CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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A National Cancer Institute-supported member group of the National Clinical Trials Network

January 12, 2021

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Thank you for the reviewers' comments regarding protocol AALL1131, *A Phase III Randomized Trial for Newly Diagnosed High Risk B-Lymphoblastic Leukemia (B-ALL) Including a Stratum Evaluating Dasatinib (NSC# 732517) in Patients with Ph-like Tyrosine Kinase Inhibitor (TKI) Sensitive Mutations*. The Study Committee appreciates the reviewers' time and has provided a response to the review below. Enclosed please find Amendment #10B, which incorporates this comment.

The impetus for Amendment #10B is to add language describing the retrospective analysis of the concordance between exposure to anesthesia and long-term neurocognitive outcomes in patients who have consented to participate in the ancillary neurocognitive AALL1131 study. Section 16 of the protocol has been updated to describe this retrospective analysis.

The protocol version date and amendment number have been revised in the protocol and informed consent documents. Revisions to these documents are described in the Summary of Changes table below.

Please let me know if you have any questions or need additional information.

Sincerely,

Rachel Vasquez, Protocol Coordinator (for)

Wanda Salzer, MD, AALL1131 Study Co-Chair,
Michael Burke, MD, AALL1131 Study Co-Chair
Meenakshi Devidas, PhD, AALL1131 Study Statistician
Mignon Loh, MD, Acute Lymboblastic Leukemia Disease Committee Chair, and
Douglas S. Hawkins, MD, COG Group Chair

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	16.0	The amendment to understand the impact of anesthesia exposures on neurocognitive outcomes lacks details. There are no stated objectives, background information to justify the amendment, description of the data that will be collected, descriptions of the data that will be collected, the period of time for the collection, approach/process for the data collection, number of participants (assumed only to be those who participated in the neurocognitive study). Lastly, there is no statistical analysis. Discussion with DCP is encouraged if there are questions about the information that needs to be incorporated into the protocol in support of the proposed amendment. **PI Response: The AALL1131 study committee has consulted with the DCP regarding these concerns. The AALL1131 protocol has been revised to include information that justifies retrospective collection of data on the anesthesia CRF.**

SUMMARY OF CHANGES: PROTOCOL

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(s)	Change
1.	General	-	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.
3.	Table of Contents	2-5	Updated for re-pagination.
4.	16.1	257	Revised exploratory aim 3 to include **chemotherapy and anesthetic exposures** as disease treatments that will be evaluated for impact on neurocognitive outcome. The following language has been added for Hypothesis 3: **Lastly children with specific treatment exposures, including higher cumulative exposure to anesthesia, will have greater deficits in neurocognitive functioning.**
5.	16.2.2	259	Included language to justify the retrospective analysis that will be conducted to determine the impact of anesthesia exposure on neurocognitive outcomes.
6.	16.2.3	260	Included the following language to describe the impetus for this retrospective analysis, and how this research will be conducted: • **In addition, identification of potentially modifiable risk**

			factors for cognitive impairments, such as anesthesia exposure, would inform practice change. • **For the assessment of the impact of anesthesia on neurocognitive outcomes we will retrospectively collect anesthesia exposure data on the group of patients enrolled on AALL1131 and who co-enrolled on the embedded neurocognitive function ancillary study.**
7.	16.3.3	263	The following language has been added to clarify the nature of the data that will be analyzed: **For each subject, data on demographics and treatment will be collected as part of the parent trial. Collection of data on cumulative anesthesia exposures will include the number of anesthetic events, the total cumulative exposures to each anesthetic agent, adjusted for weight, and the total cumulative duration of anesthesia.**
8.	16.4.6	266	Provided clarifying language regarding how the retrospective data on anesthesia exposure will be collected: **The instrument to measure the key exposure of interest (anesthesia exposure) is the anesthesia case report form (A-CRF), adapted from the toll utilized in the St. Jude study, a feasible and effective tool for precise and complete data collection. Data for anesthesia exposures will be captured in the A-CRF for each event and will be collected by each COG institutional site CRA, and uploaded into the RAVE system applying COG rigorous data quality assurance systems. Training will be provided to site CRAs via a concise study guide. The study will provide central real time data review of the A-CRF submissions to ensure validity and completeness.**
9.	16.5.1	267	Provide a description of the statistical analysis plan for this retrospective analysis.
10.	References	306-318	Several references that were listed previously twice were consolidated.

SUMMARY OF CHANGES: INFORMED CONSENT—ALL

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

#	Section	Page(s)	Change
1.	General	All	Updated version date of consent to match the current version of the protocol.

Activated: 02/27/12
Closed: 08/09/19

Version Date: 01/12/21
Amendment: 10B

CHILDREN'S ONCOLOGY GROUP

AALL1131

A Phase III Randomized Trial for Newly Diagnosed High Risk B-Lymphoblastic Leukemia (B-ALL) Including a Stratum Evaluating Dasatinib (NSC#732517) in Patients with Ph-like Tyrosine Kinase Inhibitor (TKI) Sensitive Mutations

A Groupwide Phase III Study

IND Sponsor: CTEP

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CTEP Supplied Agent:
Dasatinib, NSC#732517
Other agents: Cyclophosphamide NSC#26271, Commercial
Cytarabine NSC#63878, Commercial
Daunorubicin NSC#82151, Commercial
Dexamethasone NSC#34521, Commerical
Doxorubicin NSC#123127, Commercial
Erwinia Asparaginase NSC# 106977, Commercial
Etoposide NSC#141540, Commercial
Hydrocortisone NSC# 10483, Commercial
Leucovorin NSC# 3590, Commercial
Mercaptopurine NSC#755, Commercial
Methotrexate NSC#740, Commercial
Pegaspargase NSC#624239, Commercial
Prednisone NSC#10023, Commercial
Thioguanine NSC#752, Commercial
Vincristine NSC#67574, Commercial

ABSTRACT

Recent advances within the Children's Oncology Group have resulted in a well characterized set of features that now define prognostic factors that allow risk stratification and selective application of post-Induction intensification strategies. This has led to the identification of large subsets of National Cancer Institute (NCI) high risk (HR) and standard risk (SR) ALL patients who have suboptimal early response to therapy, but have excellent outcomes with current modified augmented Berlin-Frankfurt-Münster (ABFM) based therapies; collectively described on this trial as high risk ALL (**HR B-ALL**), and another subset of NCI HR B-ALL and SR B-ALL patients who remain at very high risk of relapse collectively described on this trial as very high risk ALL (**VHR B-ALL**). Patients will receive a standard 4 drug Induction with dexamethasone for 14 days (< 10 years old) or prednisone for 28 days (≥ 10 years old) after which they will be stratified into HR and VHR subgroups and eligible to participate in a randomized question within each stratum. Standard risk B-ALL patients will receive Induction on AALL0932 and a subset will be eligible to participate in the post-Induction HR and VHR portions of this trial.

AALL1131 seeks to define optimal intrathecal agents for use with effective chemotherapy with minimal increase in toxicity and/or burden of therapy for children with HR B-ALL. Patients will be randomized to post-Induction therapy with a modified BFM backbone that includes a single Interim Maintenance (IM) phase with high dose methotrexate and a single Delayed Intensification (DI) phase (MBFM-IMHDM) with either intrathecal methotrexate (IT MTX) only – **Arm A** (Standard arm) versus triple intrathecal therapy (ITT) with methotrexate, cytarabine and hydrocortisone– **Arm B** (Experimental arm). We will also determine whether the delivery of ITT in the context of intensified systemic therapy will result in a shift in relapse patterns.

For the patients with VHR B-ALL, we will explore strategies to improve disease free survival (DFS) with more intensive post-Induction therapy using drugs not commonly used in frontline ALL trials, including fractionated cyclophosphamide (CPM), etoposide (ETOP) and clofarabine (CLOF). The backbone regimen will be a modified BFM backbone which includes IM #1 with high dose methotrexate, a single DI phase, and IM #2 with Capizzi methotrexate plus pegaspargase (MBFM-IMHDM+CMTX). Clofarabine is a nucleoside analogue that has been shown to induce remission in the treatment of relapsed and refractory ALL in Phase I/II trials. VHR B-ALL patients will be randomly assigned to receive treatment with: 1) Standard MBFM IMHDM+CMTX - **Control Arm**, or 2) CPM+ETOP - **Experimental Arm 1,** or 3) CLOF/CPM/ETOP **- Experimental Arm 2** in the last 4 weeks of Consolidation and Delayed Intensification. Therapy for the first 4 weeks of Consolidation and Delayed Intensification and all other phases will be identical for all VHR B-ALL patients. This study design also includes a run-in safety phase to determine the feasibility and tolerability of CLOF in combination with CPM+ETOP (Experimental Arm 2) for the treatment of patients with VHR B-ALL. ***With Amendment #2, due to excess toxicities observed on Experimental Arm 2, accrual to the safety phase was restarted with a reduced dose of CLOF. Additionally, to enhance supportive care measures, myeloid growth factor support was given empirically to VHR B-ALL patients enrolled on Experimental Arm 2 after chemotherapy administration during Consolidation Part 2 and Delayed Intensification Part 2. As of Amendment #3B, due to continued toxicities observed, Experimental Arm 2 of this study was***

permanently closed 9/12/2014. The VHR randomization of AALL1131 reverted to a 2-arm study comparing Control and Experimental Arm 1 with Amendment #3B.

Patients with Down syndrome (DS) and HR B-ALL continue to experience significant morbidity and mortality with current treatment strategies. To facilitate further study and improve outcomes of this biologically and clinically unique subgroup, DS patients with HR B-ALL on AALL1131 will be non-randomly assigned to receive reduced intensity Induction and post-Induction with a modified BFM backbone therapy including Interim Maintenance with intermediate dose methotrexate (MBFM-IMIDM) 2000 mg/m^2 every 2 weeks for 4 doses with earlier leucovorin rescue, reduced Maintenance pulse frequency and reduced Maintenance duration for boys, with recommendations for enhanced supportive care. MBFM-IMIDM is modified for DS patients due to their enhanced sensitivity to MTX, and will be administered under close toxicity monitoring guidelines.

