcome or treatment targets based on protein expression and activation, we will use Hierarchical Clustering, Principal Component Analysis (PCA), Self Organizing Maps (SOM) and other class discovery methods.[269] Cluster stability will be accessed using reproducibility measures, including a modified GAP,[270] known as stability GAP (prototype clustering) (Qutub et al, manuscript in review),[271] as well as robustness and discrepancy indices.[272]

Differentially expressed proteins will be found using paired t-test as well as repeated measures, mixed effect ANOVA and ANOVA with contrasts. We will use the Bonferroni correction to account for multiple comparisons in the RPPA analysis.[273]

To determine if dynamic changes in specific protein pathways predict chemoresistance, we will use different regression and classification methods: SOM (when no outcome is used), class prediction methods such as logistic regression, Support Vector Machine,[274] Random Forest,[275] Binary Tree Prediction, Bayesian Compound Covariate Predictor, Discriminant analysis (http://linus.nci.nih.gov/techreport/Manual32.pdf), and

finally, Cox proportional hazard models for survival analysis. We will use different boosting methods[276] to combine different models for the purpose of producing more accurate classification and regression models.

All patients with evaluable sample data will be randomized 1:1 into training and testing sets. We will use cross-validation and permutation methods to estimate the model accuracy and to select a preferable model using the training dataset. To provide an unbiased estimate of the model accuracy on the training set, the model construction, including selection of proteins, will be repeated from scratch for each iteration. The selected classifier or regression model will be validated using the test dataset.

To perform high level statistical analysis, as well as for visualization and integration of the results, we will use different software packages. The software will include but not be limited by Bioconductor (http://www.bioconductor.org), Partek (http://www.partek.com), BRB Array Tools (http://linus.nci.nih.gov/BRB-ArrayTools.htm, dChip (http://biosun1.harvard.edu/complab/dchip), SAS (http://www.sas.com), and R (http://www.r-project.org). We will follow new developments and use new software packages if more advanced ones are developed by the time of analysis. We will use scatter plots, multidimensional scaling, PCA, hierarchical clustering, volcano plots and other visualization methods for visualization of initial data and for results.

e) Integration of RPPA and SCPFC results to build an integrated protein expression classifier:
All patients with evaluable RPPA and SCPFC (aim 2) will be included in the analysis plan for this aim. Protein expression levels as continuous variables (determined by RPPA) will be correlated with each SCPFC nodal output using ANOVA statistics for each protein. P-values will be adjusted for multiple comparisons using the Bonferroni method. We will also analyze GEP and protein datasets using other methods previously developed for the integration of genomic and proteomic data, including linear correlation analysis[277] and cluster analyses[278] as reviewed in Cox et al.[279] These methods will enable us to determine the utility of transcript profiling for prediction of protein expression levels.[280] Data will also be integrated at the level of protein interaction networks as previously described.[263,281-283]

f) Assessment of protein classifiers:
For this aim, all T-ALL samples with usable RPPA and SCPFC (aim 2) analysis will be evaluable (n≈476) and will be included in the analysis plan. In addition to comparison of the ROC performance characteristics, we will also be identifying classifiers whose operating characteristics minimize the false positive rate (1-specificity) while having an acceptable true positive rate (sensitivity). A cutoff point for the classifier will be selected that maximizes the likelihood ratio (LR) of identifying standard and intermediate risk patients that have a "high-risk" protein classifier (i.e. an acceptable true positive rate (> 50%) with a low false positive rate (< 10-20% for this study). This will identify SR and IR patients in need of additional therapy, while avoiding potential overtreatment of SR and IR patients that have been falsely identified as high-risk by the molecular profile.

g) Determination of clinical usefulness:
Our objective is to improve the detection of the patients with a high risk signature in the SR and IR groups that would ultimately relapse, with the objective of improving SR and IR EFS. In this study we will assess 476 patients for aberrations in protein cell stress pathways. Of this number, it is estimated that 90% will be either LR or IR (n=428); this will be the sample set available for analysis. Depending on the change in EFS for those correctly identified as having the putative high risk protein expression classifier, Table 7 demonstrates the relative risks that can be used to identify the clinical usefulness of applying the protein expression classifier to the SR and IR patients (overall 4-year EFS 89%).

Table 7: Range of 4-yr EFS and relative risk reduction that will be used to determine the clinical usefulness of the protein profile classifier (n=428; alpha=5%, one-sided log-rank test)

Proportion of patients classifier negative (sample size in classifier - and + grps)	EFS associated with classifier negative group	EFS associated with classifier positive group	Relative Risk classifier+ /classifier (-) Signature	Power

0.5 (n1=214, n2=214)	0.97 0.95	0.81 0.83	6.92 3.63	>0.99 0.99
0.6 (n1=256, n2=172)	0.95 0.94	0.80 0.81	4.35 3.41	>0.99 0.99
0.7 (n1=299, n2=129)	0.93 0.92	0.80 0.82	3.08 2.38	0.99 0.92
0.8 (n1=342, n2=86)	0.92 0.91	0.77 0.81	3.13 2.23	0.99 0.86

The table above will be used to calculate the sample size in each scenario that would lead to a high probability of correctly identifying a significant difference between patients with the high-risk protein classifier in the SR and IR groups. Our goal would be to identify a classification signature that outperforms the current method of risk stratification.

E. Specific Aim 2: To identify biomarkers and mechanisms of chemotherapy resistance and response in T-ALL, focusing on ETP ALL.

