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The world's childhood cancer experts

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June 29, 2018

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Cancer Therapy Evaluation Program
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Re: **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*. ~ ***Amendment #11***

Dear Ms. Kruhm,

Enclosed you will find **Amendment #11** to the protocol and informed consent forms for the study **AALL0434**. This study is primarily being amended to redesign the nelarabine randomization based on better than expected overall outcomes. In addition this amendment includes a change in response to Dr. Johnson's July 11, 2014 notice regarding preparation instructions for nelarabine (506U78).

Other administrative changes have been made for consistency and clarity between documents; specific changes are detailed below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked in the protocol but not specified below.

Thanking you in advance for your review of this amendment,

With kind regards,

Sarah L. Vargas, Ph.D., Protocol Coordinator (on behalf of)

Kimberly Dunsmore, M.D., Study co-Chair, AALL0434
Stuart Winter, M.D., Study co-Chair, AALL0434
Robert Hayashi, M.D., Study Vice-Chair, AALL0434
Meenakshi Devidas, Ph.D., Study Sr. Statistician, AALL0434
Peter Adamson, Group Chair, Children's Oncology Group

AALL1231 SUMMARY OF CHANGES
SUMMARY OF CHANGES: PROTOCOL DOCUMENT

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

Section	Page	Comments
Throughout	Throughout	Update of section numbers and version date.
Title Page	1	Update of version date and amendment number.
Table of Contents	2-6	Update of the TOC.
Study Committee	9	The protocol coordinator contact information has been updated.
4.9.1	70	Added * next to “d” on day 29, for proper association with footnote instructions.
6.10	113	The nelarabine monograph was revised in response to Dr. Johnson’s July 11, 2014 notice regarding preparation instructions for nelarabine (506U78).
10.1.1.1	129	Included the new section to describe the study re-design with amendment #11.
10.3.2	135	Included the new section to describe the study re-design power calculations for nelarabine randomization with amendment #11.

SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENTS

The version date has been updated.

Activated: 01/22/07
Closed: 7/25/14

Version Date: 03/24/16
Amendment: 11

CHIL DREN'S ONCOL OGY 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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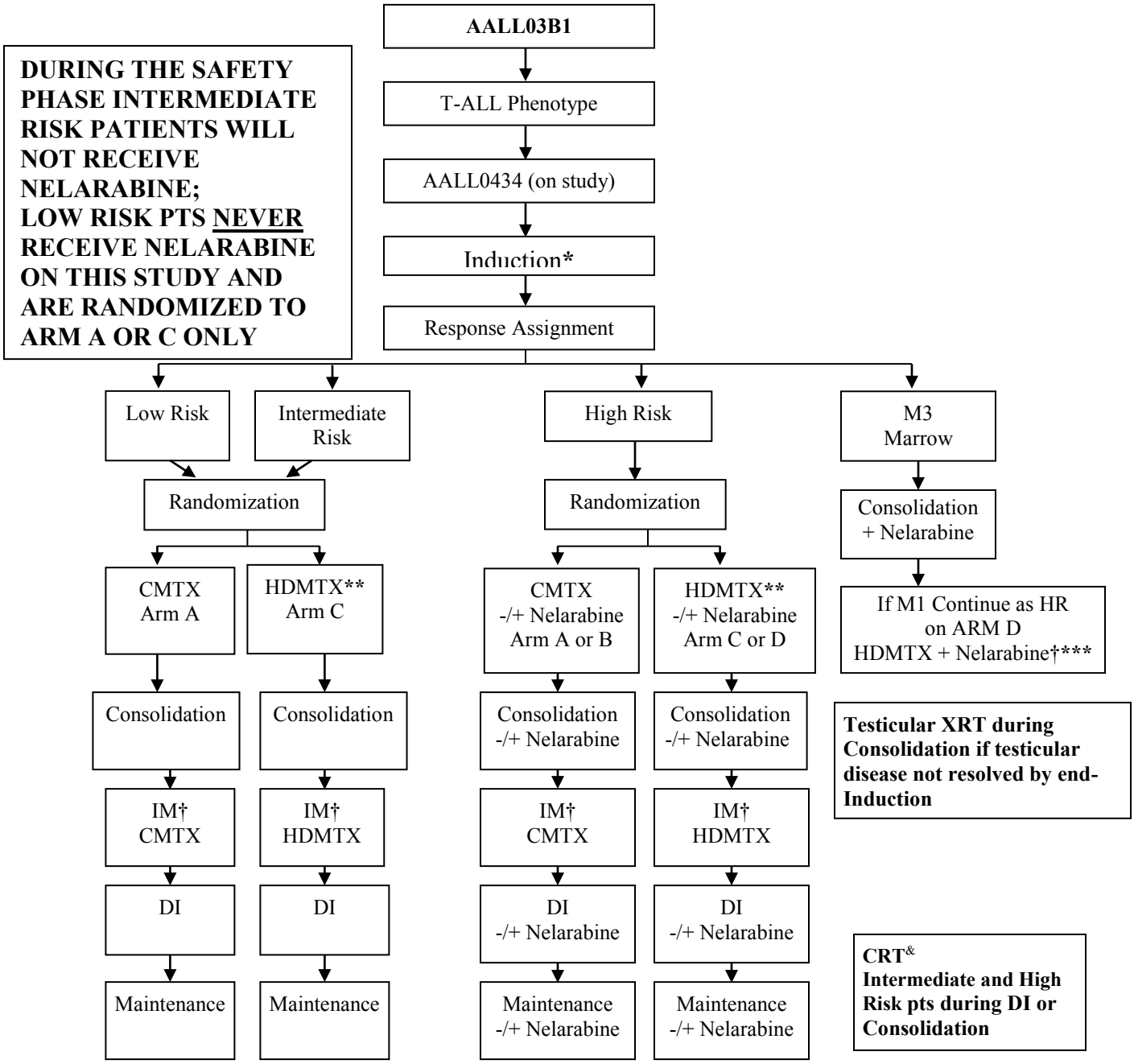
AGENT	NSC#	AND IND#
Nelarabine	NSC# 686673	IND#52611
(IND Sponsor: NCI)		
Cyclophosphamide	NSC# 026271	Exempt
Cytarabine	NSC# 063878	Exempt
Daunorubicin	NSC# 082151	Exempt
Dexamethasone	NSC# 034521	Exempt
Doxorubicin	NSC# 123127	Exempt
Erwinia Asparaginase	NSC#106977	Exempt
Leucovorin	NSC# 003590	Exempt
6-Mercaptopurine	NSC# 000755	Exempt
Methotrexate	NSC# 000740	Exempt
Pegaspargase	NSC# 624239	Exempt
Prednisone	NSC# 010023	Exempt
6-Thioguanine	NSC# 000752	Exempt
Vincristine	NSC# 675574	Exempt

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 ≥ 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.

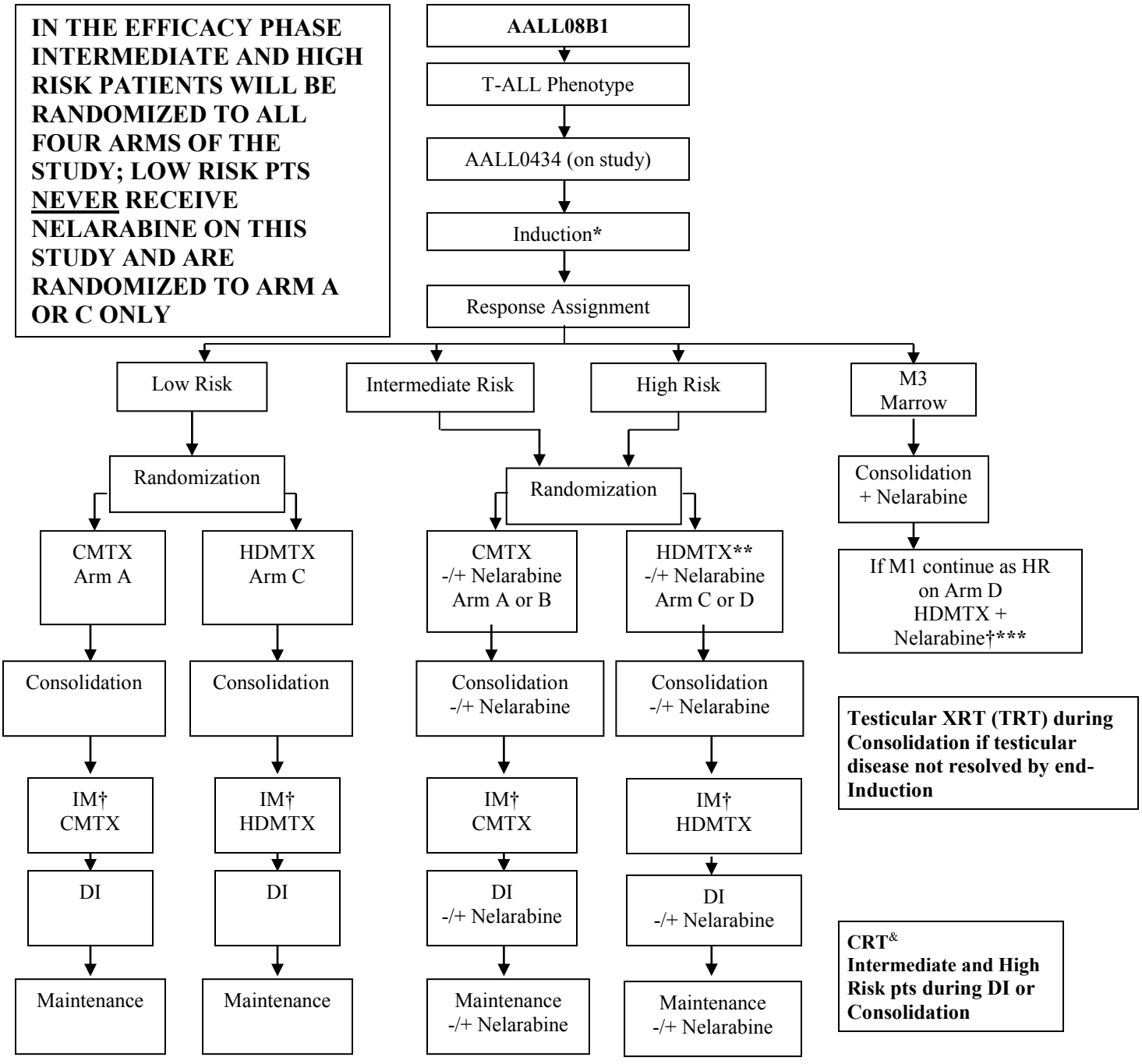
CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
IM = Interim Maintenance
DI = Delayed Intensification

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

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
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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.

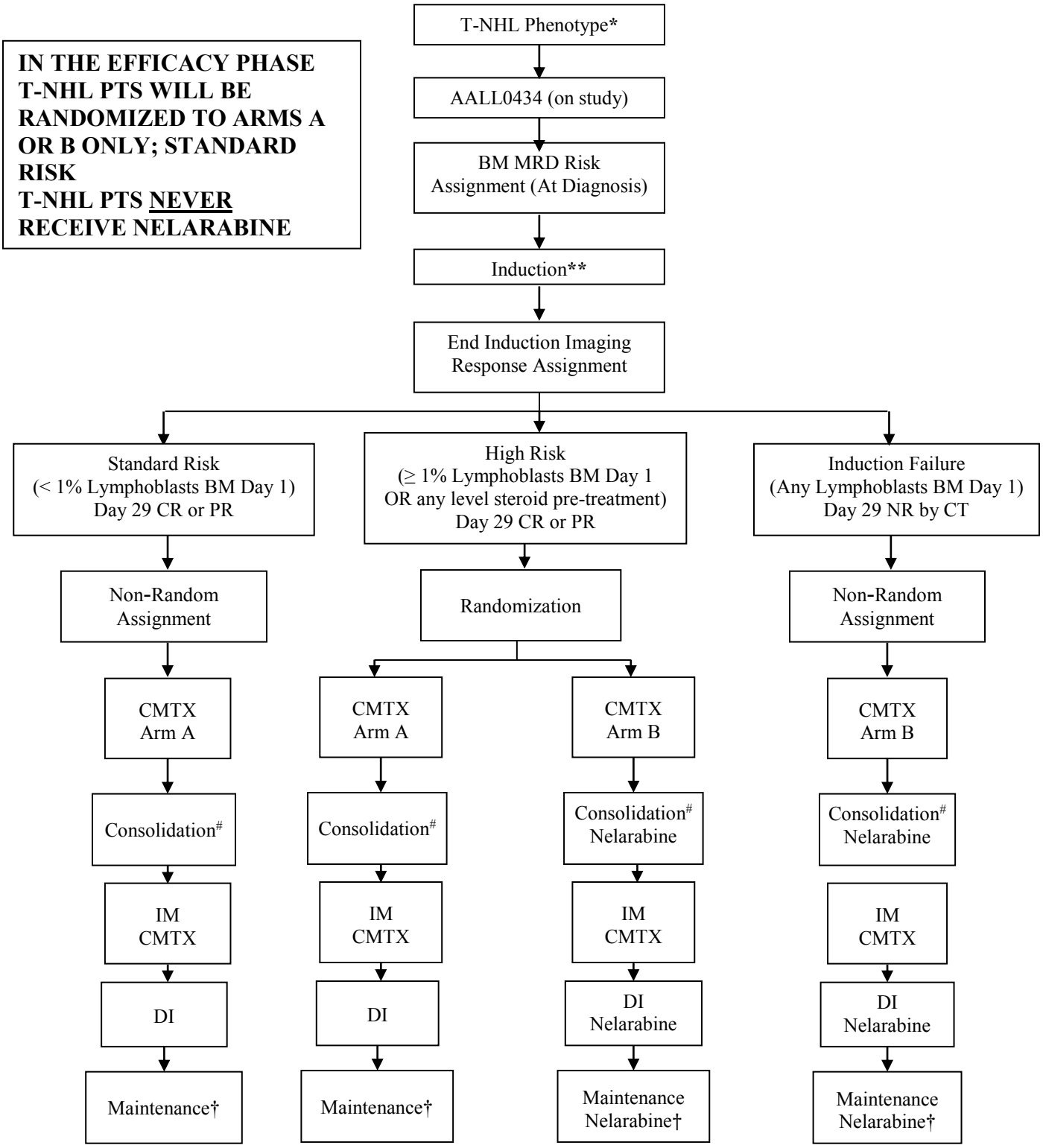
CMTX = Capizzi escalating MTX
HDMTX = High dose MTX
IM = Interim Maintenance
DI = Delayed Intensification