This study will also incorporate studies of HR B-ALL genomics and molecular risk classifiers, for the early identification of patient subsets at risk of relapse. We will also determine the incidence of long and short term therapy-associated side effects with studies of the natural progression of osteonecrosis via MRI (patients ≥ 10 years old at the time of B-ALL diagnosis), and declines in neurocognitive function (patients 6 to 11 years old at the time of ALL diagnosis) in non-DS children receiving post-Induction therapy on AALL1131 for HR- or VHR B-ALL.

Amendment #5A includes the evaluation of patients who receive Induction therapy on AALL1131 with low-density array (LDA) card technology and subsequent molecular testing to identify patients with a Philadelphia-like (Ph-like) phenotype. Patients identified as Ph-like with a predicted TKI-sensitive mutation will be eligible to continue on non-randomized post-Induction treatment with dasatinib on the MBFM-IMHDM backbone (Dasatinib Arm), and will not be eligible for randomization on the HR or VHR arms of this study. Patients who received Induction therapy on AALL0932 will not be evaluated with low-density array (LDA) card technology to identify Ph-like as part of the AALL0932 study and thus will NOT be eligible for post-Induction treatment with dasatinib on the MBFM-IMHDM backbone (Dasatinib Arm), but may continue in the randomization that would have been otherwise defined by their risk group (HR or VHR) on AALL1131.

Patients who receive Induction therapy on AALL1131 and are identified as having a Ph-like gene expression with a CRLF2r or JAK/STAT pathway kinase mutation may have the option of enrolling onto the AALL1521 ruxolitinib study or continuing on AALL1131 in the randomization that would have been otherwise defined by their risk group (HR or VHR).

Amendment #5A also requires the addition of twice weekly intrathecal therapy during Induction for patients who are CNS2. Patients should receive additional IT Cytarabine on Day 4, 5 or 6 during Induction, IT Methotrexate on day 8, and then IT Cytarabine on day 11 or12. If the CSF at all three of these time points is negative for blasts, patients will receive their next IT therapy with Methotrexate on Day 29. If the CSF remains positive after the initial LP, patients will continue IT Cytarabine twice weekly during Induction until the CSF is clear for three consecutive LPs. All patients will receive IT therapy with Methotrexate on Day 29 at the end of Induction regardless of CSF evaluations.

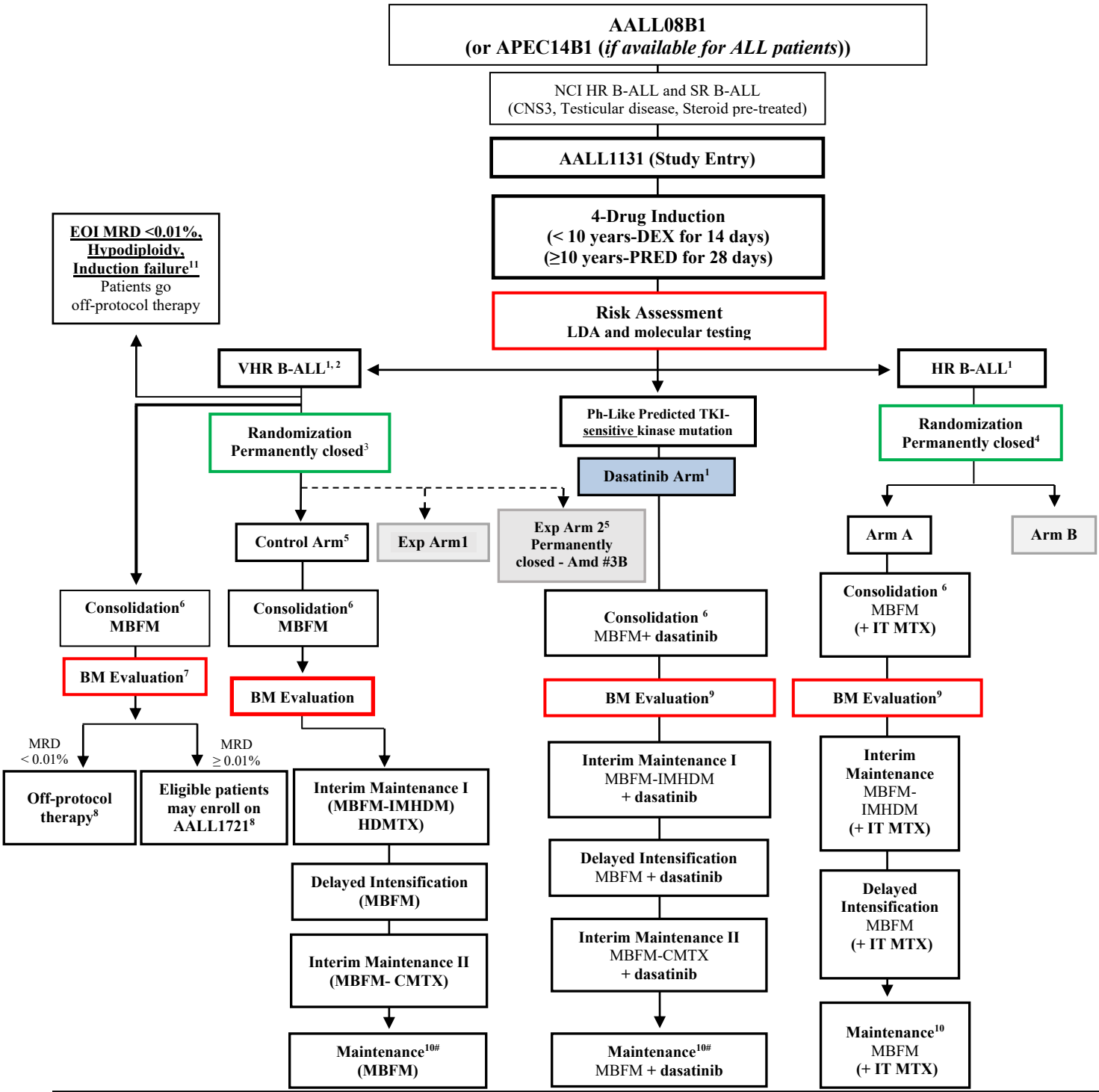
Amendment #5A further includes enhanced supportive care guidelines for patients with HR B-ALL and DS. Interim analysis of patients with HR B-ALL and DS demonstrated that treatment-related mortality continues to be higher for patients with DS compared to non-DS patients. Based on this interim analysis, hospitalization and antimicrobial prophylaxis during intensive treatment phases may be considered in children with DS-ALL due to their increased risk of infection-related mortality.

Planned interim analysis revealed that a futility boundary was crossed and the study would not be able to demonstrate that the VHR Experimental Arm 1 is superior to the Control Arm, as such, effective February 15, 2017 the VHR arms closed to accrual. Amendment #6 reflects this closure and revises the expected accrual completion for the High Risk arm, and also provides details to keep VHR EOI MRD positive NCI HR patients on study through Consolidation therapy. Amendment #6 also provides details

to keep AALL1131 open as a screening protocol for Ph-like, Ph+, as well as continued accrual to the Dasatinib (for patients with predicted TKI-Sensitive Mutation) and Down syndrome arms. In addition, information regarding eligibility for patients who are Ph-like with a predicted TKI-sensitive mutation (dasatinib arm) with respect to dasatinib availability have been added, details about Ph-like testing methodologies have been updated, and the eligibility age for the ancillary neurogonitive study has been increased to 13 years of age to allow us to meet accrual goals.

Amendment #7A incorporates the High Risk randomization closure that took place on March 19, 2018 and to update expedited CTEP-AERS reporting instructions per the release of CTCAE version 5.