Overview: The objective of this aim is to systematically evaluate the biochemical signature of T-ALL leukemic blasts at diagnosis and in response to chemotherapy in order to identify a biomarker for patients at high risk of relapse. T ALL is a genetically heterogeneous disease with variable responses to therapy. The behavior of a given patient's leukemia and its response to therapy are determined by the accumulation of genetic mutations and epigenetic alterations. To date, the genetic heterogeneity of T-ALL has precluded risk-adapted therapy based on genetic abnormalities. (Epi)genetic aberrations are manifest biochemically as changes in signal transduction and cellular responses. However, recent data suggests that genetic abnormalities in T-ALL may converge on a more limited set of biochemical abnormalities. We predict that these biochemical signatures may serve as biomarkers predictive of chemotherapy response or resistance. We will focus on the ETP, a newly identified phenotype of T ALL with a particularly poor prognosis in some reports[284] in order to identify new biomarkers for enhanced risk stratification and better treatment strategies for high-risk T-ALL patients.

We will test two hypotheses: 1) that the signaling network profile of patients with ETP ALL will be distinct from non-ETP ALL and 2) that these differences in signal network wiring will predict whether the leukemia responds to chemotherapy (with or without bortezomib).

The rationale for this work is two-fold. First, ETP ALL blasts frequently have mutations more commonly associated with myeloid leukemia, including mutations in histone-modifying proteins and in genes that regulate RAS and cytokine receptor signaling. Our approach will be to delineate signaling in 1) the basal state, 2) in response to *in vitro* stimulation, or 3) in response to exposure to chemotherapy using SCPFC. In light of the observed biologic and clinical heterogeneity of T-ALL and the recent trend towards the development of "targeted" therapeutics, identification of patients likely to benefit from biologic therapies such as bortezomib would allow consideration at diagnosis for including these alternative therapeutic strategies. Second, successful completion of this aim will also allow us to identify a high-risk classifier of chemotherapy resistance in a large clinical trial and to directly compare the predictive power of this technology with RPPA (SA1). Our expectation is that understanding the biochemical aberrations that reflect the genetic and epigenetic alterations in the leukemic blasts will enable identification of biomarkers that predict risk of relapse and inform the use of targeted agents in future clinical trials. Given that intracellular staining of protein epitopes is a mainstay of the diagnostic evaluation of T-ALL (e.g., TDT and cytoplasmic CD3 staining), addition of a protein biomarker to future clinical trials should be technically feasible as an integral study.

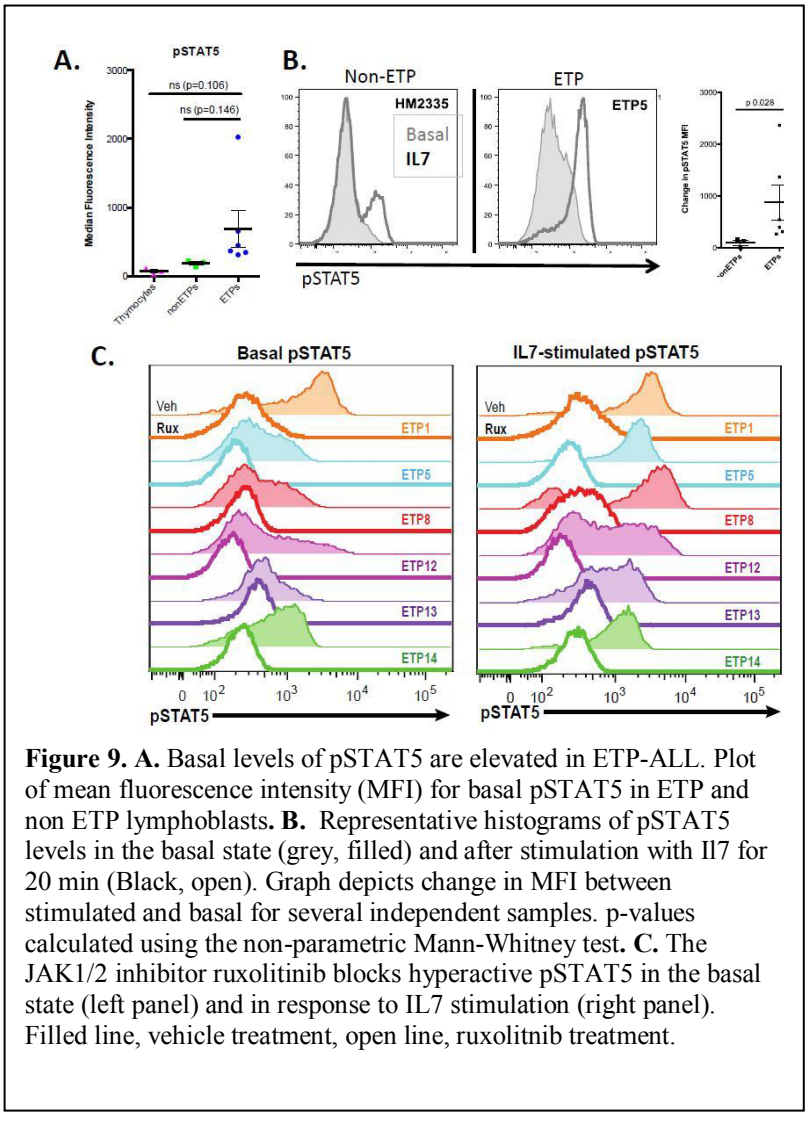


Figure 9. A. Basal levels of pSTAT5 are elevated in ETP-ALL. Plot of mean fluorescence intensity (MFI) for basal pSTAT5 in ETP and non ETP lymphoblasts**. B.** Representative histograms of pSTAT5 levels in the basal state (grey, filled) and after stimulation with Il7 for 20 min (Black, open). Graph depicts change in MFI between stimulated and basal for several independent samples. p-values calculated using the non-parametric Mann-Whitney test**. C.** The JAK1/2 inhibitor ruxolitinib blocks hyperactive pSTAT5 in the basal state (left panel) and in response to IL7 stimulation (right panel). Filled line, vehicle treatment, open line, ruxolitnib treatment.