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 <u>NEVER</u> RECEIVE NELARABINE



***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.

2.0 BACKGROUND

T-cell lymphoid malignancies have distinct biochemical, immunologic and clinical features which set them apart from non-T-lymphoid malignancies.[1-6] Historically, the diagnosis of T-ALL portended a worse prognosis than other forms of non-T childhood ALL.[1,7,8] Over the past three decades, the introduction of intensive, high-dose, multi-agent pulse chemotherapy has significantly improved the EFS for patients with T-ALL from 15%-20% to 40%-73%.[9-12] Current trials have further improved outcomes for children with T-ALL, but have plateaued in the 70%-75% EFS range, as shown by Dana Farber Cancer Institute (DFCI) 85-01, [13] DFCI 87-01 and Berlin-Frankfurt-Münster (BFM)-86.[14] The recent Pediatric Oncology Group (POG) T-cell ALL protocol, POG 9404, randomized the addition of high dose methotrexate (HDMTX) to the DFCI regimen and found a statistically significant improvement in 4-year EFS rates for NCI High Risk patients treated with and without HDMTX of 77.9% vs. 65.5%, respectively. The 76.9% EFS at 5 years for patients with T-ALL, treated on CCG 1961, regimen C, without HDMTX, is comparable to that seen on 9404 with HDMTX. The majority of patients with T-ALL and NCI standard-risk features clearly fare better with more aggressive therapy, as demonstrated by EFS rates of 71% on CCG 1952/1962 versus 87.4% on POG 9404 (89.2% within the HDMTX arm). Based on a projected 2 year EFS rate of 85% for T-cell patients compared to 94% for pre-B ALL patients treated on the CCG 1991 study [RHR of 3.12 (p = .002)], T-ALL patients will no longer be eligible for COG SR-ALL trials and will be treated on the T-cell specific AALL0434 trial.

Lymphoblastic lymphoma (LL) accounts for approximately 25% of all pediatric non-Hodgkin lymphoma (NHL) cases. The history of the treatment for LL over the past 3 decades reflects the

evolution of treatment from conventional lymphoma-based treatment to ALL-based treatment.[11,15-17] With current therapies for LL, the majority of patients, including those with advanced stage disease, can expect a likelihood of 80%-90% disease free survival (DFS) utilizing regimens modified from ALL-based regimens. While effective, this intensive chemotherapy does produce short- and long-term side effects.[18] Unfortunately, identifying risk categories for this disease has been difficult.[19,20] Even conventional staging classifications have failed to segregate High Risk patients from the remaining population as most studies have failed to demonstrate major survival differences between patients of different stages. In addition, the salvage rate remains poor for LL patients who relapse, with survival of these patients ranging from 10%-15%. The ability to identify High Risk patients likely to recur early in the course of therapy would provide the opportunity to test novel therapies in these patients.

Rarely does one find a drug with lineage-specific cytotoxicity as recently discovered for Nelarabine. Nelarabine (2-amino-9-B-D-arabinofuranosyl-6-methoxy-9H-purine) is a water-soluble prodrug of araG (9-B-arabinofuranosylguanine), a synthetic deoxyguanosine derivative that is resistant to cleavage by endogenous purine nucleoside phosphorylase and is cytotoxic to T-lymphoblasts at micromolar concentrations. Cytotoxicity is mediated by the accumulation of araG nucleotides, especially d-araGTP, in T-cells greater than in B-cells, resulting in inhibition of ribonucleotide reductase and inhibition of DNA synthesis. This differential cytotoxicity between B-cells and T-cells has created interest in using this compound to treat T-cell malignancies.

Earlier T-ALL studies have not included risk stratification due to the lack of predictive clinical or laboratory based prognosticators.[6,12] Recently, the international BFM and GIMEMA cooperative groups reported that children and adults with Day 29 MRD levels of greater than 1% were at a very high risk of relapse.[21,22] In the International BFM study, patients who had MRD levels of 10^{-2} or greater had five to ten fold higher relapse rates at 3 years (39% - 86%), and in the GIMEMA study, the probability of relapse at 2 years for MRD-positive patients at preconsolidation was 81.5% vs., 38.9% for MRD-negative patients. In addition, measurable MRD, of prognostic significance, was identified more often in children with T-ALL than those with B-lineage ALL.[22] Based on these results, MRD-based treatment stratification will be used in AALL0434. Low levels of MRD at end Induction (< 0.1%) will be required along with other clinical features to be classified as Low Risk (LR), and high levels of end-Induction MRD (≥ 1%) will be considered equivalent to an M2 (5%-25% blasts) marrow.

In an attempt to develop better prognostic indicators for T-NHL, A5971 tested the feasibility of detecting low levels of disease in marrow and peripheral blood at diagnosis and its clearance in peripheral blood during Induction, using a BFM leukemia treatment backbone. Analysis from the completed trial revealed that 72% of patients had lymphoma cells (CD3+/TdT+ cells) detectable in the bone marrow and blood by flow cytometry, although most patients had no lymphoma cells detectable morphologically. High levels of disease by flow cytometry were significantly associated with a poorer outcome: 2-year EFS was 68.1% ± 11% for patients with > 1% lymphoblasts detected in the bone marrow at the time of diagnosis, as compared to 90.7% ± 4.4% for patients who had less disease detected (P = 0.031). Thus, it appears that quantitation of low levels of disease in the bone marrow can identify High Risk patients for treatment stratification.

2.1 Rationale for Augmented Intensity BFM Therapy

The CCG 1961C or augmented BFM (aBFM) with one Delayed Intensification phase (aBFM) regimen will be used as the standard backbone therapy for this study. Patients will be randomized to receive high dose methotrexate (HDMTX) versus Capizzi-style methotrexate plus PEG Asparaginase (CMTX) in Interim Maintenance and to either receive or not to receive Nelarabine in Consolidation, Delayed Intensification and Maintenance. MRD will be monitored at the end of Induction, and at the end of Consolidation/beginning of Interim Maintenance for observational correlations with response to therapy among patients who are at an increased risk of relapse (High Risk patients as defined below, patients with a slow early response and those that fail Induction).

The aBFM backbone was chosen over POG 9404 for the following reasons: 1) The overall result for aBFM was accomplished without the use of CRT in patients with a rapid early response; 2) The aBFM regimen includes significantly less anthracycline; 3) aBFM is most similar to the POG pilot study, AALL00P2 which incorporates Nelarabine into a multi-agent backbone, allowing for the application of pilot toxicity data to the incorporation of Nelarabine in a randomized trial; 4) aBFM is the backbone for COG AALL0232 for patients with High Risk B-lineage disease. The use of the same aBFM backbone, for patients with B and T-lineage ALL will increase provider familiarity with the therapy, enhancing patient care and, importantly, allowing for the continued comparison of response measures, including the significance of MRD among patients with T- and B-lineage leukemias, and; 5) MRD measurements using the BFM backbone have produced compelling European data that response to Induction chemotherapy may be useful as a tool for risk-stratification.[22]

To further assess the toxicity of Nelarabine in the context of multi-agent chemotherapy, Nelarabine was incorporated into a modified BFM86 backbone in AALL00P2, which opened for accrual in April 2001, using Nelarabine at 400 mg/m^2/day, Days 1 through 5. During the first phase of AALL00P2, no Grade 3 or higher central or peripheral nervous system toxicities attributable to Nelarabine were observed. Based on these results, AALL00P2 was re-opened and amended to increase the Nelarabine dose from 400 to the Phase II-recommended dose of 650 mg/m^2. To supplement the data accrued on AALL00P2, MRD positive patients with T-ALL (High Risk) will be randomly assigned in AALL0434 to either receive or not to receive Nelarabine at 650 mg/m^2 IV daily for 5 days. This cohort of patients will be assessed for toxicity at approximately 24 months and again at 36 months into the trial. During this analysis, only High Risk patients will continue to be randomized to all four arms of the study. If patients receiving Nelarabine are found to have an acceptable toxicity profile during this safety phase, the study will be opened to also allow randomization of Intermediate Risk patients to all four arms of the study during the efficacy phase.

The efficacy phase will include a post-Induction randomization to receive or not receive Nelarabine for all Intermediate and High Risk patients. Low Risk patients (NCI standard Risk, RER, without testicular disease at diagnosis, CNS1 and Day 29 MRD < 0.1%) will be eligible for randomization to aBFM with either Capizzi methotrexate or High Dose methotrexate [Arm A (CMTX) or Arm C (HDMTX), respectively]. They will not be eligible for the Nelarabine randomization, and will not receive CRT because these patients have an excellent outcome and, due to their young age, are more susceptible to neurotoxicity. T-NHL patients will be assessed

for the presence of disease in the bone marrow at diagnosis using flow cytometry. Patients with ≥ 1% disease in the bone marrow or any level of steroid pre-treatment will be considered High Risk and randomized to either Arm A (CMTX) or Arm B (CMTX + Nel). Those with < 1% disease in the bone marrow will be considered Standard Risk and will be non-randomly assigned to Arm A (CMTX). Results from two prior group wide studies (POG9404 and A5971) have failed to demonstrate a superior outcome for patients receiving HDMTX. Thus, a design that would include yet another randomization of these patients to the addition of HDMTX is not justified. As a result treatment assignment for patients classified as High Risk for T-NHL will be restricted to 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. CRT will not be delivered to any lymphoma patients on this study as recent reports have demonstrated excellent outcomes without radiation. Treatment plans for T-NHL risk groups are designed to closely parallel those for the T-ALL risk groups. Since patients with high risk T-NHL do not get cranial radiation in contrast to patients with T-ALL, those high risk patients randomized to Arm A invariably receive 4 less IT Methotrexate administrations during Maintenance compared to patients with standard risk T-NHL non-randomly assigned to treatment Arm A. This difference in the total number of IT administrations (21 for standard risk verses 17 for high risk T-NHL) is not felt to be significantly different and is comparable to the number of IT administrations in the recently closed A5971 (19 for Arms A1 and A2, 13 for Arms B1 and B2) which had excellent CNS disease control. CNS-positive and testicular disease T-NHL patients will not be eligible for this study.

This study fits in with development of other studies within the ALL committee by using a backbone which allows for comparative data, utilizing a new agent with disease specificity and allowing for incorporation of biologic questions and cancer control questions within the context of the clinical trial.

The use of CRT with aBFM for patients with T-ALL may significantly enhance the outcome for patients with T-ALL, whose failures on CCG 1961 disproportionately involved the CNS. Additionally, aBFM did not include high dose MTX. *In vitro* and *ex vivo* studies of T-lymphoblasts demonstrate a decrease in accumulation and polyglutamation of MTX when compared to B-lineage blasts[23-27]. Consistent with these observations, POG 9404 demonstrated a clear improvement in outcome for T-lineage NCI standard and high risk patients through the addition of HD MTX and BFM-90 produced a superior EFS as compared to BFM-86 with an increase in the MTX dose from 0.5 to 5.0 gm/m^2.[28] Thus, it is important to assess, in a randomized study, whether the addition of HD MTX to aBFM will enhance outcome.

Osteonecrosis (ON)

Results from CCG-1961 showed that the use of discontinuous dexamethasone (Days 1-7 and 15-21, rather than Days 1-21) during DI decreased the rate of ON. Specifically, the rate of ON among patients 10+ years of age on CCG-1961, all of whom received prednisone during Induction therapy, was 18% for those treated with continuous dexamethasone in a single DI (regimen C) vs. 6% for those treated with discontinuous dexamethasone in 2 DI phases (regimen D). However, very little ON was observed in CCG-1961 among patients less than 13 years of age. Based on these findings, the COG High Risk ALL study (AALL0232) initially used discontinuous dexamethasone during DI for patients 13+ years of age, and continuous dexamethasone during DI for patients 1-12 years of age. Interim analysis of AALL0232 in 2006

revealed a higher than expected rate of ON in 10-12 year olds receiving continuous dexamethasone during DI. Based on these findings, AALL0232 Amendment #3A (09/11/06) changed dexamethasone dosing during DI to discontinuous for patients 10-12 years of age.

Ongoing analysis in April 2008 demonstrated higher than expected reported incidence of ON in AALL0232 as compared to that observed in CCG-1961. The overall incidence of ON at 24 months is 10.4%. The incidence of ON is related to patient age and type of Induction steroid. The incidence rates by age group are 1-9 years: 2.7%, 10-12 years: 16.0%, and 13+ years: 14.7%. Patients who received dexamethasone during Induction have experienced a higher rate of ON compared to those who received prednisone (11.6 vs. 8.7%; p-value = 0.014); although there is no difference in ON rates in patients 1-9 years of age related to steroid administered during Induction therapy (2.2% dexamethasone vs. 2.6% prednisone).