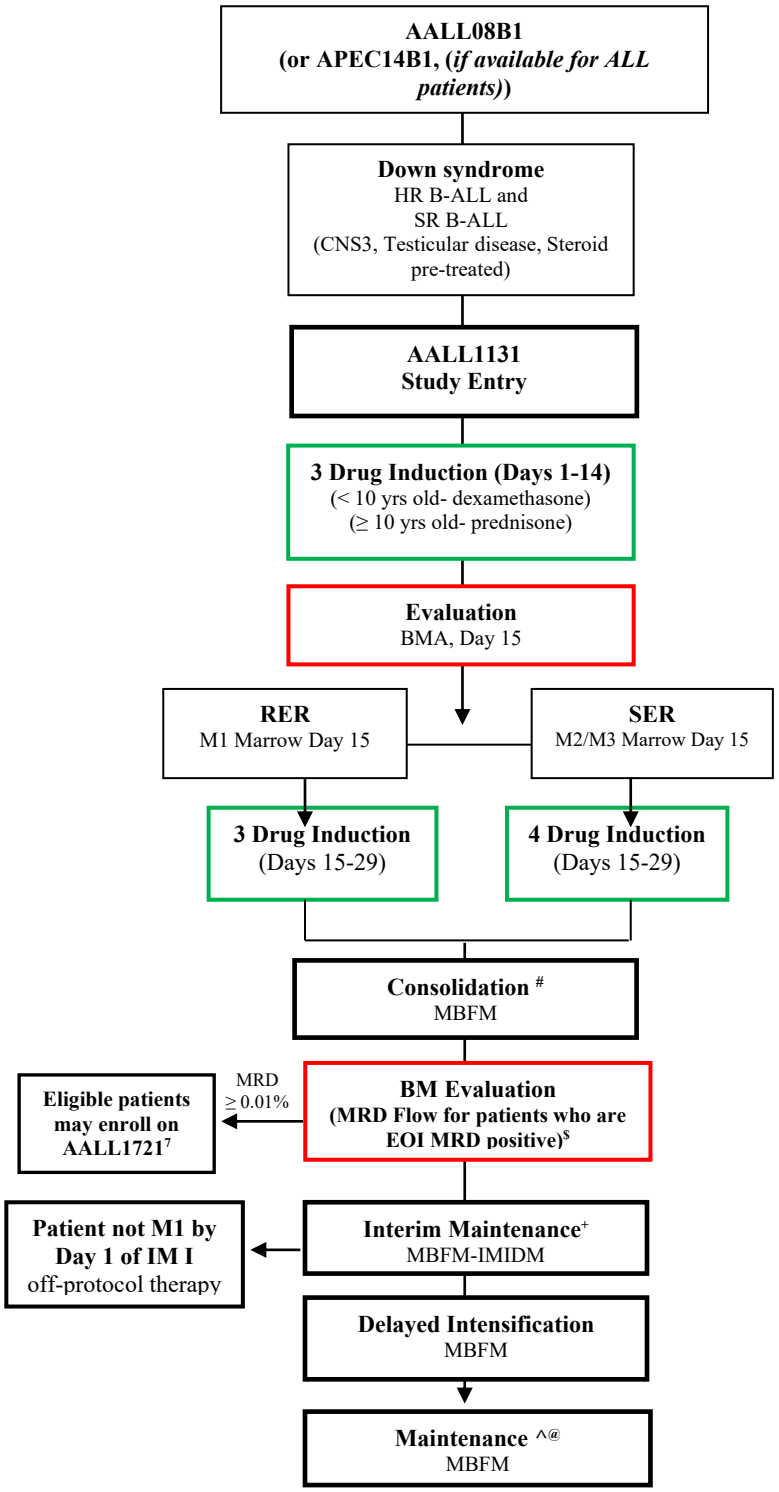
EXPERIMENTAL DESIGN SCHEMA –NON DOWN SYNDROME PATIENTS



[1]See Section 3.3 for details on risk stratification. [2] Effective Amendment #6, eligible patients continue on to Consolidation therapy (see Section 3.3). [3] Randomization to the VHR arms is permanently closed effective 02/15/17. [4] Randomization to the HR arms is permanently closed effective 03/19/2018. All HR patients receive single IT MTX in-place of ITT. See Section 2.3.13 and 3.3 [5]VHR patients receiving therapy prior to Amendment #6 may continue on the control arm. [6]Patients with clinically evident or biopsy-proven testicular disease at end of Induction receive testicular irradiation early in Consolidation. [7] Decentralized testing does not apply to this specimen, see Section 7.4 for details. [8] EOC MRD positive patients may enroll in AALL1721 (if open). EOC MRD positive patients who decline enrollment on AALL1721, and EOC MRD negative patients who otherwise meet criteria for the VHR arm, go off-protocol therapy (See Section 4.1.1 for details). [9]BM evaluation for HR B-ALL patients is ONLY for those patients with Induction Day 29 MRD ≥0.01%. [10]Standard therapy with prednisone and vincristine pulses given every 4 weeks, timed from the start of Interim Maintenance I for a total of 2 years for girls, and 3 years or boys. [11] Induction failure patients with a dasatinib sensitive mutation may continue on the Dasatinib arm. # Patients with CNS3 leukemia at diagnosis receive cranial irradiation in Maintenance Cycle 1.

ITT: Triple intrathecal therapy	VHR B-ALL: Very high risk B-ALL	MBFM: Modified Berlin Frankfurt Munster
IT MTX: Intrathecal methotrexate	HR B-ALL: High risk B-ALL	MRD: Minimal residual disease
HDMTX: High dose methotrexate	BMA: Bone marrow aspirate	IMHDM: Interim Maintenance with HDMTX
CLOF: Clofarabine	CPM: Cyclophosphamide	ETOP: Etoposide
DEX: Dexamethasone	PRED: Prednisone	CMTX: Capizzi methotrexate

EXPERIMENTAL DESIGN SCHEMA - DOWN SYNDROME PATIENTS



Males with clinically evident or biopsy-proven testicular disease at end of Induction receive testicular irradiation early in Consolidation.
+ BM evaluation is ONLY for those patients with Induction Day 29 MRD ≥0.01%.
^ Therapy with prednisone and vincristine pulses given every 12 weeks, timed from the start of Interim Maintenance I for a total of 2 years for both girls and boys.
$EOC MRD positive patients may enroll on AALL1721 if eligible.
@ Patients with CNS3 leukemia at diagnosis receive cranial irradiation in Maintenance Cycle 1.

Note: Patients will receive leucovorin rescue in all phase of therapy except Maintenance.

RER: Rapid early responder
SER: Slow early responder
BMA: Bone marrow aspirate
DS HR B-ALL: High risk B-ALL
DS SR B-ALL: Standard risk B-ALL
DS HR B-ALL: Down syndrome with HR B-ALL
MBFM: Modified Berlin Frankfurt Munster
IMIDM: Interim maintenance intermediate dose methotrexate
IMIDM: Interim Maintenance with intermediate dose methotrexate

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1
To determine if the administration of post-Induction age adjusted ITT on an MBFM-IMHDM backbone will improve 5-year DFS of children with HR B-ALL compared to age adjusted IT MTX. (**Completed effective March 19, 2018**)

1.1.2
To determine, in a randomized fashion, if the cyclophosphamide + etoposide containing regimen (Experimental Arm 1) will improve the 4-year DFS of children, adolescents, and young adults with VHR B-ALL compared to a modified MBFM-IMHDM regimen that contains a second IM (Control Arm). (**Completed effective February 15, 2017**.)

1.2 Secondary Objectives

1.2.1
To determine the toxicity and tolerability of post-Induction age adjusted ITT compared to age adjusted IT MTX in children with HR B-ALL. (**Completed effective March 19, 2018**)

1.2.2
To determine the toxicity and tolerability of Experimental Arm 1 compared to the Control Arm in children, adolescents, and young adults with VHR B-ALL. (**Completed effective February 15, 2017**.)

1.2.3
To determine whether a single-arm, modified Induction with limited anthracycline exposure and post-Induction therapy regimen with MBFM-IMIDM and reduced vincristine/steroid pulse frequency and enhanced supportive care in children with DS and HR B-ALL will result in a ≥ 65% 5-year DFS and < 10% Induction mortality.

1.2.4
To describe the outcomes for children and young adults with Ph-like B-ALL and a predicted TKI-sensitive mutation treated with dasatinib plus MBFM-IMHDM.

1.2.5
To determine the toxicity and tolerability of MBFM-IMIDM in children with DS and HR B-ALL.

1.2.6
To estimate overall survival (OS) rates both overall and by regimen a) for HR B-ALL and b) VHR B-ALL patients.

1.2.7
To determine the incidence of ON, defined by MR imaging, and to characterize the natural history of clinically silent ON in children, adolescents and young adults 10 years of age and greater and to assess the role of drugs (i.e., asparaginase and methotrexate) in addition to corticosteroids, in the risk for development of ON. (**Completed accrual July 2016**)

1.2.8
To determine if the prevalence of cognitive deficits measured by CogState, in children (ages 6 to < 13 years) with HR- and VHR B-ALL at 1 year off therapy, is significantly higher than the normative population (> 14%) in the following domains: working memory, executive function, visual motor, processing speed, and visual attention.

1.3 Exploratory Objective

1.3.1
To determine if the reduction of MRD from end-Induction to end-Consolidation is greater for children, adolescents, and young adults with VHR B-ALL receiving Experimental Arm 1 compared to the Control Arm. (**Closed effective Amendment #6**)

2.0 BACKGROUND

With modern combination chemotherapy regimens, more than 80% of pediatric acute lymphoblastic leukemia (ALL) patients are cured, and current studies suggest that that number will continue to improve to over 90%-95% for some patient subsets.[1-3] Over the past 25 years, refinement of the diagnostic features that contribute to prognosis and outcome has been carried out in legacy Pediatric Oncology Group (POG), Children's Cancer Study Group (CCSG) and Children's Cancer Group (CCG) clinical trials, such that today, within the Children's Oncology Group (COG), a well-characterized set of features has been defined and remains predictive of outcome for children with ALL.[4] Based on clinical and biological features present at diagnosis, such as the occurrence of particular sentinel cytogenetic and/or molecular abnormalities (i.e., favorable chromosome trisomies, hypodiploidy, *MLL* rearrangement *BCR-ABL1* or *ETV6-RUNX1* fusion, intrachromosomal amplification of chromosome 21 [iAMP21]),[5-18] and response to Induction therapy as reflected by end-Induction minimal residual disease (MRD) burden, prognostic factors have been defined which allow risk-stratification and selective application of post-Induction intensification strategies.[4,19-25] These data have been critical to establishing the new risk classification algorithm (AALL08B1) for the next generation of COG ALL trials. Key features of the AALL08B1 risk classification algorithm include using Day 8 peripheral blood (PB) and Day 29 bone marrow (BM) minimal residual disease to assess early response rather than Day 8 and Day 15 BM morphology, and redefining the Day 29 BM MRD threshold used to define poor responders from 0.1% to 0.01%.

Early data from AALL0331 and AALL0232 indicate that subsets of National Cancer Institute (NCI) high risk and MRD positive NCI standard risk (SR) patients can be identified that have a very good outcome with current augmented Berlin-Frankfurt-Münster (ABFM)-based therapies with 5-year disease free survival (DFS) of 88%-90%. Although these patients remain at higher risk of relapse and therapeutic strategies will continue to be directed toward improving their DFS, they do not appear to be appropriate patient subgroups in which to test therapeutic interventions that may be associated with significant increases in toxicity and/or burden of therapy. These groups, collectively termed high risk B-ALL (HR-B-ALL) on this protocol, include NCI high risk (HR) patients < 13 years of age at diagnosis without adverse cytogenetic features or central nervous system (CNS) leukemia that attain negative (< 0.01%) Day 29 BM MRD, NCI SR B-ALL patients lacking favorable cytogenetics (*ETV6-RUNX1* fusion or trisomy of chromosomes 4 and 10) with Day 8 PB MRD ≥ 1% and Day 29 BM MRD < 0.01%, and NCI SR B-ALL patients with favorable cytogenetics and Day 29 BM MRD ≥ 0.01%.