1. Subaim 2a. To determine if differences in activation of the NF-κB, MAPK, PI3K/AKT/mTOR, and/or JAK/Stat pathways between ETP and non-ETP T cell subtypes will serve as indicator of chemotherapy resistance.

a. Rationale and preliminary data. Multi-parameter phosphoflow cytometry represents a powerful and highly sensitive approach for analyzing and interpreting post-translational protein modifications (e.g. phosphorylation, acetylation, cleavage etc.) at the single cell level in minimal sample size ($0.5x10^6$ cells/assay). Measurements are made on endogenous proteins before and after exposure to extracellular modulators such as growth factors, cytokines and drugs. This enables a comprehensive, dynamic, and functional assessment of signaling pathways within heterogeneous populations of primary cells.[285] SCPFC has been used to demonstrate that hyperactivation of STAT5 and PI3K/mTOR pathway signaling is a common feature of human CRLF2-rearranged pre B-ALL.[227] This approach has also been successfully applied to pediatric AML bone marrow samples to identify and validate a classifier for prediction of response and to build a single cell network profiling (SCNP) classifier in adult AML and pediatric AML studies have confirmed the importance of the JAK/STAT pathway.[230] These classifiers are now being validated in a phase three prospective clinical trial (AML1031). While these studies

demonstrate the feasibility and clinical utility of SCPFC, this approach has yet to be systematically applied to pediatric T-ALL.

Hyperactivation of signaling networks in ETP ALL. The Mullighan laboratory performed a comprehensive genetic analysis of ETP ALL.[284,286,287] Activating mutations in signaling proteins and inactivating mutations in proteins regulating hematopoietic development were common. The Hermiston laboratory performed a biochemical analysis of a subset of these leukemias using SCPFC. Relative to normal human thymocytes, the MAPK, PI3K/AKT/mTOR pathway and the JAK/STAT pathways were hyper-responsive to stimulation.[284,286,287] There was excellent correlation between genetic mutations and the occurring phenotype. For example, IL7 receptor mutations were associated with constitutive pSTAT5 activation while T-ALL samples with Ras pathway mutations were not.[284,286,287]

Evidence of common signaling changes despite heterogeneous genetic alterations in ETP T-ALL. Interestingly, gene expression profiling suggested hyperactivation of the JAK/STAT pathway in ETP ALL whether or not there was an underlying cytokine signaling pathway mutation. This was tested using SCPFC. Regardless of their mutation status, ETP lymphoblasts were hyper-responsive to IL-7 stimulation relative to normal thymocytes or non-ETP T-ALL (FIG 9A). Activation of pSTAT5 in the basal state or in response to IL7 could be completely inhibited by the JAK1/2 inhibitor ruxolitinib *in vitro* and correlated (FIG 9B) (Maude et al., manuscript submitted). These data suggest that hyperactivation of the IL7/JAK/STAT pathway may be a common feature of ETP-ALL and support the notion that multiple genetic (or epigenetic) mutations may converge on a more limited set of deregulated cell signaling pathways.

Correlation of MRD status with *in vitro* response to dexamethasone. To test the hypothesis that analysis of signaling profiles in response to conventional and/or targeted therapeutics *in vitro* could facilitate identification of resistant T-ALL/LL at diagnosis or relapse and facilitate choice of optimal therapy in high-risk patients, we successfully developed a Caspase-3 (a marker of commitment to apoptosis) based assay to monitor response to drug therapy *in vitro* (Figure 10B). An advantage of this approach is the ability to gate on the viable, chemotherapy resistant, Caspase-3 negative cells to further interrogate mechanisms of chemotherapy resistance. Because the upfront prednisone response can be predictive of outcome, especially in T-ALL,[288] we tested the hypothesis that *in vitro* sensitivity to dexamethasone would correlate with prognosis as defined by end of induction MRD status. As anticipated based upon clinical response, MRD negative samples were quite sensitive to drug while the majority of ETP and MRD positive samples were resistant (FIG 10 A, B). Interestingly, dexamethasone resistance did not correlate with expression of the glucocorticoid receptor (data not shown), suggesting that other mechanisms are mediating drug resistance.