While it is too early in the conduct of AALL0434 to analyze the occurrence of ON in this trial, AALL0434 therapy is highly similar to that administered in AALL0232 and the risks for ON are likely very similar. Amendment #2A implements several changes in steroid administration to attempt to decrease the rate of ON. All patients, regardless of age, will receive discontinuous dexamethasone dosing during DI. In addition, all patients, regardless of age, will receive every 4 week 5-day pulses of prednisone 40 mg/m^2/day, rather than dexamethasone 6 mg/m^2/day, during Maintenance therapy.

2.2 **Preliminary Data**

In a phase I study of Nelarabine a striking response rate was observed. Fourteen complete (CR) and 9 partial responses (PR) were documented among 28 evaluable patients with relapsed T-ALL. Responses were observed at all dose levels (5 mg/kg - 75 mg/kg), with Nelarabine given on Days 1-5. Dose-limiting neurotoxicity, consisting of weakness, ataxia, confusion and coma, was observed in 3 of 4 adults treated at the 60 mg/kg dose level, 2 of 31 adults treated at the 40 mg/kg dose level, and 1 of 11 children treated at the 60 mg/kg dose level. No neurotoxicity was observed in children treated at the 40 mg/kg or 1200 mg/m^2 level.[29] Thirty percent of the adults treated at a dose of 40 mg/kg experienced reversible somnolence on Day 6-7 after starting therapy with Nelarabine. POG P9673, a pediatric Phase II trial of Nelarabine in T-ALL and T-NHL accrued 153 (two were ineligible for evaluation) patients from June 1997 to July 2002. By definition, all patients treated with Nelarabine on this trial had failed earlier therapy, which incorporated other known neurotoxic agents. Patients in first bone marrow relapse had a complete response rate of 55%, and 27% of patients with a second or subsequent relapse achieved a CR. Available details about the PNS (≥ Grade 2) and CNS (≥ Grade 3) toxicities reported from POG 9673 are presented in Tables 1 and 2. Among 151 patients who received at least 1 dose of Nelarabine, there were 47 episodes of any Grade of CNS or PNS toxicity in 34 patients (23%). Twenty-five patients experienced CNS or PNS toxicities that were possibly or probably attributable to Nelarabine (Table 1), while 9 patients experienced neurotoxicity unlikely to be related to Nelarabine (Table 2). Twelve of the 25 patients experiencing Nelarabine-related neurotoxicity, twelve (nearly half) had complete resolution of neurologic signs and symptoms within a few hours to one year. Eight experienced toxicity with insufficient follow-up to determine the completeness of resolution; four patients died from other causes prior to resolution of their neurologic findings and one patient died, comatose, with the death attributed to Nelarabine. Based on these data it appears that even in a heavily pretreated group of patients that the majority of PNS and/or CNS events will resolve.

Table 1
(table continues on next page)

Patient Dose (mg/m^2)	PNS Grade	CNS Grade	Comments
1200		4	Somnolence; died of progressive disease before resolution
900		3	Somnolence; resolved without problem
900	2		Lower extremity weakness; resolved within 1 year
900	4	3	Guillain-Barré like polyneuropathy after 4 doses; died before resolution
650		4	Seizures 5 days after Nelarabine, 2 days after intrathecal therapy in second cycle. Started on anticonvulsants; did not recur.
650	2		Lower extremity paresthesias after 7 cycles; resolved within weeks
650	3		Lower extremity weakness after 3 cycles; resolved within 3 months
650	3	1	Lower extremity paresthesias after 1 cycle; lost to follow-up
650	3	1	Lower extremity paresthesias after 3 cycles
650	2	1	Lower extremity weakness after 7 cycles; stable 2 months off therapy
650		5	Death from Nelarabine preceded by coma; history of 1 prior seizure; etiology unknown
650	2		Lower extremity paresthesias cycle 4; resolved within 5 months
650	3		Painful lower extremity paresthesias cycles 1 and 2; improved over 3 months but died prior to complete resolution
650	2	2	Headache, lower extremity paresthesias with second dose; not rechallenged.
650	3		Hand numbness/ neck pain attributed to musculoskeletal origin
650		3	Hallucination after 1 dose; rechallenged without recurrence
650	3	2	Lower extremity weakness after 4 doses; improved within days
650		4	Seizure 22 days after Nelarabine during metabolic derangement
650	2	2	Headache, lower extremity paresthesias, in cycle 2. Neurologic exam normal 2 months later.
400		3	Somnolence during acute illness; resolved
400	4		Guillain-Barré like polyneuropathy after high dose cytarabine 6 weeks after last Nelarabine; died before resolution
400	4	3	Cranial nerve palsy attributed to Nelarabine by treating physician
400	2	4	Grade 2 hand and foot pain during course 1; did not recur during course 2. 9 weeks after last Nelarabine developed retrobulbar neuritis/demyelinating disease after stem cell transplant
400	2		Hand/foot numbness during cycle 1, resolved within 24 hours
400		3	Headache during Nelarabine infusion

Table 1. Details of PNS and CNS adverse events that were likely attributable to Nelarabine on P9673

Table 2

Dose (mg/m^2)	PNS Grade	CNS Grade	Comments
900		3	Hallucinations while septic; resolved
900	3		Foot drop attributed to prior vincristine
400	4		Weakness, loss of reflexes; associated with fungal brain abscess and hemorrhage during first cycle; died before resolution
400	3	3	Back pain and lower extremity weakness after cycle 1 due to spinal cord metastases
400	1	3	Seizure (?) due to dilantin toxicity; rechallenged with Nelarabine without problem
400		3	Intermittent confusion during terminal illness
400		3	Hallucinations attributed to narcotics; resolved
400		4	Seizure after first dose of intrathecal therapy on first course; associated with increasing CSF blasts
400	3	1	Due to disease; improved on Nelarabine

Table 2. Details of CNS and PNS adverse events *unlikely* to be attributable to Nelarabine on P9673

COG Study AALL00P2 (opened for accrual in April 2001) incorporated Nelarabine into a modified BFM86 backbone and gave Nelarabine at 400 mg/m^2/daily for 5 days during weeks 6, 25, 35, 43, 51 and 59 of therapy. In phase I of this study, no Grade 3 or greater central or peripheral nervous system toxicities attributable to Nelarabine, given with either 1260 cGy CRT (CNS1/CNS2) or 1800 cGy (CNS3) and HDMTX, were observed. Based on this very re-assuring absence of significant neurotoxicity, AALL00P2 was re-opened with an amended increase in the Nelarabine dose from 400 mg/m^2 IV Days 1-5 to the Phase II recommended dose of 650 mg/m^2 IV daily for 5 days.

Several large study groups have reported that MRD analyses are more reliable for risk classification in childhood ALL than age, presenting white blood count (WBC), extramedullary disease and other existing clinical and biological predictors.[30-33] Leukemic cell phenotype contributes to the prognostic value of MRD detection, as recently demonstrated by outcome predictions that were more accurate for patients with T-ALL than for children having precursor B-ALL.[22,34] The measurement of MRD at critical time points during the ALL treatment course is an important method to gauge the effectiveness of therapy. Using flow-based techniques, the detection of one or more leukemic cells among 10,000 normal bone marrow cells was associated with an increased risk of relapse, but especially so for patients with more than 1% leukemic blasts at the end of Induction.[31-34] Alternatively, favorable EFS rates were realized in cases where MRD was first detected but later became undetectable during the treatment course, underscoring the importance of intensive post-Induction chemotherapy as a means of eradicating residual disease burden.[33] As previously noted for other patients with higher risk ALL, such as those with the Philadelphia chromosome,[35,36] children with T-ALL are more likely to have detectable levels of MRD at the end of Induction and at later points during treatment.[22,34] As a result of this supportive data, we propose to use MRD-based risk stratification strategies to either intensify or reduce therapy in this study.

Experience on COG P9900 with over 3000 ALL patients has shown that flow cytometric detection of end-Induction MRD is feasible in more than 95% of patients, and that end-Induction

MRD burden correlated with 3 years EFS. This method of MRD detection will be used in contemporary COG ALL trials. Preliminary data from COG P9900 suggest that MRD measurement in peripheral blood (PB) by flow cytometry at Day 8 Induction adds prognostic value to Day 29 MRD burden in B-precursor ALL. To confirm and extend these data, frontline COG ALL studies (AALL0434, AALL0232 and AALL0331) will include optional Day 8 PB MRD determinations. In addition, we also wish to explore whether assessment of BM MRD at Day 15 of Induction may help to improve our ability to discriminate between good and bad responders. Currently, about 50% of patients have a BM aspiration performed to assess morphology at Day 15 of Induction (all patients not M1 at Day 8). Day 15 MRD samples will be sent to COG Reference labs for those patients already scheduled to have a BM aspiration performed. Consent for these extra specimens is included with AALL08B1.

2.3 Determination of Early Response

All T-ALL patients on study will be stratified on the basis of early response as assessed by marrow morphology at Day 8/15 and MRD on Day 29. Patients who are M1 on Day 8 will be considered rapid early responders (RER) pending the results of Day 29 BM and MRD levels. Patients who are M2 or M3 on Day 8 will have a Day 15 BMA and, if M1 on Day 15, they will be considered RER pending results of Day 29 MRD. Patients who are M2 or M3 on Day 15 will be considered SER, regardless of Day 29 MRD result. All patients with ≥ 0.1% MRD on Day 29 are considered SER regardless of Day 8/15 marrow morphology. Treatment randomization will be affected by categorization into Low, Intermediate and High Risk status. Low Risk patients are those who are NCI standard risk by age and WBC, lack testicular disease at diagnosis, are CNS1, and are RERs (M1 marrow on Day 8 or 15, and have an M1 marrow with < 0.1% MRD on Day 29). Low Risk patients are excluded from receiving Nelarabine and CRT (see Sections 4.1.1 and 10.1 for further details).

High Risk T-ALL patients are those who are either NCI standard or high risk, RER or SER status, and have an M2 marrow or ≥ 1% MRD on Day 29. Patients in the High Risk category will be eligible for randomization to all four study arms during both the safety and efficacy phases of this study.

Intermediate Risk T-ALL patients are those who are NCI standard risk with SER, CNS2 or CNS3 disease, or testicular disease, or NCI high risk, RER or SER, any CNS and testicular status, but with an M1 marrow on Day 29 with less than 1% MRD. They will be eligible for randomization to receive Nelarabine in the efficacy phase (which is now open), but not the safety phase of this study (which is now closed). This trial does not include the administration of a second Interim Maintenance or Delayed Intensification for the SER patients, as was included in CCG 1961. Support for this change in therapy is derived from the absence of any definable subset of NCI high risk RER patients that gained benefit from the second IM/DI on CCG 1961. Statistically, this suggests that the smaller subset of SER patients, are also unlikely to derive significant benefit from the second IM/DI. The continued assessment of RER vs SER status is required, however, to allow for an ongoing evaluation of outcome for the SER patients. Should they fare poorly on this trial as opposed to 1961; the study will be closed to the SER patients while therapy is adjusted.

T-ALL patients with M3 marrow on Day 29 will be considered Induction failures. Given the notable responses to Nelarabine for patients with refractory disease, patients who have failed

Induction will be eligible to remain on study, and will be non-randomly assigned to receive Nelarabine and HD MTX. If patients in this subset have an M3 marrow after the first block of therapy during Consolidation, they are to be taken off study and treated at the investigator's discretion. Moreover investigators may decide on subsequent non-protocol therapy such as bone marrow transplantation after exposure to Nelarabine. These patients may be taken off study without penalty.

Risk assessment for T-NHL patients will be based upon disease burden in the bone marrow at diagnosis and disease response, as measured radiographically and by bone marrow morphology, at the end of Induction. The results to date from A5971 indicate that we possess the means to detect minimal disease in bone marrow and peripheral blood samples in T-NHL patients, and that the extent of disease, as measured by flow cytometry at diagnosis in the bone marrow, may predict those patients at increased risk for bone marrow recurrence. Review of data from A5971 found that all relapses in patients with low or undetectable disease in the bone marrow at diagnosis were at the primary site only and not in the bone marrow. Thus, disease quantification in the bone marrow at diagnosis may be limited to assessing the risk of relapse in the bone marrow and may fail to identify patients at risk for local recurrence. An additional means of assessing disease burden using radiologic methods may complement analysis of the marrow to fully characterize a patient's risk status. Thus, conventional CT will be obtained at diagnosis and at the end of Induction to assess radiologic clearance of bulky disease.

T-NHL patients with < 1% disease in the marrow at diagnosis will be considered Standard Risk and non-randomly assigned to Arm A (CMTX). T-NHL patients with ≥ 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 who fail to achieve at least a radiologic partial response (PR) or clearance of their marrow by morphology at the end of Induction will be considered Induction Failures and non-randomly assigned to Arm B (CMTX + Nel).