In contrast, other subsets of NCI HR and SR patients can be identified who remain at very high risk of relapse with expected 4-year DFS < 80% and are appropriate candidates for more intensive, and potentially more toxic, therapeutic strategies designed to improve DFS. These groups, collectively termed very high risk ALL (VHR B-ALL) on this trial, include patients ≥ 13 years of age; NCI HR patients with

positive (≥ 0.01%) Day 29 BM MRD; NCI SR patients lacking favorable cytogenetics with Day 29 BM MRD ≥ 0.01%; or any patients with CNS3 disease, *MLL* rearrangements, iAMP21, severe hypodiploidy (< 44 chromosomes and/or a DNA index < 0.81), or Induction failure with M3 BM (> 25% blasts) at Day 29.[1, 4, 8, 14, 15, 21, 25-33] There is some heterogeneity in the outcome of these patient subgroups, but all have a significantly worse expected outcome than the HR B-ALL group. While the outcome of patients with BM MRD <0.01% at end Induction is significantly better than that of those that with MRD ≥ 0.01%,[25] there is a clear trend toward increasingly inferior outcome with increasing age among the patients with MRD <0.01%. Dichotomizing patients into 2 groups based on a continuous variable is challenging and inexact, but 13 years of age was selected as this appears to best represent where differences in outcome become evident. Furthermore, there is also a clear inverse correlation between age at initial diagnosis and potential for long-term survival post relapse. On CCG 1961, NCI HR patients 1-9 years old at initial diagnosis had a 3-year post relapse survival rate of 48.6% vs. 35.4% for those 10-15 years, and 14.7% for those 16+ years old (p=0.001).[2]

The outcome of patients with intrachromosomal amplification of chromosome 21 (iAMP21) has been monitored during the conduct of COG AALL0232 and AALL0331. This monitoring was based on reports from other groups of inferior outcomes associated with iAMP21.[34-36] COG ALL trials detect iAMP21 due to FISH screening for the *ETV6-RUNX1* fusion. While earlier analyses suggested that iAMP21 patients had outcomes similar to those of non-iAMP21 patients on COG AALL0232 and AALL0331, new analyses with larger patient numbers and longer follow-up have shown that the outcomes of children with iAMP21 (n=158) are inferior to those without iAMP21 (n=7641) with 4-year EFS of 64.2% SE 12.8% vs. 88.1% SE 0.7%; p <0.0001 (Meenakshi Devidas, PhD, unpublished data June 2011). Among NCI SR patients treated on AALL0331 the outcomes for iAMP21 patients (n=75) were inferior to non-iAMP21 patients (n=4985) overall (4-year EFS 70.4% SE 9.3% vs. 91.8% SE 0.7%; p <0.0001) and among those with Day 29 MRD <0.01% (4-year EFS 81.1% SE 11.1% vs. 94.1% SE 0.7%) and those with Day 29 MRD ≥0.01% (55.6% SE 15.1% vs. 84.2% SE 2.2%). For NCI HR patients treated on AALL0232 the overall EFS for patients with iAMP21 (n=83) was similar to that of non- iAMP21 patients with 4-year EFS 70.0% SE 10.6% vs. 81.3% SE 1.3%; p =0.46) with trends toward inferior outcomes for those with day 29 MRD <0.01% (81.3% SE 14.4% vs. 88.2% SE 1.3%) and those with Day 29 MRD ≥0.01% (57.8% SE 21.7% vs. 66.6% SE 3.2%). Given the overall inferior outcome of the iAMP21 patients, patients with iAMP21 will be identified during central FISH review, and patients with either SR B-ALL enrolled on AALL0932 or HR B-ALL enrolled on AALL1131 that are identified to have this abnormality will be assigned as Very High Risk for post-Induction therapy. iAMP21 will be defined as at least 4 copies of *RUNX1* on a single chromosome.

Patients with Down Syndrome (DS) present unique challenges. It is estimated that 2%-3% of ALL patients have DS (DS-ALL), and have an increased risk of treatment related mortality.[37] Recently, COG suspended accrual of DS B-ALL children to trials for SR (AALL0331) and HR (AALL0232) B-ALL because of excess mortality. The trials were subsequently reopened after a safety amendment introduced treatment modifications for DS B-ALL patients and there has not been excess toxicity since the safety amendment in DS children with SR B-ALL. However, excess toxic deaths among DS HR B-ALL patients continued following the original safety amendment, leading to permanent closure of AALL0232 to patients with DS in January 2008.[38] In light of the excess toxicity observed in DS patients on AALL0232, this study includes a separate, nonrandomized stratum for DS HR B-ALL patients. The study hypothesis is that limiting Induction anthracycline exposure, replacing Capizzi escalating methotrexate during Interim Maintenance I with intermediate dose methotrexate, reducing Maintenance duration and vincristine/steroid pulse frequency, and implementing standardized enhanced supportive care recommendations, will lead to an acceptable 5-year DFS > 65% and Induction mortality < 10% in DS patients.

2.1 Rationale for Study Design

2.1.1 Induction therapy

The COG AALL0232 randomized patients to receive dexamethasone 10 mg/m^2/day for 14 days versus prednisone 60 mg/m^2/day for 28 days during Induction and high dose methotrexate (HD MTX) versus Capizzi escalating methotrexate during Interim Maintenance I, forming 4 arms: DH, DC, PH, and PC. In June 2008, the study was amended to exclude patients > 10 years of age from the Induction steroid randomization due to an excessive incidence of osteonecrosis (ON). The 5-year event free survival (EFS) for patients 1-9 years of age randomized to receive DH, DC, PH, or PC was 93.7 + 5.4%, 84.1 + 8.4%, 81.2 + 7.7%, and 84.0 + 6.9%, respectively, p=0.03. The 5 year EFS of patients > 10 years of age randomized to dexamethasone versus prednisone prior to June 2008 was 74.7 + 4.6% and 76.5 + 4.6%, respectively, p=0.80. The incidence of osteonecrosis at 36 months for patients 1-9 years and > 10 years of age was 3.1 + 0.9% and 19.6 + 1.6%, respectively. For patients > 10 years, there was a higher rate of ON among those randomized to dexamethasone before June 2008 as compared to prednisone (24.3% versus 15.1%, p=0.0007). The DH arm was the superior arm for patients 1-9 years of age. There was no EFS advantage for patients > 10 years of age receiving dexamethasone versus prednisone during Induction, but there was a significantly higher risk of ON with dexamethasone.[39]

Patients with NCI HR B-ALL will enter this study at initial diagnosis and receive a 4-drug (steroid based on age (dexamethasone <10 years; prednisone 10+ years), vincristine, daunorubicin, and pegaspargase) Induction regimen with all pegaspargase given intravenously (IV). In addition, NCI SR patients with CNS3 status or testicular leukemia or those patients between the ages of 1-9 years who have received steroid pretreatment without a pre-steroid white blood cell count (WBC) will not be eligible to receive Induction chemotherapy on the SR B-ALL trial (AALL0932), but will be eligible for this study at diagnosis. Amendment #5A requires the addition of twice weekly intrathecal therapy during Induction for non-DS CNS2 patients until three consecutive lumbar punctures show no blasts (see Section 2.3.8 for details). At the end of Induction therapy, patients that received Induction on this trial will be stratified into HR B-ALL and VHR B-ALL subgroups based on age, CNS and testicular status, sentinel cytogenetic lesions, and MRD response. In parallel, NCI SR patients will receive a 3-drug (dexamethasone, vincristine, pegaspargase) Induction on AALL0932. Those NCI SR patients initially treated on AALL0932 that are found to have adverse cytogenetic lesions, Induction failure, or high PB MRD at Day 8 (≥ 1% without favorable cytogenetics) or BM MRD ≥ 0.01% at Day 29 will not be eligible to continue on AALL0932 post-Induction, but will be eligible to receive post-Induction therapy on this trial. See Section 3.3 for complete details on risk stratification.

2.1.2 Backbone Chemotherapy for HR B-ALL and VHR B-ALL

2.1.2.1 Modified Berlin-Frankfurt-Münster (MBFM) Backbone Chemotherapy

Since the Berlin-Frankfurt-Münster (BFM) group introduced protocol II or "Delayed Intensification (DI)" in the 1970s,[40] post-Induction intensification of therapy has been a key element of CCG, and now COG ALL protocols. CCG-106 demonstrated an improvement in 7-year event free survival (EFS) from 40% to 63% with BFM-76 based therapy, which was independent of age, sex, or white count at diagnosis.[41] Subsequently, the CCG developed the "augmented BFM" regimen by lengthening Consolidation therapy to 8 weeks and adding doses of vincristine and asparaginase during expected periods of neutropenia during Consolidation and re-Consolidation, using Capizzi style escalating dose intravenous methotrexate (MTX) without leucovorin rescue plus vincristine and asparaginase during Interim Maintenance (IM), and adding second IM and DI phases. CCG-1882 demonstrated that the augmented BFM (ABFM) regimen improved EFS and overall survival (OS) of HR B-ALL patients with a slow early response (SER) to initial Induction therapy (>25% BM blasts at Day 8).[42] More recently, CCG 1961 established that increasing intensity but not duration of post-Induction intensification therapy improved outcomes for children with HR B-ALL.[43] The post-Induction treatment backbone for both HR and VHR patients will be

based on the COG "augmented BFM" backbone used on CCG 1882 and 1961.[42, 43] Based on the recent interim analysis of AALL0232 (discussed below in Section 2.1.2.3), Interim Maintenance #1 (IM I) will consist of HD MTX for both HR and VHR patients and Capizzi methotrexate plus pegaspargase (CMTX/ASNase) for VHR patients who receive a second IM (IM II). The length of therapy will be 2 years from the start of IM I for girls (27 months total) and 3 years for boys (39 months total). During Maintenance therapy, all patients will receive 5-day pulses of prednisone with a dose of vincristine on Day 1 of the pulse, given every 4 weeks. Males who have testicular leukemia at diagnosis and are enrolled in AALL1131 will only receive testicular irradiation if the testicular leukemia does not resolve completely by the end of Induction therapy. The same approach was used on COG AALL0232 and there have been only 4 testicular relapses (< 0.5% of males) on that study.