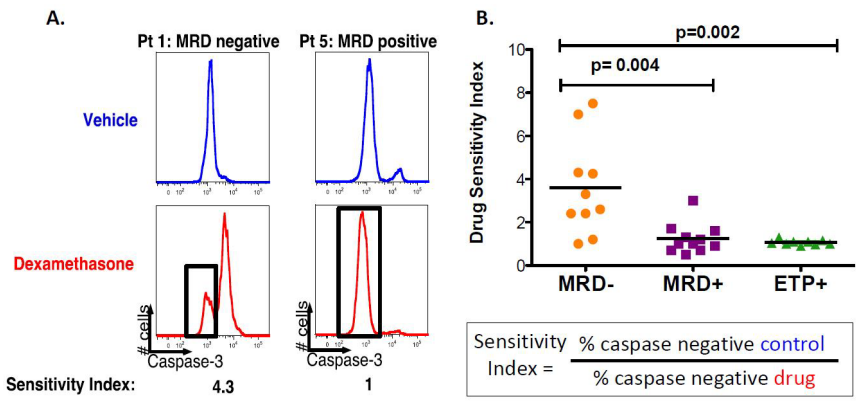


Figure 10. Interrogating chemotherapy resistance and response with SCPFC. A. Representative MRD negative and MRD positive diagnostic samples from AALL0434 were incubated with vehicle or 10 uM dexamethasone for 48 hours *in vitro* and analyzed by phosphoflow cytometry. Histograms depict Caspase-3 induction. **B.** Drug sensitivity index was calculated for each diagnosic sample. Statistical significance was determined using the Student T test.

4.) T-ALL cells rewire their signaling networks in response to genotoxic stress. The mechanisms mediating chemotherapy resistance in T-ALL are unclear It is clear in normal biologic systems that cells upregulate multiple signaling pathways in response to stress. We hypothesized that chemotherapy resistant cells might similarly rewire their signaling networks in response to genotoxic stress. In addition to the obvious advantage of requiring many fewer cells, an advantage of SCPFC relative to traditional biochemistry using western blots is the opportunity to gate on drug-resistant, Caspase-3 negative cells and to interrogate signaling networks that are activated or inhibited in response to drug. We find that chemotherapy resistant cells upregulate the MAPK and PI3K/AKT/S6 pathways as well as pro-survival proteins such as survivin in T-ALL samples when exposed to genotoxic chemotherapy (FIG 11 A, B). Similar signal network rewiring has been reported as a mechanism of chemotherapy resistance in breast cancer[289]

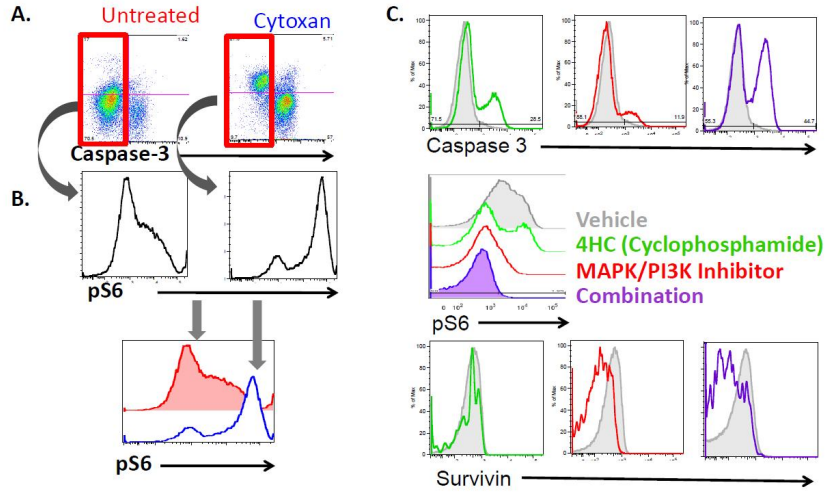


Figure 11. A. T-ALL cells were incubated with vehicle of 4-HC (the active metabolite of cyclophosphamide) for 24 hours and processed for SCPFC.An advantage of SCOFC is the ability to gate on the Caspase-3 negative cells and interrogate mechanism of chemotherapy resistance. **B.** Caspase-3 negative rewire their signaling networks and upregulate pS6 in response to genotoxic stress .**C.** Top, ALL cells were treated with vehicle, 4HC (the active metabolite of cyclophosphamide), and/or a dual mTOR/PI3K inhibitor. Combination therapy shows enhanced cell death relative to either agent alone. Gating on Caspase-3 negative cells (middle and lower panels) shows inhibition of pS6 with inhibitor and correlation with downregulationof the pro-apoptotic mediator Survivin.

5. Targeted inhibitors prevent network rewiring and restore chemosensitivity. Network rewiring can be prevented with the addition of the appropriate targeted inhibitor. Interestingly, our preliminary data of chemotherapy resistant T-ALL (as defined by end-induction MRD) suggests that despite adequate inhibition of the target and downregulation of the pro-survival protein Survivin, targeted agents generally are not cytotoxic as monotherapy. However, when combined with standard genotoxic chemotherapy, a synergistic effect is often seen. SCPFC enables analysis of the mechanistic basis for this observation. In the presence of targeted inhibitor, cells are no longer able to rewire their signaling networks, leading to downregulation of survivin and other pro-survival proteins and increased chemosensitivity when cytotoxic agents are added (FIG 11C). These data argue that identifying the signaling pathways that are hyperactivated in the basal state or after exposure to chemotherapy could be of clinical benefit in determining which targeted therapy would be most beneficial for a given patient. Thus, a goal of this aim will be to determine the relative frequencies that common signaling pathways are deregulated in ETP-TALL.

Experimental design.

1.) Compare signal network wiring in the basal state and in response to IL7 or targeted inhibitors in ETP and non-ETP T-ALL. The goal of this experiment is to determine whether alterations in single network profiles can be identified and whether these correlate with MRD status and/or EFS. Diagnostic samples (either fresh bone marrow or peripheral blood, provided the blast count is greater than 1000 cells/HPF, collected and shipped in heparinized tubes) will be subject to SCPFC using established methods[287]. Briefly, cells will processed on a ficol gradient to remove red blood cells and cellular debris, rested 30 minutes in serum free media, treated with

vehicle, signal pathway inhibitors, or IL7 for 20 minutes, then rapidly fixed, permeablized, and stained with fluorescently conjugated monoclonal antibodies.