2.4 Integration of Radiation Therapy

Patients with T-ALL have an increased risk of relapse in the central nervous system and CNS relapse has become a major cause of treatment failure with improved prevention of BM relapse using the ABFM regimen. To date, there have been a total of 77 relapses among 411 T-ALL patients enrolled in CCG 1961, including 24 CNS relapses (31% of total relapses) (unpublished data, 12/05). Comparison of events between RER patients (who did not receive CRT) and SER patients (who received 1200 cGy CRT) suggests a critical role for CRT in CNS control for T-ALL patients. There were 20 CNS relapses among 252 RER T-ALL patients (7.9%) versus 1 CNS relapse among 121 SER T-ALL patients (0.8%). Twelve of the 20 CNS relapses in RER patients occurred in the first year of therapy, with approximately half occurring in the first 6 months of therapy. These observations suggest that CRT is a critical component of therapy for T-ALL patients treated with aBFM therapy and should be delivered relatively early in treatment. On this trial, Intermediate and High Risk patients assigned to CMTX (Arms A or B) will receive CRT during the Consolidation phase of theapy in the first 2-3 months of treatment. In contrast to these results, early administration of HD MTX allows CRT to be delayed in patients with T-ALL. Among 123 patients with T-ALL enrolled in ALL-BFM 90 that had a good response to a prednisone prophase, there were only 3 relapses that involved the CNS (1 isolated CNS, 2 combined marrow and CNS).[37] Based on these and other similar data, CRT will be administered

during the second half of Delayed Intensification in those patients assigned to receive HDMTX in order to decrease the risk of neurotoxicity.

CRT will not be delivered to any lymphoma patients on this study as recent reports have demonstrated excellent outcomes without radiation.[38] The safety of withholding CRT in this study is reinforced by the results of the recently completed A5971. Two hundred fifty-seven patients with Stage III/IV disease with no CNS disease at diagnosis were treated without prophylactic XRT. Three patients (1.2%) subsequently were found to have disease in the CNS at relapse. These results were in the face of an excellent overall outcome of the patients in this study (80% 5 year EFS) (personal communication, Dr. Thomas Gross). Thus, the exclusion of prophylactic CRT for this population would not be expected to alter the disease control for these patients and would spare them of the long term effects of such therapy.

As described above, COG Study AALL00P2 (opened for accrual in April 2001) incorporated Nelarabine into a modified BFM86 backbone and gave 1260-cGy CRT (CNS1/CNS2) or 1800 cGy (CNS3) as well as four courses of HDMTX. In phase I of this study, no Grade 3 or greater central or peripheral nervous system toxicities attributable to Nelarabine were observed. Based on this very re-assuring absence of significant neurotoxicity, AALL00P2 was re-opened with an amended increase in the Nelarabine dose from 400 mg/m2 IV Days 1-5 to the Phase II recommended dose of 650 mg/m2 IV daily for 5 days. The study is now closed with only one episode of neurotoxicity (Grade 3 Guillain-Barre like syndrome) probably attributable and 2 episodes of neurotoxicity possibly attributable (Grade 3 PNS, Grade 3 extrapyramidal) to Nelarabine among 65 patients enrolled at the 400 mg/m^2 dose level and 8 patients enrolled on the 650 mg/m^2 dose level. All of these toxicities occurred at the 400 mg/m^2 dosing level.

Testicular leukemia is present in 1%-2% of boys with ALL at the time of initial diagnosis. The optimal treatment of testicular leukemia is unknown. While TRT is routinely administered to patients with testicular leukemia by some centers and cooperative groups, its role in preventing relapse is unproven and this treatment modality is associated with significant late toxicities. For these reasons, many large centers and cooperative groups do not routinely prescribe TRT for boys with overt testicular leukemia. A recent report from St. Jude Children's Research Hospital concluded that irradiation appears to provide no survival advantage to this patient population.[39] In an effort to decrease the burden of therapy, contemporary COG ALL trials no longer recommend routine use of TRT for all boys with testicular leukemia. In this trial, boys with T-ALL and overt testicular disease will be assigned to HDMTX regimens (Arms C or D). No TRT will be given to those patients with testicular leukemia that resolves by the end of Induction therapy; those that have persistent testicular involvement at end Induction will receive 2400 cGy TRT during Consolidation. T-NHL patients with testicular disease are not eligible for this study.

2.5 **Biological Correlates**

T-ALL arises from transformed progenitors in the bone marrow (BM) microenvironment. Adjusted for NCI clinical risk status, patient outcome in High Risk T-ALL remains inferior to other childhood leukemias. This study seeks to identify new prognostic markers and identify new targets for pharmaceutical intervention. We will couple our previous work with BM stroma-supported growth of T-ALL cells and our gene microarray analysis in order to identify novel prognostic markers and new therapeutic targets. Our underlying premise is that tumor survival is dependent on signaling pathways, communicated in large part through cell-cell contact, that stimulate growth, angiogenesis, or the production of anti-apoptotic factors, all of which help sustain tumor cell

growth, spread, and survival. The "setting" in which these cellular interactions take place is often termed the microenvironment. The genetic alterations associated with malignancy may alter cellular responses to the microenvironment or alter the response of the microenvironment to the malignant cells. Thus, targeting the microenvironment for drug therapy has gained considerable interest, including small cell carcinoma, multiple myeloma, and other hematopoietic tumors.

T-ALL cell survival in the BM microenvironment is a tightly regulated multistep process that involves many of the biologic features of normal T-cell precursor sub populations, as illustrated by shared patterns of cell surface protein expression.[40-42] The careful analysis of clonal chromosomal abnormalities in leukemic blast cells has been a catalyst for the development of new diagnostic and therapeutic strategies. Since genetic alterations involving transcriptional regulators and other growth regulatory molecules may result in T-cell leukemogenesis[43-45] and regulate minimal residual disease (MRD) status,[21,22] we postulate that genetic alterations might directly or indirectly interfere with transcriptional networks that normally regulate T-ALL survival on BM stromal cells as well as patient response to therapy as measured by MRD.

For T-NHL, specimens to characterize the biologic nature of the disease will focus on 4 major areas: 1) immunophenotyping; 2) cytogenetic characterization by fluorescence in situ hybridization (FISH); 3) NOTCH mutation analysis; and 4) comparative genomic hybridization and gene expression profiling. Tissue should be collected prior to treatment initiation. Patients with T-NHL do not enroll onto AALL08B1. 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 should be obtained whenever possible. All available biologic specimens should 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. Please see Sections 15 & 16 for details regarding collection, processing, shipping and analysis of the tissue.

2.6 Exclusion of Patients with Down syndrome

Due to a high number of toxic deaths seen in Down syndrome patients on AALL0232, and the many similarities in the basic therapeutic approaches for patients with Down syndrome between AALL0232 and this study, we are excluding this vulnerable patient population from enrollment onto AALL0434. At this time, we do not have specific recommendations for the management of T-ALL in patients with Down syndrome.

2.7 Phase 1 Safety Phase Data Analysis

The required 20 High Risk (HR) patients were randomized to Arms B (CMTX + Nel) and D (HDMTX + Nel). Data current as of 02/15/2010 were used in the safety assessments by the DSMC. As of 02/15/2010, a total of 57 patients were randomized to either receive or not receive Nelarabine; of these 28 randomized to Nelarabine-containing regimens (12 on Arm B [CMTX + Nel] and 16 on Arm D [HDMTX + Nel]). A total of 29 patients were randomized to non-Nelarabine containing regimens (13 on Arm A [CMTX] and 16 on Arm C [HDMTX]). All adverse event data submitted as of this date were included in the analyses.

Post-Induction treatment regimens for the 57 High Risk patients:

- Arm A: CMTX, no Nelarabine (13)
- Arm B: CMTX, plus Nelarabine (12)
- Arm C: HDMTX, no Nelarabine (16)
- Arm D: HDMTX, plus Nelarabine (16)

Grade 3 and higher toxicities were examined. There was 1 Grade 5 (death) on Arm D in Consolidation due to disseminated intravascular coagulation (DIC), reported as unrelated to study drug.

2.7.1 Toxicity and Adverse Events

In general, most toxicities occurred for treatment arms A, B, C and D during the Consolidation, IM and DI phases of therapy. The toxicities of interest were rather evenly distributed for all treatment arms. In comparing the toxicities across all arms, there appears to be an increased number of events of elevations of AST/ALT and febrile neutropenia in Arms A and B as compared to Arms C and D. However, these events do not seem increased over those reported in similar intensive treatment regimens for T-ALL. Importantly, there were few neurological toxicities reported for any of the arms. Of note, there were no Grade 4 motor or sensory toxicities reported in any of the High Risk patients. The motor and sensory toxicities will be discussed separately.

2.7.1.1 *Motor Neuropathy*

There were 5 events on Arm A among 13 patients, 6 on Arm B among 12 patients, 1 on Arm C among 16 patients, and 4 on Arm D among 16 patients. There were only 2 Grade 3 motor neuropathy toxicities reported: 1 in Arm B and 1 in Arm D, both of which were attributed to vincristine. The patient in Arm B developed footdrop greater than 3 months after his last Nelarabine and in conjunction with vincristine. The patient in Arm D developed vocal cord dysfunction in Consolidation after vincristine and prior to Nelarabine. There was 1 Grade 2 motor neuropathy on Arm A (during DI) in a patient who had a history of neurotoxicity. Another patient who experienced a Grade 2 event (on Arm D, IM) did not receive Nelarabine. There does not appear to be any difference in overall motor neuropathy rates between Arms A and B and also Arms C and D.

2.7.1.2 *Sensory Neuropathy*

There were no sensory neuropathies reported on Arm A (N=13). There were 5 on Arm B (N=12), 7 on Arm C (N=16), and 5 on Arm D (N=16). There were only 4 Grade 3 sensory neuropathy toxicities reported. One was reported in Arm B in DI, 1 in Arm C in Maintenance Cycle #1 and 2 in Arm D. The 2 in Arm D were reported on the same patient. The first event occurred in DI prior to the administration of Nelarabine, and the second event occurred in Maintenance 1. One of the Grade 2 events on Arm B was due to vincristine. With respect to sensory neuropathies, Arm B appears to have more when compared to Arm A, but only 1 of them was a Grade 3. The rates are similar on Arms C and D.

The data analysis revealed that the addition of Nelarabine to the CMTX and HDMTX arms does not result in excessive toxicity for either the targeted neurotoxicities or non-neurologic toxicities. While all arms of the protocol are myelosuppressive and thus, produce infectious toxicity, these toxicities appear similar to those found on other intensive chemotherapy regimens to treat T-ALL. The protocol has, therefore, been opened to the efficacy phase.

2.7.1.3 *Rhabdomyolysis*
Three cases of rhabdomyolysis have been seen in patients receiving nelarabine; two were reported as rhabdomyolysis, and one was reported as elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), elevated creatine phosphokinase (CPK), and myalgia. Two cases from AALL0434 are clear cut and isolated incidents; nelarabine administration was stopped for these patients and the adverse effects resolved. The third case from a 2004 special exception trial (protocol E04-5299) was fatal, but confounded by multi-organ system failure resulting in death; direct causality in this case cannot be established. Narratives for these patients are provided in Appendix IX.

Thus far, approximately 1175 patients have been treated with nelarabine. Two of the patients mentioned above were treated on AALL0434 by the Children's Oncology Group. They received augmented BFM with either Capizzi methotrexate or high dose methotrexate and nelarabine. To date, 876 patients have been treated thus far on this study; the targeted accrual is 1580. Of these patients, 126 were randomized to and received nelarabine.

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]

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

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:

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

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.

PrediSONE: 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/m²/dose	Days 1, 8, 15 & 22	+ Or infusion via minibag as per institutional policy **Maximum dose of 2 mg**	
PrediSONE (PRED)	PO (may give IV*)	30 mg/m²/dose BID	Days 1-28 (no taper)	Total daily dose: 60 mg/m²/day, divided BID *For IV substitution see Sec 4.2	
DAUNOrubicin (DAUN)	IV Push Over 15 min	25 mg/m²/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/m² **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____m²**

Date Due	Date Given	Day	IT ARAC ___mg	VCR ___mg	PRED ___mg ___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 **(1 dose)**			
		5								
		6								
		7								
		8		___mg		___mg		___mg	a, c, dᵝ, e, g^	
		9								
		10								
		11								
		12								
		13								
		14							l*	
		15		___mg		___mg		___mg#	a, c, dᵝ, 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^α, e, fᵝ, 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)

α T-NHL only, if morphologically positive at diagnosis (see Section 7.2 for details) β T-ALL only (see Section 7.1 for details)

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

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, fβ, &, 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)

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
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 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

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								
		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 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 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 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, 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**
PrediSONE (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**
PrediniSONE (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.

PrediniSONE: 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**
PrediSONE (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	One or more	25,000 IU/m^2/dose IM

Maintenance, Delayed Intensification, or phases of therapy in which pegaspargase doses are 13+ days apart	doses of pegaspargase (2,500 IU/m^2)	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 methylmercaptopurine 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.

6.0 DRUG INFORMATION

6.1 ASPARAGINASE ERWINIA CHRYSANTHEMI (ERWINIA *CHRYSANTHEMI*, ERWINASE®, ERWINAZE™, CRISANTASPASE) NSC #106977 (02/29/12)

Source and Pharmacology:

L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. Neoplastic cells associated with acute lymphoblastic leukemia, acute myeloid leukemia and lymphoblastic lymphosarcoma are asparagine-dependent but lack asparagine synthetase activity. The administration of L-asparaginase produces an anti-neoplastic effect by catalyzing asparagine into aspartic acid and ammonia. As a result, these cells lack the ability to produce the asparagine necessary for protein metabolism and survival. Deamination of glutamine may also play a role in the antineoplastic activity of asparaginase.