2.1.2.2 Use of a Single Delayed Intensification Phase

The full ABFM regimen originally tested in CCG 1882 included 2 IM and DI phases.[42] The recent CCG 1961 trial established definitively that second IM and DI phases provided no benefit for NCI HR patients with a RER to Induction chemotherapy.[43] In parallel, CCG 1991 found that adding a second DI phase (all patients received 2 IM phases) provided no benefit for NCI SR patients with a RER to Induction chemotherapy, but did not address the role of 1 versus 2 IM phases.[44] In both of these trials, patients with a SER received full augmented BFM therapy with 2 IM and DI phases. While the relative merits of adding second IM/DI phases have never been tested in patients with a poor initial response in recent COG ALL trials, subset analyses of CCG 1961 and 1991 have not identified any patient groups that benefitted from a second DI phase. Thus, in the absence of data showing a benefit for 2 DI phases, it is reasonable to extrapolate from CCG-1961 and 1991 that the inclusion of a second DI would potentially add to toxicity and late effects while providing no realistic outcome benefit. As such, this trial will use a modified BFM backbone including Interim Maintenance with high dose methotrexate (MBFM-IMHDM) and only 1 DI phase for all patients. The second IM and DI phases were eliminated for slow responding patients in the COG AALL0434 T-ALL trial and ongoing study monitoring has not shown any decrease in expected outcome for SER patients in that trial.

2.1.2.3 Interim Maintenance Phases

As noted above, there was no benefit to adding second IM and DI phases for RER HR B-ALL patients on CCG 1961.[43] Subset analyses of patients treated on 1961 that are most similar to the HR B-ALL group treated in this trial (B-ALL patients 1-12 years old with an RER based on Day 8 BM morphology) show no suggestion of benefit to second IM and DI phases (CCG 1961 unpublished data). Based on these results, HR B-ALL patients will be treated with a single IM phase on this trial. In contrast, the potential benefit of a second IM phase has not been answered definitively for patients with an SER. Given that SER patients who are not CNS3 will not receive pre-symptomatic cranial irradiation on this trial (see 2.1.2.4 below), the CNS protection provided by the Capizzi IV MTX IM phases on CCG 1991,[44] and the limited toxicity of a second IM phase, VHR B-ALL patients enrolled on this trial will receive 2 IM phases. The AALL0232 study recently closed to accrual due to an interim analysis demonstrating a superior event free survival (EFS) for those patients randomized to HD MTX versus Capizzi MTX during IM I. The 5-year EFS for HD MTX (n=1209) versus Capizzi MTX (n=1217) was 82.0 ± 3.4% versus 75.4 ± 3.6%, respectively (2 sided p=0.006; RHR=1.4), which crossed the efficacy criteria of p=0.007 for the MTX comparison at this interim time point. Based on these results, all patients on this study (AALL1131) will receive HD MTX during IM I and Capizzi MTX during IM II, for those receiving a second IM. Patients with DS will receive modified intermediate dose methotrexate (ID MTX) of 2000 mg/m^2 and earlier leucovorin rescue due to the increased sensitivity of this patient group to MTX.

2.1.2.4 The Role of Cranial Irradiation in VHR B-ALL

Historically, many CCG, POG, COG, Dana Farber Cancer Institute Consortium, BFM and St. Jude Children's Research Hospital (SJCRH) ALL trials have shown that patients with overt CNS leukemia (>5 blasts per high powered field defined as "CNS3" status) at diagnosis have inferior outcomes compared to

B-ALL patients without overt CNS leukemia.[4 2, 3, 45, 46] For example, the 5-year EFS for POG CNS3 patients treated in the 1984-2001 era was 56%, which is quite similar to the 57% 5-year EFS of CCG patients treated in 1996-2002 era trials.[2, 3] With irradiation, the major cause of treatment failure in these populations is typically BM, rather than CNS failure. On CCG 1961, HR B-ALL patients with CNS3 status all received 2400 cGy of cranial and 600 cGy spinal irradiation and all patients received ABFM therapy with 2 IM and DI phases. There were a total of 49 B-ALL CNS3 patients enrolled in that study, only 24 of whom remain in 1st remission[43](unpublished data). Among CNS3 patients with a RER, 17 of 32 remain in first remission. There were a total of 21 relapse events, including 16 BM relapses, 3 CNS relapses, and 2 testicular relapses. Based on this poor outcome, all CNS3 patients will be assigned VHR B-ALL. While 2 recent studies have reported that cranial irradiation (cXRT) can be eliminated from treatment for children with B-ALL, these trials have not provided convincing evidence of excellent disease control for CNS3 patients.[47, 48] The SJCRH Total XV study reports a 5-year EFS of 85.6% and overall survival (OS) of 93.5%, but included only 9 CNS3 patients who had a 5-year EFS of 43.2%.[49] The DCOG ALL-9 study yielded a 5-year EFS of 87%, and included 21 CNS3 patients who had a 5-year EFS of 67%.[47] Given the relatively small numbers of CNS3 patients included in these 2 studies and the suboptimal EFS obtained, it seems imprudent to discontinue cranial irradiation for the CNS3 patient subset. Hence, this study will administer 1800 cGy cXRT to CNS3 patients during the first month of Maintenance therapy. The cXRT dose of 1800 cGy is that used for CNS3 patients in other recent CCG and COG studies (CCG 1991, AALL0232, AALL0434), while earlier CCG studies (CCG 1961) used higher doses. Recently, the outcome for patients with late (> 18 months post diagnosis) isolated CNS relapse treated with 1200 cGy cranial irradiation on AALL02P2 was found to be inferior to that of similar patients treated on the predecessor POG 9412 trial with 1800 cGy cranial irradiation. Patients receiving therapy on CCG 1961 with CNS3 leukemia received ABFM therapy with Capizzi during IM I, double DI, and craniospinal radiation during Consolidation (2400 cGy cranial and 600 spinal). The 4-year EFS of patients with CNS3 leukemia (n=17) was 55.9 ± 9.0%. Whereas patients receiving therapy on AALL0232 with CNS3 leukemia received ABFM therapy with HD MTX during IM I, double DI, and cranial radiation during Consolidation (1800 cGy) post amendment 2 or craniospinal radiation during the first year of the study (1800 cGy cranial and 600 spinal) pre-amendment 2. The 4-year EFS of patients with CNS3 leukemia (n=62) was 78.8 ± 8.6%. These data suggest that ABFM therapy with HD MTX during IM I and cranial radiation (1800 cGy) provides a superior outcome compared to historic controls receiving therapy on CCG 1961. Given these findings, the cXRT dose for CNS3 patients on AALL1131 will remain at 1800 cGy.

The recent COG HR B-ALL trial AALL0232 defined SER as M2/M3 BM at Day 15 or MRD ≥ 0.1% at Day 29 of Induction and SER patients received full ABFM therapy with 1200 cGy cXRT. However, the effective components of ABFM therapy have never been dissected in this patient population and the role of cXRT for patients without overt CNS disease at diagnosis is uncertain. The CCG-1882 trial does not address whether or not cXRT is needed for SER patients because 1800 cGy cXRT was administered to patients randomized to either the standard or augmented treatment arms. Thus, the improvement in outcome observed for SER patients treated on CCG 1882 with ABFM therapy is due to more intensive systemic chemotherapy, and not to cXRT.[42] During the same time period, the COG has not used prophylactic cXRT for NCI SR patients with an SER on CCG 1991 (M2/M3 Day 15) or in AALL0331 (M2/M3 BM at Day 15 or MRD ≥ 0.1% at Day 29). The SER patients treated with full ABFM therapy without cXRT on CCG 1991 had an excellent outcome with 4-year EFS 85% and OS 90%.[49] As well, current UK HR B-ALL trials, based on past CCG studies, have eliminated cXRT in all patients except those with CNS3 disease and have reported very low rates of CNS relapse (communication with A Vora). Given the lack of proven efficacy of cXRT for patients with CNS1 or CNS2 that meet the criteria for entry on this trial, the change in definition of slow response (Day 29 BM MRD ≥ 0.01% rather than 0.1%), the differing approaches of cXRT use in NCI HR and SR patients with poor early response in recent COG ALL trials, and the encouraging results of the SJCRH trial Total XV and UK trials, cXRT

will only be used for patients with overt CNS leukemia (CNS3 status) at diagnosis. This approach will limit the use of cXRT in 2010 era B-ALL COG trials to only 2% of patients.

2.1.3 Randomized Study of Intrathecal Chemotherapy Regimens in HR B-ALL

2.1.3.1 Rationale for the use of Triple Intrathecal Therapy (ITT)

The expected outcome for HR B-ALL patients with hABFM therapy is excellent with an estimated 88%-90% 5-year EFS (unpublished data, COG AALL0232 and AALL0331). Central nervous system (CNS) relapse is a major contributor to failures in these patients. On CCG-1961,[43] 113 events occurred among 430 RER patients randomized to standard post-Induction therapy and 24/113 events were isolated CNS relapses (21% of total events). Among the 450 RER patients randomized to augmented post-Induction therapy, 77 events occurred, 16 of which were isolated CNS relapses (21% of total events). Including combined marrow and CNS relapses, approximately one-third of the total events that occurred among HR patients enrolled in CCG 1961 had a CNS component, arguing that improvements are needed in CNS-directed therapy. COG AALL0232 explored 2 approaches to improve CNS control, dexamethasone versus prednisone during Induction (for patients < 10 years old), and high dose methotrexate (HD MTX) versus Capizzi methotrexate during IM. This study recently closed to accrual due to an interim analysis demonstrating superior EFS for those patients randomized to HD MTX versus Capizzi MTX (CMTX) during IM I. For patients who received the HD MTX arm, there were a total of 67 relapse events with 33% having a CNS component (42 bone marrow; 22 isolated CNS; 3 testicular) compared to the CMTX arm which reported 105 relapse events, 31% with a CNS component (68 bone marrow; 1 combined marrow/CNS; 32 isolated CNS; 1 testicular; 3 other). Thus while HD MTX decreased the total number of events compared to CMTX, the pattern of relapse did not significantly differ between the 2 arms as still a third of relapses involved the CNS. Another potential way to improve CNS control is through more effective intrathecal (IT) chemotherapy. CCG 1952 randomized children with SR B-ALL to receive triple intrathecal therapy (ITT) vs. IT MTX after one initial dose of IT cytarabine.[50] Although the use of ITT significantly improved CNS control with rates of isolated CNS relapse of 3.4% vs. 5.9% with IT MTX (p=0.004), the overall 6-year EFS was similar between the 2 groups (80.7% vs. 82.5%, p=0.2) due to more BM and testicular relapses in the patients randomized to ITT. Because there were lower salvage rates for patients with a BM relapse, those randomized to ITT had a lower overall 6-year OS (90.3% vs. 94.4%, p=0.01). However, the CCG 1952 chemotherapy backbone was clearly inadequate compared to contemporary regimens, with 7-year EFS for RER patients 81.5% vs. 5-year EFS 90.7% on the successor CCG 1991 SR B-ALL trial.[44, 51] Other trials incorporating ITT with effective systemic control have reported excellent outcomes and CNS control. Patients enrolled in SJCRH Total XV received 1 dose of IT cytarabine followed by 13-25 (adjusted based on risk group) doses of ITT.[48] On that study, the overall incidence of isolated CNS relapse among all patients was 2.7%, with 3.9% of patients having a relapse with any CNS involvement. These data suggest that, with effective systemic therapy, ITT use results in a low incidence of CNS relapses. On the successor SJCRH trial Total XVI intensive ITT is solely used for CNS directed therapy. There have not been any CNS relapses observed since the study opened in 2007 and the therapy has been well tolerated (Personal communication, C. Pui, M.D. January 2010). As the available data do not support an improvement in CNS failures with the use of cXRT in HR patients with CNS1 or CNS2 status,[47, 52] the current study will randomize HR B-ALL patients to either post-Induction age-adjusted ITT with methotrexate, hydrocortisone, and cytosine arabinoside or IT MTX alone. Patients will continue to receive age-adjusted IT MTX therapy during their Induction therapy, after the initial IT cytarabine at time of diagnosis, to prevent the randomization of ITT vs. IT MTX from influencing day 29 MRD.