Based on a conservative estimate of the number of pretreatment lymphooblasts obtained from 2 mL PBMC (2-5x10^6 cells), we estimate that we will have sufficient sample to test a minimum of 10 biological conditions (modulators, kinetic time points), with 2 to 3 proteins measured in each condition, resulting in approximately 25 nodes representing relevant leukemia biology. The proteins assessed by SCNP will include the same proteins analyzed by RPPA. We will focus on the MAPK (pERK1/2, pMEK), JAK/STAT (pSTAT5), and PI3K/Akt/mTOR (pAKT, pS6) pathways and treat cells with a inhibitors specific to each of these key signaling nodes (i.e., a MEK inhibitor, ruxolitinib (JAK1 inhibitor), or rapamycin (mTOR inhibitor). The phosphatase inhibitor pervanadate will be used as a positive control. These pathways were chosen based on the high frequency of dysregulation in T-ALL and ETP ALL. Over 20% of T-ALL have aberrant PI3K/Akt/mTOR signaling.[290] Early data suggest over 40% of ETP ALL samples have mutations in genes that regulate MAPK and that JAK/STAT pathway activation may be a universal feature of this T-ALL subset.[287] To identify leukemic blasts, cells will be stained with monoclonal antibodies (previously validated for SCPFC[287]) that recognize cell surface proteins (e.g., CD3, CD5, CD7) and signaling proteins (pS6, p-Akt, p-MEK1/2, p-ERK1/2, active NF-κB). Activated Caspase-3 will be used to identify cells committed to apoptosis. The well characterized T-LBL cell line Jurkat and normal human thymocytes (obtained under an IRB approved protocol) at the same developmental stage as defined by cell surface staining will be used as positive controls. Cells will be processed on a FACSverse 2 housed in the Hermiston laboratory. An advantage of the FACSverse is that it contains an algorithm for controlling for day-to-day machine variability. Inclusion of the well-characterized Jurkat cell line with each sample analysis will be used to control for any potential technical variability.

B. Evaluate in vitro responsivness to dexamethasone. The goal of this experiment is to validate whether *in vitro* resistance to dexamethasone correlates with MRD responsiveness. We will also test whether chemotherapy resistant cells upregulate specific signaling pathways in response to dexamethasone exposure. After ficol, 0.5x10^6 cells/ml will be incubated in vehicle or 5μM dexamethasone in complete media for 48 hours and then processed as outlined above for flow cytometry. Dexamethasone sensitive and resistant CEM T-ALL cells with well defined signal network rewiring responses to steroid will be used as positive and negative controls.

Data analysis We will analyze the data by gating on the leukemia population (as defined by forward and side scatter characteristics and cell surface marker expression), eliminating doublets, and then identifying the Caspase-3 negative, viable cell population using FlowJo v.9.3.1 and Cytobank software. The mean fluorescence intensity (MFI) will then be calculated for each phosphoepitope. Samples will be comparing to each other and among subsets (e.g., ETP to non-ETP, end consolidation MRD+ to MRD-). The arcsinh ratio for each plot and the fold-change in intensity relative to the basal state will be calculated in Cytobank and used to generate heat maps for subsequent unsupervised and supervised clustering with the goal of identifying a single cell network profiling (SCPFC) classifier (see statistics section below). For the dexamethasone experiment, induction of Caspase-3 will be monitored in vehicle and drug treated cells by phosphoflow cytometry. A drug sensitivity index will be calculated as the ratio of non-apoptotic (Caspase 3 negative) cells in control vehicle treated vs. drug-treated samples. Additive, synergistic, or antagonistic effects will be calculated using the universal response surface approach.[291] Multivariate analyses will be used to define the parameters that best discriminate patient populations. We expect that signal network wiring will be distinct in ETP-ALL relative to non-ETP ALL. Given that chemotherapy resistance reflects, at least in part the phenotypic consequences of genetic and epigenetic alterations in the leukemic blasts, we also anticipate that patients with persistent MRD at the end of induction and consolidation will have distinct network wiring relative to MRD negative patients, and that these phospho-signatures will correlate with EFS.

Statistical methods and justification: The objective of the statistical analysis In Aim 2a is to provide an assessment of baseline signal network wiring prior to chemotherapy in ETP versus non-ETP T-ALL and to determine whether it correlates with MRD status at the end of induction at 0.01% cutoff and/or or clinical outcome (4-year EFS).

a) SCNP sample size: Based on analysis described in Aim 1, we expect approximately 50% of patients to provide BM and 36% to provide PBMC samples. Therefore, we estimate that we will have evaluable BM samples from 476 patients and PBMC samples from 342 patients (171/treatment group) for power estimations. Given an incidence of 12.4% ETP, we estimate that we will have evaluable BM samples from 59 ETP ALL patients and evaluable PBMC samples from 42 patients.