Asparaginase *Erwinia chrysanthemi* (Erwinaze™) is asparaginase derived from cultures of *Erwinia chrysanthemi*. L-asparaginase is a tetrameric enzyme; each of the four identical subunits has a molecular weight of approximately 35 kDa. Asparaginase *Erwinia chrysanthemi* is immunologically distinct from *E. coli* L-asparaginase and may allow continued asparaginase therapy when a hypersensitivity reaction occurs to *Escherichia coli*-derived asparaginase. The package labeling states that there is insufficient information to characterize the incidence of antibodies to asparaginase *Erwinia chrysanthemi*. Several factors are involved in immunogenicity assay results and the assessment of antibodies, including assay methodology, assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medications, and the underlying disease state. The following data have been reported on each of the three preparations of asparaginase:

Clinical Pharmacology of Asparaginase Formulation	**Elimination half-life (IM)**	**% Anti-Asparaginase Antibody positive patients**
Native *Escherichia Coli*	26-30 hours	45-75
Pegylated-asparaginase	5.5-7 days	5-18
Erwinia Asparaginase	16 hours (7-13 hrs package insert)	30-50

From: Avramis, V; Panosyan, E; Pharmacokinetic/Pharmacodynamic Relationships of Asparaginase Formulations: The Past, the Present and Recommendations for the Future. Clin Pharmacokinet 2005; 44 (4): 367-393.

Effective asparaginase levels have been defined as activity of ≥ 0.1 International Units per mL. Clinical trials with asparaginase *Erwinia chrysanthemi* demonstrated that 100% of patients achieved effective asparaginase levels at 48 and 72 hours (n=35 and n=13, respectively) following the third total dose when given on a Monday, Wednesday, Friday schedule. No formal drug interaction studies have been performed with asparaginase *Erwinia chrysanthemi*.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Allergic reactions, anaphylaxis, urticaria	Local injection site reactions Fever
Prompt: Within 2-3 weeks, prior to the next course			Pancreatitis, glucose intolerance, thrombosis, hemorrhage, transient ischemic attack, disseminated intravascular coagulation, hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, hyperglycemia, hyperammonemia, vomiting, nausea, abdominal pain, headache, diarrhea, seizure.
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of L-asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk. Adequate, well-controlled studies of asparaginase *Erwinia chrysanthemi* have NOT been conducted. It is not known whether asparaginase *Erwinia chrysanthemi* will cause fetal harm or affect the ability to reproduce. It is not known if asparaginase *Erwinia chrysanthemi* is excreted into breast milk. The use of asparaginase *Erwinia chrysanthemi* should be avoided in pregnant or lactating patients.		

(L) Toxicity may also occur later.

Formulation and Stability:
Asparaginase *Erwinia chrysanthemi* is supplied as a sterile, white lyophilized powder for reconstitution in a clear glass vial with a 3 mL capacity. Each vial contains 10,000 International Units of asparaginase *Erwinia chrysanthemi* and the following inactive ingredients: glucose monohydrate (5.0 mg), sodium chloride (0.5 mg). Store intact vials between 2°C and 8°C (36° to 46ºF). Protect from light.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Use appropriate precautions for preparation of a hazardous agent. Visually inspect the powder in vial for foreign particles or discoloration prior to reconstitution. The contents of each vial should be reconstituted by slowly adding 1 mL or 2 mL of sterile, preservative-free NS to the inner vial wall. The final concentration is 10,000 International Units per mL when using 1 mL for reconstitution or 5,000 International Units per mL when using 2 mL for reconstitution. Gently mix or swirl the contents to dissolve the contents of the vial. Do not shake or invert the vial. The resulting solution should be clear and colorless. Discard if any particulate matter or protein aggregates are visible. **Withdraw the appropriate dosing volume into a polypropylene syringe within 15 minutes of reconstitution.** Polycarbonate luer-lok syringes from B-D (1 mL) are also acceptable (personal communication, EUSA Pharma). Discard any unused drug; do not save or use any unused drug remaining in the vial.

Administer the dose within a 4 hour time period from reconstitution. If the dose is not used within this time period, discard the dose. Do not freeze or refrigerate the reconstituted solution.

Administer the dose intramuscularly (IM). No more than 2 mL should be given at any one injection site. Doses larger than 2 mL should be divided and given in separate administration sites.

Drug Ordering:
In the United States, asparaginase *Erwinia chrysanthemi* (Erwinaze™) is distributed by Accredo Health Group, Inc. An institutional contract with Accredo is required in order to purchase the product. Accredo's contact information is as follows:

Accredo Health Group, Inc.
1640 Center Parkway, Suite 8
Memphis, TN 38134
Phone: 1-877-900-9223
Fax: 1-866-628-8942
Email: wholesalefax@accredohealth.com

CANADIAN SITES
Asparaginase *Erwinia chrysanthemi* is commercially available in Canada. Canadian sites may purchase the Canadian commercial supply from EUSA via CGF Pharmatech, Montreal, Quebec, a subsidiary of EUSA (order desk phone: 1-514-343-0344 or 1-866-343-0344, fax: 1-514-343-0340). CGF requests that a site fax a Purchase Order number. There is no special fax order form. Shipments are sent Monday to Wednesday only and usually arrive at the site within 48-72 hours.

6.2 CYCLOPHOSPHAMIDE INJECTION (Cytoxan) NSC #26271 (03/05/13)

Source and Pharmacology:
Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late:			Secondary malignancy (ALL, ANLL,

Any time after completion of treatment			AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1] *Dependent on dose, age, gender, and degree of pubertal development at time of treatment.*
[2] *Risk increased with pulmonary chest irradiation and higher doses.*
(L) Toxicity may also occur later.

Formulation and Stability:
Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30ºC (86ºF).

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Cyclophosphamide for Injection:
If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution further dilute in dextrose or saline containing solutions for IV use.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.3 **CYTARABINE** (Cytosine arabinoside, Ara-C, Cytosar®) NSC #063878 (05/06/11)
Source and Pharmacology: Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{½}$ of about 10 minutes, with a secondary elimination phase $t_{½}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a $t_{½}$ of about 2 hours.

Toxicity: (Intravenous, SubQ, IM)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, anorexia	Flu-like symptoms with fever, rash	Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, malaise, conjunctivitis), anaphylaxis
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia), stomatitis, alopecia	Diarrhea, hypokalemia, hypocalcemia, hyperuricemia	Hepatotoxicity, sinusoidal obstruction syndrome (SOS, formerly VOD), urinary retention, renal dysfunction, pain and erythema of the palms and soles
Delayed: Any time later during therapy, excluding the above conditions			Asymptomatic nonoliguric rhabdomyolysis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cytarabine have been noted in humans. It is unknown whether the drug is excreted in breast milk.		

Toxicity: (Intrathecal)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoiditis	Rash, somnolence, meningismus, convulsions, paresis
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia
Delayed: Any time later during therapy, excluding the above condition			Necrotizing leukoencephalopathy, paraplegia, blindness (in combination with XRT & systemic therapy)

Formulation and Stability: Cytarabine for Injection is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. It is also available at a 20 mg/mL concentration with benzyl alcohol (25 mL per vial) or as a preservative free solution (5 mL, 50 mL per vial),, and at a 100 mg/mL concentration with benzyl alcohol (20 mL vial) or as preservative free solution (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Cytarabine solutions should be protected from light.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

IV Infusion:
Reconstitute the lyophilized powder with Bacteriostatic Water for Injection or NS. Solution

containing bacteriostatic agent should not be used for the preparation of doses > 200 mg/m^2. May be further diluted with dextrose or sodium chloride containing solutions. May give by IV push injection, by IV infusion, or by continuous infusion.

Low Dose (≤ 200 mg/m²/dose): For administration by IV push, reconstitute to a concentration of 20-100 mg/mL.

Stability: When reconstituted with Bacteriostatic Water for Injection, cytarabine is stable for 48 hours at room temperature. Solutions reconstituted without a preservative should be used immediately. Discard if solution appears hazy. Diluted solutions in D5Wor NS are stable for 8 days at room temperature; however, the diluted cytarabine should be used within 24 hours for sterility concerns.

Subcutaneous:
Dilute with Bacteriostatic Water for Injection or NS to a concentration not to exceed 100 mg/mL. Rotate injection sites for subcutaneous administration.

Intrathecal:
For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free NS, lactated Ringer's injection, Elliot's B solution. The volume of CSF removed should be equal to at least ½ the volume delivered.

Patient Age (years)	Recommended volume	10% CSF volume	CSF Volume*
1 – 1.99	5–10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	5-10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	5-10 mL	13 mL	130 ± 30 mL (adults)

* Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone 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.

Intrathecal cytarabine mixed in NS, lactated Ringer's injection, or Elliot's B solution is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.4 **DAUNORUBICIN** (Daunomycin, rubidomycin, Cerubidine®) NSC #82151 (05/09/11)
Source and Pharmacology: Daunorubicin is an anthracycline antibiotic isolated from cultures of *Streptomyces coeruleorubidus*. Daunorubicin is closely related structurally to doxorubicin only differing in that the side chain of daunorubicin terminates in a methyl group rather than an alcohol.

The cytotoxic effect of daunorubicin on malignant cells and its toxic effects on various organs are similar to those of doxorubicin and are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of daunorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of cytocidal activity. Daunorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of daunorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•) which may lead to DNA damage or lipid peroxidation. Daunorubicin is metabolized more rapidly by aldoketoreductases to the active metabolite, daunorubicinol, than is doxorubicin. Daunorubicin hydrochloride is rapidly and widely distributed in tissues, with the highest levels in the spleen, kidneys, liver, lungs, and heart. Daunorubicin serum decay pattern is multiphasic. The initial t½ is approximately 45 minutes followed by a terminal t½ of 18.5 hours. By 1 hour after drug administration, the predominant plasma species is daunorubicinol, which disappears with a half-life of 26.7 hours. Twenty-five percent of an administered dose of daunorubicin is eliminated in an active form by urinary excretion and an estimated 40% by biliary excretion.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears and saliva	Hyperuricemia, sclerosis of the vein	Diarrhea, anorexia, abdominal pain, extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, rash, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, myocarditis-pericarditis syndrome, conjunctivitis and lacrimation
Delayed: Any time later during therapy			Cardiomyopathy[1] (uncommon at cumulative doses ≤ 550 mg/m², 400 mg/m² with mediastinal radiation, 300 mg/m² in children, or 10 mg/kg in children < 2 yrs or 0.5 m²) (L), hyper-pigmentation of nail beds
Late: Any time after completion of treatment		Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients), secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of daunorubicin have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

[1] *Risk increases with cardiac irradiation, exposure at a young or advanced age*
(L) Toxicity may also occur later.

Formulation and Stability: Daunorubicin is available as red-orange lyophilized powder[1] for injection in 20 mg single dose vials and a preservative free 5 mg/mL solution[2] in 20 mg (4 mL) and 50 mg (10 mL) vials.

[1] *Each vial contains 21.4 mg of daunorubicin hydrochloride (equivalent to 20 mg of daunorubicin) and 100 mg mannitol.*
[2] *Each mL contains 5.3 mg daunorubicin hydrochloride (equivalent to 5 mg of daunorubicin), 9 mg of sodium chloride, sodium hydroxide or hydrochloric acid to adjust pH, and Sterile Water for Injection.*

Powder for Injection:
Store intact unreconstituted vial at room temperature 15°C-30°C (59°F-86°F). Protect from light. Retain in carton until contents are used. Reconstitute a 20 mg vial with 4 mL SWFI to a final concentration of 5 mg/mL. After adding the diluent, the vial should be shaken gently and the contents allowed to dissolve. The reconstituted solution is stable for 24 hours at room temperature and 48 hours refrigerated. Protect from exposure to sunlight.

Aqueous Solution:
Store refrigerated 2°-8°C (36°-46°F). Protect from light. Retain in carton until contents are used.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Administer by IV side arm into a rapidly flowing infusion solution. Alternately, daunorubicin may be further diluted in saline or dextrose containing solutions and administered by infusion. Protect final preparation from light. To avoid extravasation, the use of a central line is suggested.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.5 **DEXAMETHASONE** (Decadron®, Hexadrol®, Dexone®, Dexameth®) NSC #34521 (05/09/11)
Source and Pharmacology: Dexamethasone is a synthetic fluorinated glucocorticoid devoid of mineralocorticoid effects. Dexamethasone, 0.75 mg, has potent anti-inflammatory activity equivalent to approximately 5 mg of prednisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age: 2.3 to 9.5 hours, 8 to 16 years: 2.82 to 7.5 hours, and adults (age not specified): 3 to 6 hours. The biologic half-life is 36-72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later during	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding,

therapy		weakness, osteopenia	pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of dexamethasone in children)	
Unknown Frequency and Timing:	**Fetal and teratogenic toxicities**: dexamethasone crosses the placenta with 54% metabolized by enzymes in the placenta. In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. There are no reports of dexamethasone excretion into breast milk in humans; however, it is expected due to its low molecular weight that it would partition into breast milk.		

[1] ***Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblasic leukemia. Leukemia 2003; 17: 541-6.***
(L) Toxicity may also occur later.

Formulation and Stability:
Oral: Available in 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets; liquid formulations are available in 0.5 mg/5 mL and 1 mg/1 mL concentration. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes.

Injection: Dexamethasone Sodium Phosphate Solution for Injection is available as 4 mg/mL (1 mL, 5 mL, and 30 mL vials), and 10 mg/mL (1mL and 10 mL vial sizes). Four milligrams of dexamethasone sodium phosphate is equivalent to 3.33 mg of dexamethasone. Vials are available in multi-dose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA.

Guidelines for Administration: See Treatment and Dose Modifications section of the protocol.