Neurotoxicity will be monitored closely on this study, but it is unlikely that there will be differential long-term neurotoxicity on the 2 study arms. Kadan-Lottick and colleagues recently reported detailed neurocognitive assessment performed a mean of 5.9 years after random assignment of children to IT MTX (n=82) vs. ITT (n=89) chemotherapy on CCG 1952.[53] There were no clinically meaningful

differences in neurocognitive functioning between the 2 patient groups except for a slightly slower processing speed in the IT MTX group (p=0.04) as well as more patients from the IT MTX group falling into the below-average range compared to the ITT group (19.5% vs. 6.9%; p=0.02).[53] Effective March 19, 2018 the High Risk (HR) randomization closed to accrual following an interim futility analysis revealing that Arm B (intrathecal triples, ITTs; methotrexate, cytarabine, and hydrocortisone-- on the MDFM-IMHDM backbone) would not be able to demonstrate superiority to Arm A (single IT methotrexate on the MDFM-IMHDM backbone). As such, with Amendment #7A the HR experimental Arm B has been modified to prescribe single IT methotrexate therapy in place of ITTs.

2.1.4 Randomized Study of Different Consolidation Chemotherapy Regimens in VHR B-ALL

2.1.4.1 Rationale for Testing a Clofarabine-Based Chemotherapy Regimen

While the VHR B-ALL population contains a number of different patient subgroups, the expected 4-year EFS is < 80% for each group and the expected aggregate 4-year EFS is approximately 70%. One particular VHR patient subgroup, identified by end-Induction MRD, was recently reported in the interim analysis of AALL0232, where patients with end-Induction MRD ≥0.01% had a predicted 4-year EFS of 74±5.3%%. Current post-Induction intensification strategies, which have focused on optimizing the use of drugs commonly used in ALL therapy, have delivered sub-optimal results for these VHR B-ALL patients, and in the absence of a specific targeted intervention (such as *Abl*-tyrosine kinase inhibitors in Philadelphia chromosome-positive ALL as successfully employed in AALL0031)[20] intensive chemotherapy continues to be the mainstay of treatment. We hypothesize that further optimizing or intensifying the dose and schedule of established agents or combination regimens typically used to treat newly diagnosed ALL patients is not likely to further improve outcomes for VHR B-ALL patients, and therefore novel or targeted therapies should be investigated. Given that there is not a specific molecularly targeted agent available for this patient population, this trial will test the use of different consolidation strategies based on drugs not commonly used in frontline ALL trials, including fractionated cyclophosphamide, etoposide, and clofarabine.

Clofarabine is a rationally designed, second-generation purine nucleoside analogue that has produced promising responses in single agent and combination chemotherapy trials. Nucleoside analogs are a highly effective and historically important class of drugs in the treatment of leukemias. The purine nucleoside analogs cladribine and fludarabine have activity in acute leukemias, but at doses associated with neurotoxicity. Clofarabine is a second-generation deoxyadenosine analog that has overcome some of the limitations of fludarabine and cladribine.[54-57] Clofarabine is a hybrid of cladribine and fludarabine and was designed to improve on the efficacy of these drugs while decreasing toxicity.[57] Clofarabine is resistant to deamination and shows enhanced stability. After conversion to an active triphosphate metabolite by deoxycytidine kinase (DCK), clofarabine inhibits deoxynucleic acid (DNA) synthesis through inhibition of ribonucleotide reductases 1 (RRM1) and 2 (RRM2) and DNA polymerases. This inhibition of DNA synthesis in association with the accumulation of triphosphates has been demonstrated in prior pharmacokinetic and pharmacodynamic studies.[54-58]

Clofarabine has been quite successful in inducing remissions in pediatric patients with multiple relapsed or refractory ALL when tested in the Phase I and II settings, [59, 60] leading to accelerated approval by the US Food and Drug Administration in 2004 for the treatment of pediatric patients 1-21 years of age with relapsed or refractory ALL.[61] More recently, combination studies of clofarabine (CLOF) with cyclophosphamide (CPM) and etoposide (ETOP),[58, 62] or with CPM alone[57] have been used to successfully induce remission in refractory patients. Two studies have tested the 3-drug CLOF/CPM/ETOP regimen. The CLO218 Phase I/II study included a Phase I portion that enrolled children with first or second relapses of acute myeloblastic leukemia (AML), second or third relapses of ALL, or ALL patients refractory to a first re-Induction attempt.[62] The dose escalation portion of the study was completed in December 2007 with 25 patients enrolled, and identified a recommended Phase II

combination of CLOF 40 mg/m^2/day, CPM 440 mg/m^2/day and ETOP 100 mg/m^2/day for 5 consecutive days. The overall response rate was 64%; with 10 complete remissions (CR) and 6 complete remissions in the absence of platelet recovery (CRp) noted in 20 ALL and 5 AML patients. The overall response rate for ALL patients was 55% (9 CR, 2 CRp). The combination of clofarabine, cyclophosphamide and etoposide, at very similar doses (CLOF 40 mg/m^2/day, CPM 400 mg/m^2/day and ETOP 150 mg/m^2/day for 5 consecutive days) has also recently been studied in 25 children at 6 Italian pediatric centers.[58] These patients had multiply recurrent (n=8) and refractory (n=17) B-ALL and T-ALL. Thirteen patients (52%) attained a CR and 1 (4%) had a CRp, for an overall response rate of 56%.[58] Notably, 13 of 17 patients with B-ALL, compared to 1 of 8 patients with T-ALL responded to treatment with this regimen (a 76% response rate). These response rates among patients with second or greater relapse/refractory disease are superior to the estimated 40% response rates which have been historically observed and based on the results of these 2 studies, the CLOF/CPM/ETOP regimen is attractive to test in the VHR B-ALL population. It is also known that CPM + ETOP (or the related ifosfamide (IFOS) + ETOP combination) is active in ALL,[63-68] and therefore important to assess whether any improvements in outcome observed with this 3 drug combination are related to clofarabine or the CPM + ETOP combination. Treatment blocks containing CPM + ETOP (or IFOS + ETOP) are included in a number of COG ALL trials including AALL0031, AALL0622, AALL0631, ADVL04P2 and ADVL07P1, and generally well tolerated without excess morbidity or mortality. Common toxicities noted in the Phase I portion of the CLO218 study included febrile neutropenia and fever with a Grade 3 elevation of lipase and possible veno-occlusive disease in a single patient leading to cohort expansion, during which no additional toxicities were noted.[62] The Phase II portion of the CLO218 study reported severe hepatic toxicities including hyperbilirubinemia, transaminitis, with some symptoms consistent with sinusoidal obstruction syndrome (SOS), formerly known as veno-occlusive disease (VOD) in 4 of the first 8 patients enrolled; 3 of these patients dying as a result of their toxicities and multi-organ dysfunction.[69] During the same time frame, 2 other patients on an investigator initiated study of CLOF/CPM (CPM dose 200-300 mg/m^2/dose on a Day 0, 1, 2, 3, 8, 9, 10 schedule) also experienced hepatic toxicity in the face of significant infection and capillary leak syndrome (personal communication, R. Arceci M.D, 2010). Both of these patients died as a complication of multi-organ failure. All fatal events on these 2 studies occurred in patients who developed significant viral, bacterial, and/or fungal infections while neutropenic and who had preceding capillary leak syndrome. Because of the serious adverse events (SAE), CLO218 was halted and amended to exclude patients with prior stem cell transplant, as 5 of the 6 patients reported in both of the above studies that experienced severe hepatic toxicities had undergone a stem cell transplantation between 4 and 12 months prior to study entry, and to require that patients have normal bilirubin and no concomitant hepatic infections.

Thus, VHR B-ALL patients enrolled in this trial will undergo a 3-way randomization (weighted 1:2:2, see below) between the standard MBFM-IMHDM CPM + ARAC Consolidation regimen, Experimental Arm 1 with CPM + ETOP, or Experimental Arm 2 with CLOF + CPM + ETOP. Each regimen will contain identical dosing of vincristine and pegaspargase during Consolidation. Logistically, all patients will receive one 4-week block of the standard CPM + ARAC regimen starting at Day 1 of Consolidation; with the randomized 4-week therapy blocks given at Day 29 of Consolidation and Day 29 of DI (see experimental design schemas). The study will have adequate power to detect whether or not either experimental regimen is significantly better than the standard MBFM-IMHDM backbone and to compare the outcomes achieved with the 2 experimental arms to one another.

With Amendment #3B and the closing of the Experimental Arm 2 of the study (see Section 2.4.5), the VHR study design will be modified to a 2-way randomization (weighted 1:2) between the standard MBFM-IMHDM CPM + ARAC Consolidation regimen and Experimental Arm 1 with CPM + ETOP. Each regimen will contain identical dosing of vincristine and pegaspargase during Consolidation Part 2. All patients will receive one 4-week block of the standard CPM + ARAC regimen starting at Day 1 of Consolidation Part 1; with the randomized 4-week therapy blocks given at Day 29 of Consolidation Part 2 and Day 29 of DI Part 2 (see experimental design schemas). The study will have adequate power to

determine whether the experimental regimen is significantly better than the standard MBFM-IMHDM backbone.