b) Definition of test and training sets: The statistics team, led by M. Devidas will randomize patients in approximately equal numbers to either the training or test (validation) set. The training set will be used to develop the SCNP-derived diagnostic classifier that will produce a score for each patient indicating the predicted likelihood of response or relapse. The training data will also be used to determine the decision rule (cutpoint) that will be applied to the classifier score to assign patients to one of two groups: e.g. MRD >0.01% vs. MRD <0.01%, or event vs. non-event based on 4 year EFS. The final diagnostic classifier and final decision rule will be referred to as the SCPFC classifier (DX_{SCNP}). The ability of DX_{SCNP} to predict patient's response (or relapse) will be evaluated by applying DX_{SCNP} to predict outcomes for patients in the test set. Estimates of accuracy of these classifiers will be made in the training set using out of bag (OOB) sample data for multiple bootstrapped samples. This will provide an updated estimate of the power calculation at the end of training set analysis.

c) Determine if SCNP can predict response or relapse risk in each treatment group: Differences in the classifiers among patients treated with VXAD vs. VXAD+B will be explored. Based on the estimated performance of these classifiers in the training set, a decision will be made if independent classifiers are needed for response prediction within each treatment group. Logistic regression will be used to model treatment response within each treatment group.

Specific Aim 2b. To determine if augmented NFkB signaling predicts response to induction chemotherapy +/- bortezomib.

Rationale and preliminary data: Nuclear Factor kappa B (NF-κB) is a family of transcription factors that plays an important role in cancer development by preventing apoptosis and facilitating tumor cell growth. Consistent with this, a small study of primary pediatric leukemia cases, including thirteen T-ALL cases, found evidence of constitutive NF-κB pathway activation in more than 90% of cases. [31,89] This is perhaps not surprising since NF-κB is a target of constitutively active NOTCH or PTEN/AKT/mTOR pathways, which are each mutated in over 50% to T-ALL cases. However, whether activation of the NF-κB pathway is a 'driver' mutation in these leukemias and/or contributes to chemotherapy resistance is not known. Interestingly, in other systems tumor cells in which NF-κB is constitutively active, cells are highly resistant to chemotherapy and radiation, but inhibition of NF-κB sensitizes these cells to apoptosis.[82] It is therefore of great interest to understand how deregulated NF-κB signaling can drive disease progression and to explore NF-κB inhibitors as a potential therapeutic strategy. We will test the hypothesis that activation of the NF-κB pathway correlates with chemotherapy responsiveness as measured by MRD at end induction and consolidation and EFS at four years.

Bortezomib is a proteasome inhibitor that prevents NF-κB activity by blocking proteasome-mediated degradation of IκB, a requirement for NF-κB nuclear translocation. However, despite its use in clinical trials for a variety of cancers, how bortezomib exerts its antitumor activity remains incompletely understood. Therefore there is an unmet need to study how bortezomib affects cell proliferation in T-ALL at a molecular level. Recent studies show that bortezomib can overcome or reverse chemoresistance in multiple myeloma (by sensitizing tumor cells to traditional chemotherapy drugs resulting in increased apoptosis.[19] We have developed a flow based assay to evaluate NF-κB activity (FIG 12). NF-κB activity was shown to be inhibited in early trials of bortezomib in pediatric leukemia.[235] Recent data with a larger sample sample size (n=61) collected

from patients enrolled on both Phase II trials of bortezomib in pediatric leukemia (AAML07P1 and AALL07P1) have shown that, although NF-κB is decreased in most patients, the decrease did not correlate with clinical response (CR2).[246] Whether or not this is true for T-ALL has yet to be established as there were only six T-ALL patients on AALL07P1.

Experimental Design. *Determine whether NF-κB activation at baseline and after exposure to induction chemotherapy +/- bortezomib correlates with MRD status at end induction and/or consolidation.*

We will evaluate NF-κB activation status at baseline and at 6h and 24 hours after exposure to bortezomib using the methods in subaim2A. As notch status and activation of PI3K pathway shown to enhance activation of the NF-κB pathway, we will include antisera to pAKT and pS6, components of the PI3K/mTOR signaling network, to test whether increased levels of these phosphoepitopes correlates NF-κB activation.

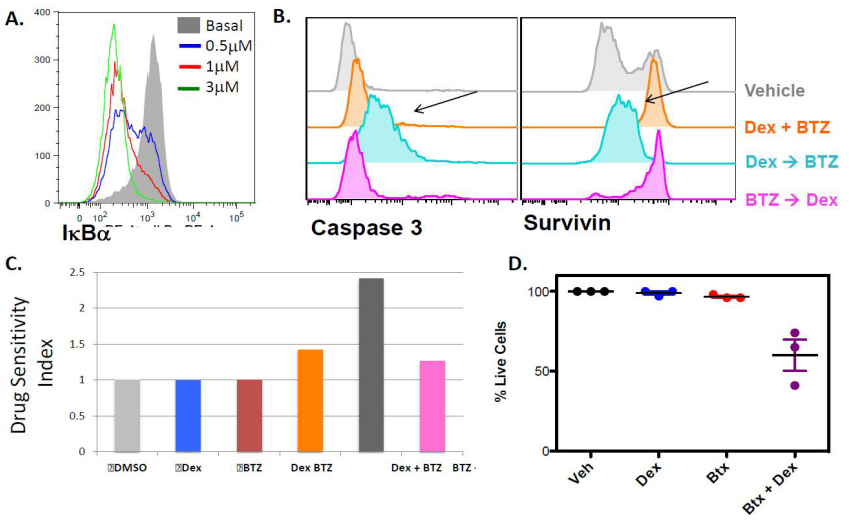


Figure 12. A. Flow-based NF-κB assay. Progressive degradation of IkBa after 20 minutes of stimulation with increasing doses of TNFalpha. **B.** The ETP-like cell line Loucey was incubated with the drugs in the order shown (24 hours drug one followed by 24 hours with drug 1 and 2). Survivin levels were evaluated in the Caspase3 negative population. Note that bortezomib induces efficient down regulation of survivin only when the cells have been pre-treated with dexamethasone first. **C.** . Induction of caspase 3 was used to calculate the drug sensitivity index. **D.** ETP xenograft samples are sensitive to the combination of borteomib and dexamethasone but not either agent alone.