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid using benzyl alcohol containing dexamethasone solutions for use in neonates. Diluted solutions that contain no preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.6 **DOXORUBICIN** (Adriamycin®) NSC #123127 (05/09/11)
Source and Pharmacology: An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron

reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) (L)	Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans.		

[1] *Risk increases with cardiac irradiation, exposure at a young or advanced age*
(L) Toxicity may also occur later.

Formulation and Stability:

Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1] vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.

[1] *Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben 1 mg per each 10 mg of doxorubicin to enhance dissolution.*

[2] *Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.*

Aqueous Solution:
Store refrigerated 2°-8°C (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection:
Store unreconstituted vial at room temperature 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration 2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50-1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Administer IV through the tubing of rapidly infusing solution of D_5W or NS preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.7 **LEUCOVORIN CALCIUM** (LCV, Wellcovorin®, citrovorum factor, folinic acid)
NSC #003590 (05/09/11)

Source and Pharmacology: Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)- l-isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid (an active metabolite of 5-FU) to thymidylate synthase and thereby enhances the inhibition of this enzyme. Peak serum levels of 5-methyl THF (an active metabolite) were reached at approximately 1.3-1.5 hours (IV/IM) and 2.3 hours for the oral form. The terminal half-life of total reduced folates was approximately 6.2 hours. Following oral administration, leucovorin is rapidly absorbed and expands the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the *l*-isomer (the biologically active form) but only 20% of the *d*-isomer is absorbed. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg doses. Both oral and parenteral leucovorin raise the CSF folate levels.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug			Anaphylaxis, urticaria,seizure
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of leucovorin in humans are unknown. It is unknown whether the drug is excreted in breast milk.		

Injection: Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral: Oral leucovorin should be spaced evenly (e.g. every six hours) throughout the day and may be taken without regard to meals. Doses > 25 mg should be given IV due to the saturation of absorption.

Leucovorin should not be administered < 24 hours after intrathecal injections which contain methotrexate unless there are special circumstances.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.8 **MERCAPTOPURINE** (6-MP, Purinethol®, 6-mercaptopurine) NSC #000755 (11/26/12)

Source and Pharmacology: Mercaptopurine is an analogue of the purine bases adenine and hypoxanthine. The main intracellular pathway for MP activation is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) which catalyzes the conversion of MP to several active nucleotide metabolites including thioinosinic acid, a ribonucleotide which can interfere with various metabolic reactions necessary for nucleic acid (RNA and DNA) biosynthesis. It can also cause pseudofeedback inhibition of the first step in de novo purine biosynthesis or convert to another ribonucleotide which can cause feedback inhibition. Mercaptopurine can be incorporated into DNA in the form of TG nucleotides as well and thus produce toxicity. The absorption of an oral dose of MP is incomplete and variable, with only about 16%-50% of an administered dose reaching the systemic circulation secondary to a first pass metabolism in the liver. Food intake and co-administration with cotrimoxazole (TMP/SMX) significantly reduces absorption of MP. After IV administration, MP has a plasma half-life of 21 minutes in children and 47 minutes in adults. Approximately 19% is bound to protein. Mercaptopurine is well distributed into most body compartments except the CSF. (With high dose IV MP the CSF to plasma ratio is 0.15.) MP is metabolized by xanthine oxidase in the liver to 6-Thiouric acid an inactive metabolite. In patients receiving both MP and allopurinol (a xanthine oxidase inhibitor) the dose of MP must be reduced by 50-75%. Since TPMT, 6-thiopurine methyltransferase, is also one of the enzymes involved in the metabolism of MP, those individuals who have an inherited deficiency of the enzyme may be unusually sensitive to the myelosuppressive effects of MP and prone to develop rapid bone marrow suppression following the initiation of treatment. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Anorexia, nausea, vomiting, diarrhea, malaise	Urticaria, hyperuricemia,
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (L)	Erythematous rash (L)	Oral lesions resembling thrush, toxic hepatitis(L), increased AST/ALT, hyperpigmentation (L), pancreatitis
Delayed: Any time later during therapy, excluding the above conditions		Oligospermia	Hepatic fibrosis(L), hyperbilirubinemia, alopecia
Late: Any time after the completion of treatment			Pulmonary fibrosis, secondary malignancies
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mercaptopurine have been noted in animals. Women receiving mercaptopurine in the first trimester of pregnancy have an increased incidence of abortion. It is unknown whether the drug is excreted in breast milk		

(L) Toxicity may also occur later.

Formulation and Stability:
Mercaptopurine is available as a 50 mg tablet containing mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid. Store at 15°-25°C (59°-77°F) in a dry place.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Do not give oral mercaptopurine with food or milk. Concurrent milk products can decrease absorption and mercaptopurine effect is enhanced if given at bedtime on an empty stomach. If allopurinol is also given, the oral dose of mercaptopurine should be reduced by 67-75%. Patients with severe myelosuppression should have their thiopurine S-methyltransferase (TPMT) status and/or their thiopurine metabolite concentrations evaluated, so that the dose of mercaptopurine can be reduced in patients with a TPMT defect. Patients with the rare homozygous deficient TPMT phenotype may tolerate only 1/10th to 1/20th the average mercaptopurine dose. TPMT testing and thiopurine metabolite measurements are commercially available.

Suspension:
For children unable to swallow the tablets whole, a 50 mg/mL oral suspension can be compounded. The suspension is prepared by crushing 50 mercaptopurine 50 mg tablets in a mortar and adding 8.5 mL sterile water for irrigation. The mixture is triturated to form a smooth paste. Next, 16.5 mL simple syrup (pH=7) are added with continuous mixing and finally cherry syrup (pH=7.1) is added to a total volume of 50 mL. The suspension is stable in amber glass bottles at room temperature (19ºC -23ºC) for up to 5 weeks. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension. (Aliabadi HM, Romanick M, Desai S et al. Effect of buffer and antioxidant on stability of mercaptopurine suspension. *Am J Heath-Syst Pharm.* 65:441-7, 2008.)

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.9 **METHOTREXATE** (MTX, amethopterin, Trexall®) NSC #000740 (02/29/12)

Source and Pharmacology: A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 µmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. After oral administration, approximately 60% of a 30 mg/m^2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. At doses > 30 mg/m² absorption decreases significantly. Even at low doses absorption may be very erratic, varying between 23% and 95%. The elimination of MTX from the CSF after an intrathecal dose is characterized by a biphasic curve with half-lives of 4.5 and 14 hours. After intrathecal administration of 12 mg/m², the lumbar concentration of MTX is ~ 100 times higher than in plasma. (Ventricular concentration is ~ 10% of lumbar concentration.) MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Transaminase elevations	Nausea, vomiting, anorexia	Anaphylaxis, chills, fever, dizziness, malaise, drowsiness, blurred vision, acral erythema, urticaria, pruritis, toxic epidermal necrolysis, Stevens-Johnson Syndrome, tumor lysis syndrome, seizures[1], photosensitivity
Prompt: Within 2-3 weeks, prior to the next course		Myelosuppression, stomatitis, gingivitis, photosensitivity, fatigue	Alopecia, folliculitis, acne, renal toxicity (ATN, increased creatinine/BUN, hematuria), enteritis, GI ulceration and bleeding, acute neurotoxicity[1] (headache, drowsiness, aphasia, paresis, blurred vision, transient blindness, dysarthria, hemiparesis, decreased reflexes), diarrhea, conjunctivitis
Delayed: Any time later during therapy, excluding the above conditions		Learning disability[1] (L)	Pneumonitis, pulmonary fibrosis (L), hepatic fibrosis (L), osteonecrosis (L), leukoencephalopathy[1] (L), pericarditis, pericardial effusions, hyperpigmentation of the nails
Late: Any time after the completion of therapy			Progressive CNS deterioration[1]
Unknown	Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted		

Frequency and Timing:	in humans. The toxicities include: congenital defects, chromosomal abnormalities, severe newborn myelosuppression, low birth weight, abortion, and fetal death. Methotrexate is excreted into breast milk in low concentrations

[1] *May be enhanced by HDMTX and/or cranial irradiation.*
(L) Toxicity may also occur later.

Intrathecal Therapy (Methotrexate Single Agent)
Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, headache	Arachnoditis: (headache, fever, vomiting, meningismus, nuchal rigidity, and pleocytosis)	Anaphylaxis, vomiting, seizures(L), malaise, confusion, back pain, rash, bleeding into subarachnoid or subdural space (risk >with platelet counts <20,000)
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia, somnolence, cranial nerve palsy, subacute myelopathy (paraparesis/paraplegia), speech disorders, pain in the legs, bladder dysfunction
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L)[1], learning disability (L)[1]	Leukoencephalopathy[1] (L)
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by HDMTX and/or cranial irradiation.*
(L) Toxicity may also occur later.

Formulation & Stability:
Methotrexate for oral use is available as 2.5 mg, 5 mg, 7.5 mg, 10 mg and 15 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: anhydrous lactose, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium carbonate monohydrate, talc and titanium dioxide and various dyes. Store at controlled room temperature 15°-30°C (59°-86°F) and protect from light.

Methotrexate for Injection is available as a lyophilized powder for injection in 1000 mg vials. The powder for injection contains approximately 7 mEq sodium in the 1000 mg vial. Methotrexate for Injection is also available as a 25 mg/mL solution in 2, 4, 8, 10, and 40 mL preservative free vials and 2 and 10 mL vials with preservative. The 2, 4, 8, 10, and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative.

Sterile methotrexate powder or solution is stable at 20º-25ºC (68º-77ºF); excursions permitted to 15º-30ºC (59- 86 Fº). Protect from light

Guidelines for Administration: See Treatment and Dose Modifications sections of protocol. Leucovorin rescue may be necessary with certain doses of methotrexate.

Oral administration: Food or milk delays absorption and reduces peak concentration. Methotrexate for oral use should preferentially be given on an empty stomach, 1 hour before or 2

hours after food or milk and at the same time each day. Methotrexate injection diluted in water can be used for oral administration (Marshall PS, Gertner E. Oral administration of an easily prepared solution of injectable methotrexate diluted in water: a comparison of serum concentrations vs methotrexate tablets and clinical utility. *J Rheumatol* 23:455-8, 1996).

For IV use: Powder for injection: Dilute 1000 mg vial with 19.4 mL of preservative free SWFI, D5W or NS to a 50 mg/mL concentration. The powder for injection may be further diluted in NS or dextrose containing solutions to a concentration of ≤ 25 mg/mL for IV use.

The 25 mg/mL solution may be given directly for IM administration or further diluted in Saline or Dextrose containing solutions for IV use. **Do not use the preserved solution for high dose methotrexate administration due to risk of benzyl alcohol toxicity.** Methotrexate dilutions are chemically stable for at least 7 days at room temperature but contain no preservative and should be used within 24 hours. Diluted solutions especially those containing bicarbonate exposed to direct sunlight for periods exceeding 4 hours should be protected from light.

High dose methotrexate requires alkalinization of the urine, adequate hydration and leucovorin rescue. Avoid probenecid, penicillins, cephalosporins, aspirin, proton pump inhibitors, and NSAIDS as renal excretion of MTX is inhibited by these agents.

For Intrathecal use: Use **preservative free** 25 mg/mL solution.

For intrathecal administration, dilute with 5-10 mL preservative free NS, lactated Ringer's, or Elliot's B solution, as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Methotrexate dose	Recommended volume	10% CSF volume	CSF Volume*
1–1.99	8 mg	5–10 mL	5 mL	50 ± 10 mL (babies)
2–2.99	10 mg	5-10 mL	8 mL	80 ± 20 mL (younger children)
3–8.99	12 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg	5-10 mL	13 mL	130 ± 30 mL (adults)

* Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone 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.

Diluted methotrexate for intrathecal administration is stable in normal saline for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

Supplier: Commercially available from various manufacturers. See package insert for further information.

6.10 **NELARABINE** (2-Amino-9-β-D arabinofuranosyl-6-methoxy-9*H*-purine, Compound 506U78) NSC# 686673; IND# 52611 (03/24/16)

Source and Pharmacology: Nelarabine (compound 506U78) is a water soluble pro-drug of 9-β-D-arabinofuranosylguanine (ara-G), a deoxyguanosine analog being developed for the treatment

of patients with T-cell and B-cell leukemias and lymphomas. Nelarabine is rapidly converted by adenosine deaminase in the peripheral blood to ara-G. In Vitro studies and biochemical studies have demonstrated that intracellular ara-G is phosphorylated via deoxycytosine kinase (dCK) and deoxyguanosine kinase (dGK) to its active 5'-triphosphate (ara-GTP). Ara-GTP incorporation into DNA is a primary cause of cell death.

The pharmacokinetics of nelarabine in humans are characterized by a rapid and extensive conversion to ara-G. The average elimination half-lives for nelarabine and ara-G were approximately 20-25 minutes and 2.6-4.0 hours, respectively. Virtually all nelarabine was converted to ara-G. Peak plasma concentration and area under the curve for both nelarabine and ara-G was essentially proportional to the administered dose. The steady-state volume of distribution of ara-G was similar in adult and pediatric patients. Neither compound showed accumulation with the dosing studies used in the pre-clinical trials with this agent. The pharmacokinetics of both nelarabine and ara-G appeared to be independent of diagnosis and gender. Intracellular leukemic blast concentrations of ara-GTP were characterized by a long elimination half-life (median approximately 24 hours) and diagnosis dependent accumulation; with T-lymphoblasts generally demonstrating greater accumulation of ara-GTP than other cell types. Nelarabine and ara-G is < 25% bound to human plasma proteins.