2.1.4.2 Stem Cell Transplantation (SCT) for a Subset of VHR B-ALL Patients

With closure of the VHR arms on AALL1131, Primary Induction Failure and severe hypodiploid patients will not continue on AALL1131 post-Induction and will go off-protocol therapy.

The current consensus is that patients with a projected 5-year EFS of less than 45%-50% merit consideration for allogeneic SCT early in treatment.[4, 70-72] Based upon this, a small subset of patients entering this study are to have the option to proceed to allogeneic SCT at the completion of Consolidation; specifically those with severe hypodiploidy (modal chromosome number < 44 and/or DNA index of < 0.81) and those with M3 BM at Day 29 of Induction therapy. Although the role of SCT versus chemotherapy has not been definitively determined in these groups, it is usually considered to be the treatment of choice for those patients who have EFS in the range of 35%-40% with chemotherapy alone.[21, 28] Patients with severe hypodiploidy (< 44 chromosomes) have a very poor outcome compared to patients with 44 chromosomes (8 year EFS 30.1% vs. 52.2%; p=0.01) and fail early in treatment (within 2 years).[21] As there are no prospective trials comparing chemotherapy alone to SCT for this subset of patients, based on the dismal EFS of < 35%, patients with severe hypodiploidy are typically treated with SCT. The limited data available suggest that patients with Induction Failure have higher EFS with allogeneic transplantation as compared to chemotherapy alone in first remission.[71, 72] Thus, patients enrolled on this study that have an M3 BM at Day 29 of Induction, or severe hypodiploidy have the option to come off protocol therapy to receive allogeneic SCT after completion of 2 cycles of Consolidation chemotherapy (Day 57 of Consolidation). Such patients are to be offered participation in ASCT0431 or successor stem cell transplant protocols, as they are available. Patients with either severe hypodiploidy or M3 BM at Day 29 of Induction therapy who decline SCT may continue treatment on AALL1131 and are to be randomized among the 3 treatment arms. However, because the choice to undergo SCT might be subject to selection bias, patients with Induction Failure or severe hypodiploidy will not be included in the primary DFS analysis but will be analyzed separately and will contribute to important secondary study questions regarding end-Consolidation MRD response, toxicity, and overall survival.

2.1.5 Dasatinib for a Subset of Patients Defined as Ph-like (LDA positive) with a Predicted TKI-Sensitive Mutation

The Ph-like phenotype of childhood B-ALL has been described by several different groups.[73-75] The common features of this subgroup are shared gene expression patterns with patients who have the *BCR-ABL1* translocation (Philadelphia-positive B-ALL) and poor prognoses with conventional chemotherapy. A more extensive molecular characterization of these cases has also demonstrated a very high frequency of *IKZF1* deletions, fusions of tyrosine kinase genes, fusions of *CRLF2* and mutations of *JAK1* and *JAK2*.[76, 77] A variety of other gene fusions involving kinase-associated pathways have also been detected.

With the advent of tyrosine kinase inhibitor (TKI) therapy for *BCR-ABL1* childhood ALL, the prognosis for these patients has greatly improved.[78, 79] At present, the menu of tyrosine kinase fusion partners who have responded well to the addition of TKIs (*in vitro* or *in vivo*) includes: *ABL1*, *ABL2*, *CSF1R, PDGFRB* and *FGFR*.[80] Given that HR B-ALL patients who are Ph-like (LDA positive) have a predicted 5-year EFS <60%,[76] identifying those with kinase fusions to introduce TKI therapy could improve survival. As the COG study AALL0622 reported both safety and feasibility in delivering the TKI dasatinib on a much more intensive chemotherapy backbone than what is currently the control arm for AALL1131, and as dasatinib provides a broader inhibition of kinase mutations compared to imatinib (e.g. Src kinases), patients on AALL1131 identified as Ph-like with a predicted TKI-sensitive mutation will be non-randomly assigned to receive dasatinib post-Induction on the MBFM-IMHDM backbone (Dasatinib Arm), and will NOT be eligible for randomization within the HR or VHR arms of this study.

2.1.6 Down Syndrome

A primary study objective for DS patients is to reduce Induction mortality to < 10%. The fatal infectious complications that occurred in DS HR B-ALL patients in prior frontline studies (CCG 1961 and COG AALL0232) typically occurred during periods of neutropenia, particularly during Induction. On CCG 1961, 4 deaths occurred during Induction therapy among 51 patients (8%) and in AALL0232, 5 toxic deaths occurred during Induction (3 in the dexamethasone arm and 2 in the prednisone arm) among 41 patients. Four additional toxic deaths occurred post-Induction: 1 during Delayed Intensification and 3 during Maintenance. Two other deaths occurred as well: 1 due to relapse and 1 due to unknown causes in a patient off study. The remission death rate for patients with DS enrolled on the AALL0232 was 4/30 (13.3%) versus 33/2211 (1.5%) of those patients without DS. Because 5/41 (12%) of children with DS HR B-ALL died during Induction on AALL0232, and fatal infectious complications typically occurred during periods of neutropenia, Induction therapy is significantly modified for these patients on AALL1131. Children with DS HR B-ALL start off receiving a 3-drug Induction (dexamethasone for patients < 10 years of age; prednisone for patients ≥ 10 years of age) and response is assessed at Day 15 by bone marrow morphology. The estimated 80%-90% of DS patients with RER at Day 15 (defined as M1 marrow morphology) will complete a 3-drug Induction. Patients with SER (M2/M3 marrow at Day 15) will receive 1 dose of "rescue" anthracycline (daunorubicin 50 mg/m^2). Thus, the majority of DS patients with RER are spared the added toxicity of anthracycline, and even those patients who do receive anthracycline receive 50% less than the cumulative amount administered on the AALL0232 Induction regimen. While it is unusual to use a 3-drug Induction in children with HR B-ALL, less intensive 3-drug regimens produced complete remission rates of 93% in the 1970s.[81]

Post-Induction therapy for children with DS HR B-ALL is similar to that given in the HR B-ALL standard arm (Arm A) except that ID MTX is given during IM I instead of HD MTX, with earlier leucovorin rescue and decreased steroid/vincristine pulses during Maintenance, intended to decrease the risk of major, including fatal, toxicities during these phases. The rationale for administering ID MTX to patients with DS during IM I is the same as for non-DS patients, to obtain the survival benefit associated with HD MTX versus Capizzi MTX on AALL0232. On CCG 1961 there were 51 DS HR B-ALL patients enrolled with 41 patients receiving protocol therapy. The 5-year DFS of children with DS HR B-ALL that were evaluable (6 patients had a toxic death and 4 were reported inevaluable) and who were RER and treated on the augmented BFM arm was 79.4 ± 10.9% (n = 15) compared to 56.3% ±12.4 (n=16) (p=NS) for RER and treated on the standard BFM arm.[82] On AALL0232 there were 44 DS HR B-ALL patients enrolled, with 1 inevaluable for the whole study and 7 inevaluable for post induction therapy. The DFS of evaluable children with DS HR B-ALL on AALL0232 was 66.5 ± 13.6% (n = 36). As these 2 studies include very small numbers of DS HR B-ALL, the differences in DFS cannot be directly compared. Patients with DS are known to exhibit increased sensitivity to MTX based on both in vitro studies and clinical experience,[83] and this sensitivity was confirmed on CCG 1991, where they were unable to escalate to doses comparable to those attained in children without DS.[84] Similarly, children with DS have required dose modifications when receiving MTX at doses of 5000 mg/m^2 on past BFM protocols[37, 85] and UKALL protocols,[86] or 1000 mg/m^2 on P9905 (personal communication, Naomi Winick MD). Chessells et al[86] provides the most detailed report of toxicities experienced by DS children receiving HD MTX 5000 mg/m^2. Among 15 DS children randomized to receive 3 HD MTX infusions, 2 patients received only 2 infusions, due to transient encephalopathy in one and transitory right hemiparesis and dysphasia in the other. The other 13 received all 3 courses, but 4 (40%) experienced complications, including minor infections, perianal blistering, and 1 neutropenia with *E. coli* sepsis. The 5-year EFS for the DS patients in this report was 53%. A more recent study demonstrated that MTX pharmacokinetics do not differ significantly between DS and non-DS children, suggesting that the increased toxicities experienced by DS children are attributable to pharmacodynamic rather than pharmacokinetic factors.[87] To balance the need to attain a threshold plasma level of MTX necessary to kill leukemic blasts and to decrease toxicity, this study employs an ID MTX in this population with earlier leucovorin rescue.

While DS children suffer excessive toxicities when receiving HD MTX 5000 mg/m^2, they do not appear to experience undue toxicity if appropriate dose modifications are employed. Buitenkamp et al[87] reviewed courses of MTX (1000 to 5000 mg/m^2) in 44 DS children and 87 non-DS controls, and found that the number of DS children requiring MTX dose reductions in second or subsequent MTX courses was only 1/27 (3.7%) for those receiving 2000 to 3000 mg/m^2, versus 3/12 (25%) for those receiving 5000 mg/m^2 (p=0.046). Current BFM studies include substantial dose modifications for DS children, with a first dose of 500 mg/m^2, followed by escalation as tolerated to 2000 mg/m^2, and finally 5000 mg/m^2 for the third course (personal communication, Martin Schrappe, MD). St. Jude Children's Research Hospital administers 500 mg/m^2 for all DS patients, with no escalation (personal communication, Mary Relling, MD). On POG 9905, DS patients received 500 mg/m^2, followed by escalation to 1000 mg/m^2 (personal communication, Naomi Winick, MD). Although outcome data have not been reported for children with DS treated with higher doses of MTX, based on the above referenced studies, it seems prudent to attempt treatment intensification in children with DS by administering ID MTX given the benefit of higher doses of MTX in all other patient subsets on AALL0232. Dosing will start at an intermediate level with earlier leucovorin rescue. This group will be closely monitored as detailed in the statistical considerations section of this study. Patients with DS HR B-ALL will receive ID MTX (2000 mg/m^2), in place of HD MTX, with leucovorin rescue beginning at hour 30 after the start of MTX infusion. If tolerated, leucovorin rescue will begin at hour 36 for subsequent courses of ID MTX.