Determine whether exposure to in vitro exposure to bortezomib increases sensitivity to dexamethasone. The goal of this experiment is to use SCPFC to determine if exposure to dexamethasone and/or bortezomib induces differences in signal transduction network wiring that predict chemotherapy resistance in ETP and non-ETP T-ALL cell subtypes. The Caspase-3 phosphoflow cytometry assay and the data analysis strategy described in Aim 2a will be used to assess apoptosis. An advantage of multiparameter flow is the ability to gate on Caspase-3 negative (i.e., drug resistant cells). This will allow us to interrogate potential mechanisms of resistance by comparing expression profiles of known target proteins (such as the cell survival mediators survivin, Bcl2, Noxa and PUMA) before and after treatment. The URSA method will be used to determine whether combinational drug treatments exhibit an additive, synergistic, or antagonistic effect. [291]

Statistical methods and justification. The statistical approaches described in Aim 1 and 2a will be applied here. We expect that bortezomib-containing chemotherapy VXAD-B will sensitize T-ALL cells to chemotherapy treatment and that combinational treatment will enhance apoptosis compared to treating cells with VXAD.

b. **Specific Aim 2c: Compare the performance characteristics of an SCNP classifier to alternative classifiers developed with RPPA data or other clinical/molecular data.**

1) *Approach:* As both RPPA and SCNP can be used a predictive models of response to therapy or risk of relapse, we plan to compare the performance characteristics of both methods. The SCNP training set will

be used to develop a predictor of response (or relapse) based on clinical variables (DX_{Clin}) that are reported in the literature to correlate to relapse. By developing and applying DX_{Clin} in this manner, the study will provide an estimate of the true predictive utility of clinical/laboratory variables compared to RPPA. This will facilitate a fair comparison of the relative contribution of DX_{SCNP}, DX_{RPPA} and DX_{Clin} to the prediction of response or relapse.

2) *Statistical hypothesis and test of significance*: Our primary hypothesis is that the empiric area under the receiver operating characteristic (ROC) curve (AUC) will be significantly greater than 0.5, based on the continuous score from the pre-specified classifier, where higher scores indicate greater probability of continuous complete response at 4 years. Our secondary hypothesis is that DX_{SCNP} contributes significantly to the prediction of treatment response after accounting for clinical variables, T-ALL subtypes and RPPA data. Based on performance characteristics of SCPFC based classifiers in previous studies,[228] we expect accuracy measured by area under the receiver operator characteristic curve (AU_{ROC}) for the prediction of response to be in the range of 0.75 to 0.85 and for the prediction of relapse to be in the range of 0.7 to 0.8. Assuming an equal split of the evaluable samples into training and validation sets, we expect 172 samples in the test set. Under an alternative hypothesis that the true AUC is 0.70, a 1-sided 0.05 level test of the null hypothesis that the AUC = 0.5 has approximately 95% power when there are 26 events (relapse (n = 23) or induction failure (n = 3)) and 146 controls. If separate classifiers are deemed necessary for each treatment group, with approximately 10-15% patients in relapse and 85-90% patients who do not for each treatment group (~85% expected 4 year EFS in VXAD and ~90% expected 4 year EFS in VXAD-B), approximately 80% power is expected for the primary objective if the true area under the ROC curve for each classifier is greater than 0.7.

Expected Results: We expect to be able to provide prospective "validation of clinical usefulness" for both the RPPA and the SCNP method by determining the operating characteristics of both RPPA and SCNP using this data set. Using the same set of prospectively collected samples, we expect to be able to directly compare the predictive power of the RPPA and SCNP classifiers. When successfully completed, the results will significantly advance our knowledge of the predictive capability of two methods and allow for the development of a simple, robust classifier that can aid with therapy risk stratification early in therapy. It will also allow us to determine which SR and IR groups have a "high-risk" protein expression profile that may benefit from more intensive (HR) therapy.

APPENDIX XIII: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for AALL1231 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

APPENDIX XIV POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Bortezomib

Drugs that may interact with bortezomib
• Antibiotics ○ Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin, tetracycline • Antidepressants and antipsychotics ○ Aripiprazole, citalopram, clozapine, escitalopram, fluoxetine, nefazodone, sertraline • Antifungals ○ Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Antiretrovirals and antivirals ○ Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, telaprevir • Anti-seizure medications ○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications ○ Amiodarone, clopidogrel, diltiazem, nicardipine, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: ○ Aprepitant, bosentan, cimetidine, cyclosporine, deferasirox, esomeprazole, haloperidol, ivacaftor, lomitapide, mifepristone, omeprazole, pimozide

Food and supplements that may interact with bortezomib*
• Echinacea • Grapefruit, grapefruit juice, Star fruit, Seville oranges • Green tea or a major component of green tea called ECGC • St. John's Wort • Vitamin C, ascorbic acid, or multivitamins/minerals containing vitamin C or ascorbic acid • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Green tea, ascorbic acid (vitamin C), and other antioxidants may decrease the activity of bortezomib. To avoid the interaction, you should stop taking the following products/foods from 1 day before the start of bortezomib until 3 days after the last dose of bortezomib:

1. Green tea and its components
2. Vitamin products containing vitamin C and antioxidants
3. Foods with high vitamin C content, such as fruits
4. Herbal products and any products containing flavonoids or other antioxidant compounds

Drinking grapefruit juice or eating grapefruit may increase the concentration of bortezomib in the blood. Therefore, eating grapefruit or drinking its juice should be avoided for the duration of treatment with bortezomib.