Toxicity:
Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Nelarabine (Compound 506U78, NSC 686673)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 458 patients*. Below is the CAEPR for nelarabine (Compound 506U78).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to Nelarabine (Compound 506U78) (CTCAE 4.0 Term) [n= 458]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr. 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr. 3)***
CARDIAC DISORDERS			
	Sinus tachycardia		***Sinus tachycardia (Gr. 3)***
EYE DISORDERS			
	Blurred vision		***Blurred vision (Gr. 3)***
	Eye pain		***Eye pain (Gr. 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr. 3)***
	Anal mucositis		***Anal mucositis (Gr. 3)***
	Diarrhea		***Diarrhea (Gr. 3)***
	Mucositis oral		***Mucositis oral (Gr. 3)***
Nausea			***Nausea (Gr. 3)***
	Pancreatitis		***Pancreatitis (Gr. 3)***
	Rectal mucositis		***Rectal mucositis (Gr. 3)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr. 3)***
	Vomiting		***Vomiting (Gr. 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr. 3)***
Fatigue			***Fatigue (Gr. 3)***
	Fever		***Fever (Gr. 3)***
	Gait disturbance		
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr. 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr. 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr. 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr. 3)***
	CPK increased		***CPK increased (Gr. 3)***
Lymphocyte count decreased			***Lymphocyte count decreased (Gr. 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr. 3)***
Platelet count decreased			***Platelet count decreased (Gr. 3)***
	Serum amylase increased		***Serum amylase increased (Gr. 3)***
	Weight gain		***Weight gain (Gr. 3)***
White blood cell decreased			***White blood cell decreased (Gr. 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr. 3)***
	Dehydration		***Dehydration (Gr. 3)***
	Hyperglycemia		***Hyperglycemia (Gr. 3)***
	Hyperuricemia		***Hyperuricemia (Gr. 3)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr. 3)***

	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr. 3)***
	Hyponatremia		***Hyponatremia (Gr. 3)***
	Tumor lysis syndrome		***Tumor lysis syndrome (Gr. 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr. 3)***
	Bone pain		***Bone pain (Gr. 3)***
	Generalized muscle weakness		***Generalized muscle weakness (Gr. 3)***
	Musculoskeletal and connective tissue disorder - Other (muscle twitching)		***Musculoskeletal and connective tissue disorder - Other (muscle twitching) (Gr. 3)***
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
	Myalgia		***Myalgia (Gr. 3)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Ataxia		***Ataxia (Gr. 3)***
Depressed level of consciousness			***Depressed level of consciousness (Gr. 3)***
	Dizziness		***Dizziness (Gr. 3)***
	Dysphasia		***Dysphasia (Gr. 3)***
	Encephalopathy		***Encephalopathy (Gr. 3)***
	Headache		***Headache (Gr. 3)***
	Memory impairment		***Memory impairment (Gr. 3)***
	Nervous system disorders - Other (Guillian-Barre syndrome)		***Nervous system disorders - Other (Guillain-Barre syndrome) (Gr. 3)***
	Paresthesia		
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr. 3)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr. 3)***
	Pyramidal tract syndrome		***Pyramidal tract syndrome (Gr. 3)***
	Seizure		***Seizure (Gr. 3)***
	Tremor		***Tremor (Gr. 3)***
PSYCHIATRIC DISORDERS			
	Agitation		***Agitation (Gr. 3)***
	Anxiety		***Anxiety (Gr. 3)***
	Confusion		***Confusion (Gr. 3)***
	Depression		***Depression (Gr. 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Epistaxis		***Epistaxis (Gr. 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr. 3)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr. 3)***
	Tracheal mucositis		***Tracheal mucositis (Gr. 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Purpura		***Purpura (Gr. 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Gastrointestinal hemorrhage may include Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal

hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

Also reported on nelarabine (Compound 506U78) trials but with the relationship to nelarabine (Compound 506U78) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Cardiac arrest; Left ventricular systolic dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ear hemorrhage); Hearing impaired; Middle ear inflammation
EYE DISORDERS - Conjunctivitis; Eye disorders - Other (blindness); Keratitis
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Gastrointestinal hemorrhage[3]; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Pain
INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; Fibrinogen decreased; Investigations - Other (hypobicarbonatemia); Lipase increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperkalemia; Hypoglycemia; Hypomagnesemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lymphoma)
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Dysarthria; Intracranial hemorrhage; Oculomotor nerve disorder
PSYCHIATRIC DISORDERS - Insomnia; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Laryngeal hemorrhage; Pleural effusion; Pneumonitis; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Skin and subcutaneous tissue disorders - Other (dermatitis allergic); Skin and subcutaneous tissue disorders - Other (herpes zoster)
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Nelarabine (Compound 506U78) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Pregnancy and Lactation:
Fetal toxicities and teratogenic effects of nelarabine are unknown. It is unknown whether the drug is excreted in breast milk.

Formulation and Stability:
Nelarabine (compound 506U78) is formulated to provide 5 mg of nelarabine per mL in 0.45% saline solution. Nelarabine Injection consists of a clear, colorless solution, contained in a clear 50 mL glass vial with a gray rubber closure and lacquered overseals made of polypropylene and

aluminum. The drug is supplied as a 5 mg/mL liquid in 50 mL vials with a total of 250 mg nelarabine per vial. The pH of the solution is between 5 and 7.

Intact 50 mL glass vials containing 250 mg of nelarabine for injection should be stored at or below 30°C (86°F). Do not store vials in the refrigerator as crystallization of the product may occur. Nelarabine as a clear colorless solution is stable in glass vials for at least 30 months at 30°C.

Guidelines for Administration: See the Treatment and Dose Modifications Sections of the protocol.

All vials should be visually inspected for any particulate matter prior to use. **The solution is intended to be used full strength directly from the vials with no further dilution.** Glass or plastic containers may be used. Nelarabine is stable in polyvinylchloride (PVC) infusion bags, ethyl vinyl acetate (EVA) infusion bags and glass containers for up to 8 hours at up to 30°C.

CAUTION: The single-use dosage form contains no antibacterial preservatives. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Supplier: Supplied by GlaxoSmithKline and distributed by the NCI DTCD. **Do not use commercially available drug**.

Obtaining the Agent

NCI supplied agent may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx>. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Accountability

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs for the Procedures for Drug Accountability and Storage and http://ctep.cancer.gov/forms/default.htm to obtain a copy of the DARF and Clinical Drug Request form.)

Investigational Agent Returns

Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs. The appropriate forms may be obtained at: http://ctep.cancer.gov/forms/docs/return_form.pdf.

6.11 **PEGASPARGASE** (PEG-asparaginase, PEGLA, PEG-L-asparaginase, polyethylene glycol-L-asparaginase, Oncaspar®)

NSC #624239 **(03/13/13)**

Source and Pharmacology:

Pegaspargase is a modified version of the enzyme L-asparaginase. L-asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Pegaspargase is derived from *Escherichia coli* which is purchased in bulk from Merck, Sharp and Dohme. L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. The ability to synthesize asparagine is notably lacking in malignancies of lymphoid origin. Asparaginase depletes L-asparagine from leukemic cells (especially lymphoblasts) by catalyzing the conversion of L-asparagine to aspartic acid and ammonia. In predominately L-asparaginase naive adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration of pegaspargase were determined. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with Pegaspargase. The approximate $t_{½}$ in adult patients is 5.73 days. The enzyme could not be detected in the urine. The half-life is independent of the dose administered, disease status, renal or hepatic function, age, or gender. In a study of newly diagnosed pediatric patients with ALL who received either a single intramuscular injection of pegaspargase (2500 IU/m^2), *E. coli* L-asparaginase (25000 IU/m^2), or *Erwinia* (25000 IU/m^2), the plasma half-lives for the three forms of L-asparaginase were: 5.73 ± 3.24 days, 1.24 ± 0.17 days, and 0.65 ± 0.13 days respectively. The plasma half-life of pegaspargase is shortened in patients who are previously hypersensitive to native L-asparaginase as compared to non-hypersensitive patients. L-asparaginase is cleared by the reticuloendothelial system and very little is excreted in the urine or bile. Cerebrospinal fluid levels are < 1% of plasma levels.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Allergic reactions (total likelihood of local, and or systemic reaction especially if previous hypersensitivity reaction to native asparaginase), pain at injection site, weakness, fatigue, diarrhea	Allergic reactions (total likelihood of local, and or systemic reaction if **no** previous hypersensitivity reaction to native asparaginase), rash	Anaphylaxis, hyper/hypotension, tachycardia, periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lip edema, arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures (L), hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Hyperammonemia (L), coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) (L)	Hyperglycemia, abnormal liver function tests, pancreatitis (L), increased serum lipase/amylase	Hemorrhage (L), DIC, thrombosis, anorexia, weight loss, CNS ischemic attacks, edema, azotemia and decreased renal function, mild leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, hemolytic anemia, infections (sepsis with/without septic shock, subacute bacterial endocarditis [SBE], URI), CNS changes including irritability, depression, confusion, EEG changes, hallucinations, coma and stupor, paresthesias, hypertriglyceridemia, hyperlipidemia, Parkinson-like syndrome with tremor and increase in muscular tone, hyperbilirubinemia, chest pain
Delayed: Any time later during therapy			Renal failure, urinary frequency, hemorrhagic cystitis, elevated creatinine and BUN, fatty liver deposits, hepatomegaly, liver failure
Unknown Frequency and Timing:	Animal reproduction studies have not been conducted with pegaspargase. It is not known whether pegaspargase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, fetal toxicities and teratogenic effects of asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

(L)Toxicity may also occur later.

Formulation and Stability:
Each milliliter of pegaspargase contains: PEG-L-asparaginase 750 IU ± 20%, monobasic sodium phosphate, *USP* 1.20 mg ± 5% dibasic sodium phosphate, *USP* 5.58 mg ± 5%, sodium chloride, *USP* 8.50 mg ± 5% , Water for Injection, *USP* qs to 1 mL. The specific activity of pegaspargase is at least 85 IU per milligram protein. Available in 5 mL vials as Sterile Solution for Injection in ready to use single-use vials, preservative free. Keep refrigerated at 2°-8°C (36°-46°F). Do not use if stored at room temperature for more than 48 hours. **DO NOT FREEZE.** Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

For IM administration: the volume at a single injection site should be limited to 2 mL. If the volume to be administered is greater than 2 mL, multiple injection sites should be used.

For IV administration: dilute pegaspargase in 100 mL of NS or D5W and infuse over 1 to 2 hours through a NS or D5W running infusion line. Pegaspargase admixed in 100 mL of NS or D5W is stable for

48 hours at room temperature. Pegaspargase diluted in 100 mL of NS is stable for up to 72 hours refrigerated (4ºC [39°F]) (refrigerated stability data on file with Sigma-Tau). Avoid excessive agitation. DO NOT SHAKE. Do not use if cloudy or if precipitate is present.

Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for ONE hour after administration for signs of hypersensitivity reactions.

Supplier: Pegaspargase (Oncaspar®) is commercially available from Sigma-Tau Pharmaceuticals. US sites can purchase the drug through their usual ordering channels (wholesalers). If needed, the Sigma Tau Customer Service phone number for the US is 1-888-276-2217.

CANADIAN SITES

Pegaspargase is not commercially available in Canada. Sites may purchase and import the USA commercial supply directly from Sigma Tau Pharmaceuticals under the authority of the protocol's No Objection Letter (NOL). The Canadian Senior Medical Officer (SMO)'s office is responsible for coordinating the "Fax Back" for all lot numbers and expiry dates to Health Canada's Biologics and Genetic Therapies Directorate for approval for use in Canada on behalf of all Canadian sites. A list of approved lot numbers is distributed to all Canadian sites by the SMO's office. If an unapproved lot is received from Sigma Tau Pharmaceuticals, quarantine the lot and contact the COG Canada Regulatory Affairs Office at 1-780-492-7064. Note: Pegaspargase may have orders placed and Drug Accountability Logs maintained on a multiple protocol basis (Multiple Protocol—Imported Biologic) as long as each protocol has a NOL. Drug Accountability Logs (DAL) must record Lot #'s and expiry dates of shipments received and doses dispensed. Sites may use their own DAL as long as it complies with all elements of ICH GCP and Division 5 of the Food and Drugs Act. Sites may import and manage a single clinical trial supply for multiple protocols as long as each protocol has an NOL and the protocol the patient is registered on is recorded on the DAL.

6.12 **PREDNISONE** (Deltasone, Meticorten, Orasone®, Liquid Pred, Pediapred®, Sterapred®)
NSC #010023 (05/10/11)

Source and Pharmacology: Prednisone is a synthetic compound closely related to hydrocortisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Peak blood levels occur within 2 hours of oral intake. Prednisone is approximately 75% protein bound with a plasma $t_{½}$ of 3.2 to 4 hours (biologic half-life is 12-36 hours).

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), electrolyte imbalance (Na retention, hypokalemia, hypocalcemia) (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later during therapy	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of prednisone in children)	
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Corticosteroids cross the placenta (prednisone has the poorest transport). In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. Prednisone is excreted into breast milk in humans; however, several studies suggest that amounts excreted in breast milk are negligible with prednisone doses ≤ 20 mg/day.		

[1] *Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.*
(L) Toxicity may also occur later.

Formulation and Stability:
Available in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets. Also available as a solution in 1 mg/1 mL or 5 mg/mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, erythrosine sodium, mineral oil, sorbic acid, sucrose, talc and various dyes. The solution may include: 5-30% alcohol, fructose, sucrose, saccharin, and sorbitol.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Supplier: Commercially available from various sources. See package insert for further information.