Cyclophosphamide

Drugs that may interact with cyclophosphamide
• Allopurinol • Chloramphenicol • Cyclosporine • Digoxin • Etanercept • Hydrochlorothiazide • Indomethacin • Nevirapine • Pentostatin • Warfarin

Food and supplements that may interact with cyclophosphamide*
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Daunorubicin

Drugs that may interact with daunorubicin
• Some antibiotics and antifungals (clarithromycin, erythromycin, itraconazole, ketoconazole) • Some antiepileptics (carbamazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (darunavir, lopinavir; nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir) • Some heart medications (amiodarone, carvedilol, digoxin, dronedarone, nicardipine, propranolol, verapamil) • Other agents, such as atorvastatin, clozapine, cyclosporine, dexamethasone, ivacaftor, leflunomide, natalizumab, nefazodone, progesterone, rifampin, tacrolimus, tofacitinib, and trazodone

Food and supplements that may interact with daunorubicin*
• Echinacea • Grapefruit, grapefruit juice, Seville oranges, star fruit • St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Dexamethasone

Drugs that may interact with dexamethasone
• Antibiotics ○ Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics ○ Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine • Antifungals ○ Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications ○ Leflunomide, tofacitinib • Anti-rejection medications ○ Cyclosporine, sirolimus, tacrolimus • Antiretrovirals and antivirals ○ Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications ○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications ○ Amiodarone, amlodipine, dronedenarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: ○ Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Doxorubicin

Drugs that may interact with doxorubicin
• Some antiepileptics (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (stavudine, zidovudine) • Other agents, such as clozapine, cyclosporine, verapamil, and warfarin

Food and supplements that may interact with doxorubicin*
• Echinacea • Glucosamine

- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit
- Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

Etoposide

Drugs that may interact with etoposide

- Antibiotics
  - Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
- Antidepressants and antipsychotics
  - Aripiprazole, clozapine, nefazodone
- Antifungals
  - Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- Arthritis medications
  - Leflunomide, tofacitinib
- Anti-rejection medications
  - Cyclosporine, tacrolimus
- Antiretrovirals and antivirals
  - Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
- Anti-seizure medications
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, dronedenarone, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Aprepitant, atovaquone, bosentan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, sitaxentan

Food and supplements that may interact with etoposide*

- Echinacea
- Glucosamine
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

Hydrocortisone

Drugs that may interact with hydrocortisone
• Arthritis medications o Leflunomide, tofacitinib • Antiretrovirals and antivirals o Darunavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranivir • Anti-seizure medications o Carbamazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, carvedilol, dronedarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: o Aprepitant, aripiprazole, clarithromycin, cyclosporine, deferasirox, itraconazole, ivacaftor, ketoconazole, mifepristone, natalizumab, nefazodone, rifampin, tacrolimus, trazodone, warfarin
Food and supplements that may interact with hydrocortisone*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Ifosfamide

Drugs that may interact with ifosfamide
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, paliperidone, quetiapine, thioridizine, ziprasidone • Antifungals o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, dronedenarone, verapamil

- Stomach and reflux medications
  - Esomeprazole, omeprazole
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Bosentan, sitaxentan, aprepitant, dexamethasone, lomitapide, mifepristone, natalizumab, pimozide

Food and supplements that may interact with ifosfamide*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Mercaptopurine

Drugs that may interact with mercaptopurine
○ Artiritis medications: leflunomide, tofacitinib ○ Other medications, such as allopurinol, azathioprine, clozapine, febuxostat, natalizumab, olsalazine, sulfasalazine, warfarin

Food and supplements that may interact with mercaptopurine*
• Echinacea

Methotrexate (by mouth or by vein).

Drugs that may interact with methotrexate
• Some antibiotics (amoxicillin, Bactrim, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline) • Some anti-inflammatory drugs (aspirin, acetaminophen, ibuprofen, naproxen, ketorolac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, retinoids, theophylline, warfain

Food and supplements that may interact with methotrexate*
• Alcohol • Echinacea • Some vitamins, including those that contain folic acid or high doses of vitamin C

Pegaspargase

Drugs that may interact with pegaspargase
○ Leflunomide, natalizumab, tofacitinib

Food and supplements that may interact with pegaspargase*
• Echinacea

Thioguanine

Drugs that may interact with thioguanine
○ Arthritis medications: leflunomide, tofacitinib ○ Other medications, such as allopurinol, clozapine, natalizumab, olsalazine, sulfasalazine

Food and supplements that may interact with thioguanine*
• Echinacea

Vincristine

Drugs that may interact with vincristine
• Antibiotics ○ Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics ○ Aripiprazole, nefazodone, trazodone • Antifungals ○ Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications ○ Leflunomide, tocilizumab, tofacitinib • Anti-rejection medications ○ Cyclosporine, tacrolimus • Antiretrovirals and antivirals ○ Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir • Anti-seizure medications

- Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, digoxin, dronedenarone, propranolol, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vincristine*

- Echinacea
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

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