6.13 **THIOGUANINE** (6-TG, 6-thioguanine, 2-amino-1, 7-dihydro-6H-purine-6-thione, WR-1141, Tabloid®, Lanvis®) NSC #752 (10/28/12)
Source and Pharmacology: Thioguanine is a purine analogue of the nucleic acid guanine with the substitution of a thiol group in place of the hydroxyl group on guanine. The main intracellular pathway for 6-TG activation is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) which catalyzes the conversion of 6-TG to the active nucleotide, 6-

thioguanylic acid. The monophosphate nucleotide form of 6-TG inhibits *de novo* purine synthesis and purine interconversion reactions, whereas the nucleotide triphosphate metabolite is incorporated directly into nucleic acids. Incorporation of fraudulent nucleotides into DNA interferes with DNA replication and results in the formation of DNA strand breaks. The net consequence of its action is a sequential blockade of the synthesis and utilization of the purine nucleotides. The relative contribution of each of these actions to the mechanism of cytotoxicity of 6-TG is unclear. The absorption of an oral dose of 6-TG is incomplete and variable, averaging approximately 30% of the administered dose (range: 14% to 46%).

Thioguanine undergoes deamination by the enzyme guanine deaminase resulting in 6-thioxanthene, which is then oxidized by xanthine oxidase to 6-thiouric acid. In contrast to mercaptopurine, 6-TG is not a direct substrate for xanthine oxidase. Because the inhibition of xanthine oxidase results in the accumulation of 6-thioxanthene, an inactive metabolite, adjustments in 6-TG dosage are not required for patients receiving allopurinol. Since TPMT, 6-thiopurine methyltransferase, is one of the enzymes involved in the deactivation of 6-TG, those individuals who have an inherited deficiency of the enzyme may be unusually sensitive to the myelosuppressive effects of 6-TG and prone to developing rapid bone marrow suppression following the initiation of treatment.

Peak levels occur 2 to 4 hours after oral administration with a median half-life is about 90 minutes (range: 25-240 minutes). Very little unchanged drug is excreted renally.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Anorexia, nausea, vomiting, diarrhea, malaise	Urticaria, rash, hyperuricemia
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression		Toxic hepatitis (L), increased SGOT (AST)/SGPT (ALT), ataxia, mucositis
Delayed: Anytime later during therapy			Hepatic fibrosis(L), sinusoidal obstruction syndrome (SOS, formerly VOD) (L), hyperbilirubinemia
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of thioguanine have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later.

Formulation and Stability:
Each greenish-yellow, scored tablet contains 40 mg thioguanine. Store at 15°-25°C (59°-77°F) in a dry place.

For patients unable to swallow tablets, a 20 mg/mL oral suspension may be compounded. Crush fifteen (n=15) 40 mg tablets in a mortar and reduce to a fine powder. Add 10 mL methylcellulose 1% in incremental proportions and mix to a uniform paste. Transfer to a graduated cylinder, rinse mortar with simple syrup, and add quantity of simple syrup sufficient to make 30 mL. Dispense

in an amber glass bottle and label "shake well" and "refrigerate". If methylcellulose is not available, substitute 15 mL of Ora-Plus in place of the methylcellulose and qs with Ora-Sweet (in place of simple syrup) to a final volume of 30 mL. Both preparations are stable for 63 days at 19°C – 23°C. (Aliabadi HM, Romanick M, Somayah V, et al. Stability of compounded thioguanine oral suspensions. *Am J Health Syst Pharm* 2011;68:1278. Dressman JB, Poust RI. Stability of Allopurinol and Five Antineoplastics in Suspension. *Am J Hosp Pharm* 1983;40(4):616-8.)

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Administer on an empty stomach, preferably at bedtime.
Substantial dosage reductions may be required in patients with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) due to accumulation of active thioguanine metabolites resulting in a higher incidence of myelosuppression.

Supplier: Commercially available. See package insert for more detailed information.

6.14 VINCRISTINE SULFATE (8/16/12)

(Oncovin®, VCR, LCR) NSC #67574

Source and Pharmacology: Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss

Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.

Formulation and Stability:
Vincristine is supplied in 1 mL and 2 mL vials in which each mL contains vincristine sulfate 1 mg (1.08 µmol), mannitol 100 mg; SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2°-8°C or 36°-46°F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

Guidelines for Administration: See Treatment and Dose Modifications sections of protocol.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or minibag is acceptable for COG protocols. Vincristine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecally.

Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

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.

Supplier: Commercially available from various manufacturers. See package insert for more detailed information.

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

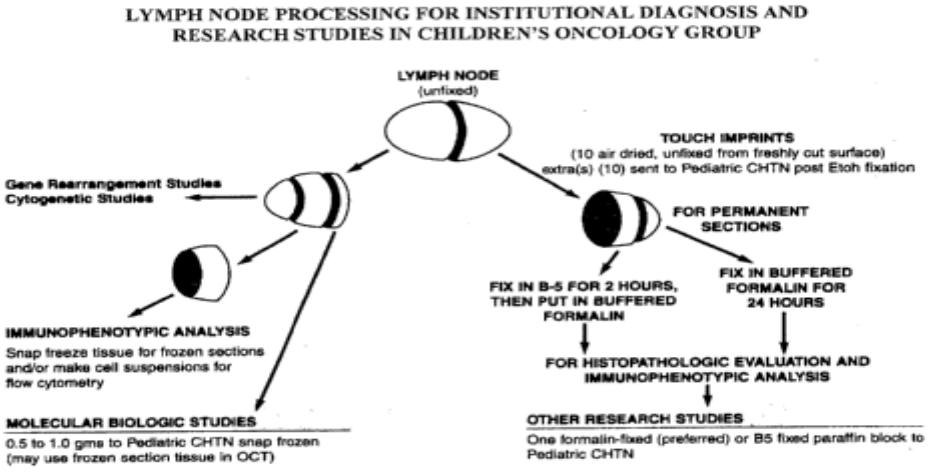
1. Provide quality control by central pathologic review with accurate diagnosis and classification of pediatric non-Hodgkin lymphoma. This is to be based on both morphologic and immunophenotypic criteria. **This study is limited to T-cell lymphoblastic lymphoma**. Patients with B-lineage lymphoblastic 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/m²

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 (m²)*	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/m²

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 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

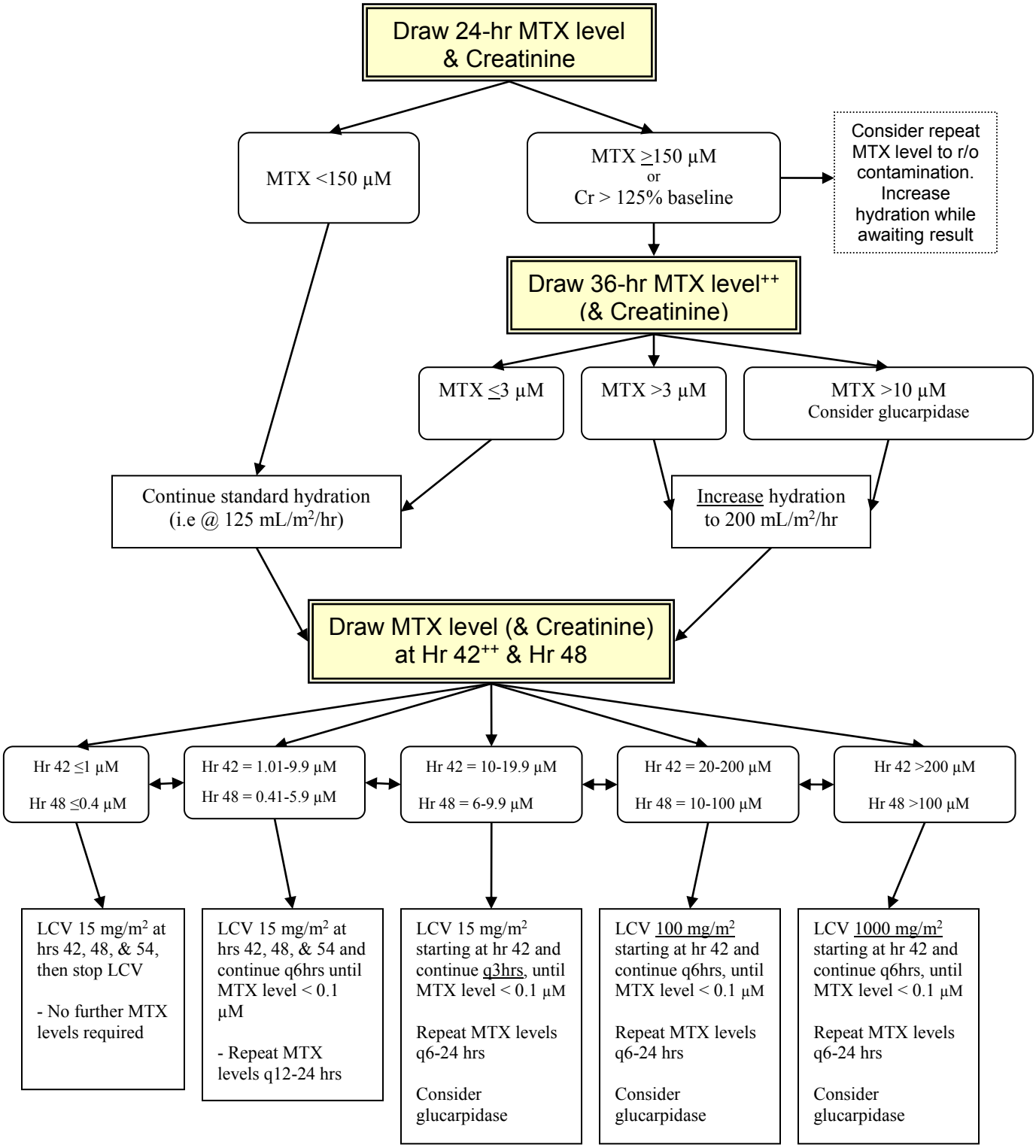
Adapted from Cytochrome P-450 Enzymes and Drug Metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th edition. Hudson, OH; LexiComp Inc. 2000: 1364-1371.

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

Modified from Murphy [Seminars in Oncology (1980) 7; 332-339]

Stage	Criteria for extent of disease
Localized	
I	A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
II	A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tumour, usually in the ileocaecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected
Disseminated	
III	Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intra-thoracic tumours (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease. All paraspinal or epidural tumours, regardless of other tumour 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

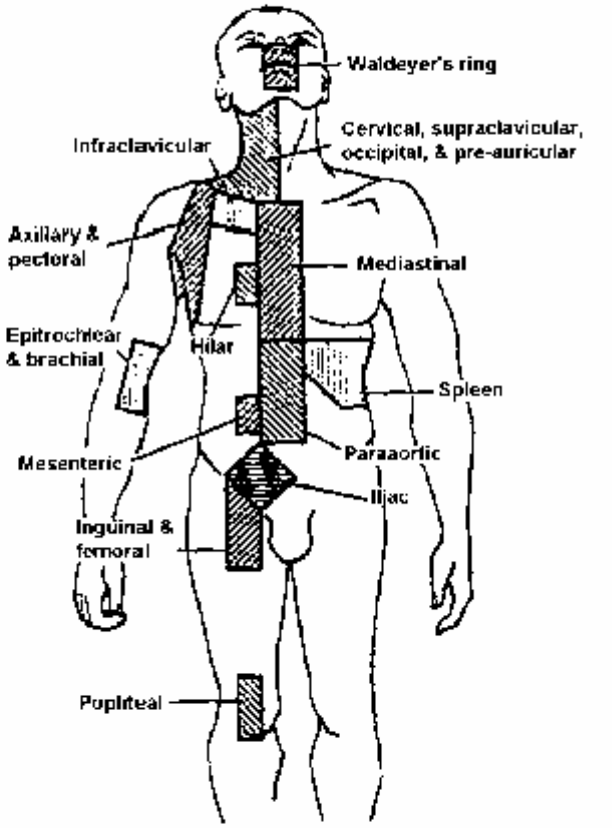
Right neck; cervical, supraclavicular, occipital, and pre-auricular
Left neck; cervical, supraclavicular, occipital, and pre-auricular
Right infraclavicular
Left infraclavicular
Right axilla and pectoral
Left axilla and pectoral
Right epitrochlear and brachial
Left epitrochlear and brachial

Central Regions

- Waldeyer's ring (including base of tongue)
- Mediastinum (including paratracheal)
- Hilar
- Mesenteric
- Paraaortic (including retrocrural, portal and celiac)
- Splenic/splenic hilar

Lower Regions

- Right iliac
- Left iliac
- Right inguinal and femoral
- Left inguinal and femoral
- Right popliteal
- Left popliteal



Anatomical Regions for the Staging Lymphoma

Clinical criteria for nodal involvement - upper torso

Above the diaphragm, the following will be considered positive for lymphoma, provided they are not obviously infected.

- Any cervical or axillary node >3 cm^3 on physical examination, ultrasound, CT or MRI scan.
- Any cluster of matted or adherent nodes.
- Any enlarged supraclavicular nodes.
- Any mediastinal adenopathy
- Any Gallium-positive nodes

Clinical Criteria for Nodal Involvement - lower torso

Below the diaphragm, the following areas of involvement will be considered positive for lymphoma unless they are pathologically proven to be negative.

- Any node >2 cm^3 on CT scan or ultrasound.
- Any Gallium-positive nodes, liver or spleen.
- A spleen or liver that has focal defects on CT or ultrasound or MRI

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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