Maintenance therapy will also be modified for children with DS HR B-ALL because deaths occurred well into Maintenance in children with DS HR B-ALL enrolled on AALL0232 and on UKALL 2003, the recently completed UK frontline ALL protocol which is very similar to AALL0232.[88] Two Maintenance deaths on AALL0232 occurred at Day 301 and Day 433 of therapy; and the 4 Maintenance deaths on UKALL2003 occurred during years 2 (n=2) and 3 (n=2) of therapy, suggesting that the key factor was the Maintenance regimen and not residual effects of the intensive therapy delivered prior to Maintenance. Administration of VCR/prednisone pulses will therefore be non-randomly reduced to every 12 weeks for all DS children during Maintenance, and the duration of therapy will be the same for both sexes, namely, 2 years from the start of IM therapy. This is similar to the BFM group which uses no VCR/steroid pulses during Maintenance and duration of therapy of boys and girls is equal. The reduction in frequency of VCR/prednisone pulses and the 1 year reduction in length of therapy for boys are instituted to attempt to decrease the risk of life-threatening complications during Maintenance. These non-random changes are justifiable in the DS population because of their substantially increased incidence of morbidity and mortality during Maintenance compared to patients without Down syndrome.

Collection of targeted data on IgG levels, infectious toxicities and febrile neutropenia on AALL1131 will identify the relevant types of infectious organisms, sites of infection, timing during ALL therapy, and the role of risk factors such as neutropenia and IgG in a large, uniformly treated DS HR B-ALL cohort. The resulting data will provide much-needed evidence for the development of improved supportive care recommendations for this subset of B-ALL patients with increased susceptibility to life-threatening infections.

2.1.7 AALL1131 as a Mechanism for Screening Ph-like, Down Syndrome, and Ph+ ALL Patients

After the HR randomization meets accrual and closes, AALL1131 will remain open as a screening protocol to identify potential Ph-like and Ph positive patients until the next NCI HR frontline trial opens. The Down syndrome and post-Induction Dasatinib arm will remain open to accrual.

Since the identification of patients with Ph-like with a predicted TKI-Sensitive Mutation (Dasatinib Arm) was only recently activated in August of 2016, AALL1131 will remain open to screen for Ph-like patients to evaluate the outcome of dasatinib therapy in this cohort (described in Section 2.1.5). Those Ph-like patients found to have a predicted ruxoltinib sensitive mutation will be eligible to enroll on AALL1521.

In addition, the Down Syndrome arm will also remain open to continue to capture data for this rare subgroup of patients being treated in a uniform matter. Considering Ph+ B-ALL patients are identified during Induction therapy on the frontline ALL trials, these patients will also continue to be identified through AALL1131, and will be eligible to enroll on AALL1631.

2.2 Significance

The COG ALL committee has developed an integrated approach to the second generation of front-line ALL clinical trials. The first generation of COG B-ALL trials was completed in 2010 and early 2011, and a second generation of COG studies are open for newly diagnosed patients with B-ALL. This series includes the classification study (AALL08B1) and studies that deliver Induction therapy to children with SR (AALL0932) and HR (AALL1131) B-ALL. At the conclusion of Induction therapy, clinical, biological, and early response data will be integrated to risk stratify patients who are eligible to participate in post-Induction trials for low or standard risk (AALL0932), high risk and very high risk (AALL1131) B-ALL.

Introduction of MRD measurements has facilitated identification of a large subset of HR B-ALL with a good early response and SR B-ALL patients with a suboptimal early response to therapy. These HR B-ALL patients enrolled in AALL1131 receive post-Induction treatment with MBFM-IMHDM and are randomized to post-Induction treatment with ITT versus IT MTX. The results of this study question will define the optimal intrathecal chemotherapy agents to use with a modern, highly effective chemotherapy backbone and should be generalizable to other subsets of childhood B-ALL patients. This trial will also determine if a shift in the pattern of relapses will occur when ITT is delivered within the context of more intensified systemic therapy.

Patients with HR B-ALL treated on AALL0232 who were MRD positive at the end of Induction had an improved 5 year disease free survival if they converted to MRD negative (< 0.01%) by the end of consolidation compared to those that remained MRD positive, 79% $\pm$ 5% vs 39% $\pm$ 7% ($p < .0001$)[89]. This trial also systematically measures MRD at 2 time points (post-Induction and post-Consolidation) in the COG Reference or COG-approved Laboratories in all VHR B-ALL patients so that the kinetics of MRD response can be compared between the different treatment arms, thereby providing data on whether MRD reduction might be a useful surrogate marker for long-term DFS in this population. These data could also be meaningful for future considerations of treatment allocation to ongoing chemotherapy vs. SCT based on the prognostic impact of persistent MRD at later time points in therapy.

Patients with Down syndrome and HR B-ALL continue to experience significant morbidity and mortality with current approaches. These toxicities resulted in the exclusion of patients with HR B-ALL and Down syndrome from the AALL0232. This study treats patients with Down syndrome on a separate stratum specifically designed to achieve an acceptable 5-year DFS > 65% and Induction mortality < 10% by modifying aspects of Induction and Maintenance therapy, while continuing to incorporate the key elements of B-ALL therapy. Induction toxicity is reduced by allowing only patients with a SER to therapy to receive daunorubicin, and even for these patients the dose is reduced to 50% of that traditionally used during a 4-drug Induction. In addition, toxicity is reduced during Interim Maintenance I by administering an intermediate dose of methotrexate (ID MTX to a maximum of 2000 mg/m^2), and toxicity is reduced in Maintenance therapy by administering the vincristine/steroid pulses every 12 weeks, instead of every 4 weeks as used on the most recent COG ALL series, and by shortening the duration of therapy by a year in boys, to match the duration of therapy in girls. These treatment modifications are specifically designed to reduce the risk of severe immunosuppression and infection, which has been the cause of increased mortality in DS patients on prior studies including AALL0232. Enhanced supportive care guidelines are also implemented to mitigate treatment-related toxicities (See Section 2.3.10).

Inclusion of DS patients on a separate stratum also makes it possible to gather clinical and biologic data to facilitate further study to improve outcomes for this biologically and clinically unique patient subgroup. Improvements in outcome for this vulnerable group require a careful balance aimed at reducing toxicity without compromising efficacy. Only a clinical trial can determine whether this balance is successfully achieved. Inclusion on this trial also facilitates further studies of the unique biology of DS HR B-ALL, which has a significant influence on outcome.[90]

Two novel genetic lesions were recently identified in DS-ALL patients: activating mutations of JAK2[91-93] and translocations or interstitial deletions that lead to over-expression of the cytokine receptor CRLF2.[94-96] Both lesions are enriched in DS HR B-ALL but also occur in up to 15% of non-DS HR B-ALL.[97, 98] Interestingly, these genetic lesions appear to have significant prognostic impact in non-DS ALL but little import in DS HR B-ALL.[99, 100] Inclusion of DS HR B-ALL patients on this trial will facilitate further understanding of the clinical and biologic impact of these novel genetic alterations.

Key toxicity data including: Grade 2 or higher (CNS hemorrhage, pancreatitis, osteonecrosis, and seizure) and Grade 3 or higher (GI bleed, encephalopathy, neuropathy, allergic reaction, ileus, mucositis/stomatitis, hyperbilirubinemia, and thrombosis), and all grades of transient ischemic attack and stroke are to be collected and linked to correlative biology studies that seek to develop biomarkers predictive of patients at risk for such events.

2.3 Relevant data

2.3.1 Results with Clofarabine/Etoposide/Cyclophosphamide in Relapsed B-ALL

This trial compares an MBFM-IMHDM regimen to experimental regimens that include a total of two 5-day cycles of either CPM + ETOP (Experimental Arm 1) or CLOF + CPM + ETOP (Experimental Arm 2) during the Consolidation and re-Consolidation phases of therapy. The rationale for combining CLOF with CPM and ETOP stems from the observation that CPM induces DNA inter-strand cross-links, which can be rapidly repaired by leukemia cells. Etoposide inhibits topoisomerase II leading to accumulation of DNA strand breaks. Clofarabine, which inhibits ribonucleotide reductase and DNA synthesis and repair, has been hypothesized to prevent or impede DNA strand break repair. In a recent study, CLOF followed by CPM was associated with increased apoptosis and DNA damage in leukemic blasts.[57]

The data from the Phase I portion of the CLO218 3-drug CLOF/CPM/ETOP study were discussed above, along with those of the Italian Phase II study of a very similar regimen (see Section 2.1.4.1). Following completion of the Phase I portion of CLO218, the dose expansion Phase II portion (clofarabine 40 mg/m^2/day, etoposide 100 mg/m^2/day and cyclophosphamide 440 mg/m^2/day) has now completed enrollment of an additional 25 patients on this dose and schedule. The median time to count recovery on the CLO218 Phase I study was 34 days (range 23-75 days), on the Phase II Italian study was 26 days (range, 18-42 days) and 28 days (range, 18-57 days) for neutrophil and platelet recovery, respectively.[58, 62] Common toxicities noted in the Phase I portion of the CLO218 study reported above included febrile neutropenia and fever.[62] One patient in Cohort 4 (clofarabine 30 mg/m^2/day, etoposide 100 mg/m^2/day and cyclophosphamide 440 mg/m^2/day) of the CLO218 study experienced a dose limiting toxicity (DLT) that resolved (Grade 3 elevation of lipase) and possible veno-occlusive disease leading to cohort expansion, during which no additional toxicities were noted.[62] When the Phase II expansion phase of the study began, 4 of the first 8 patients enrolled experienced severe hepatic toxicities including hyperbilirubinemia, transaminitis, with some symptoms consistent with SOS; 3 of these patients died as a result of their toxicities and multi-organ dysfunction.[69] During the same time frame, 2 other patients on an investigator-initiated study of clofarabine/cyclophosphamide (cyclophosphamide dose 200-300 mg/m^2/dose on a Day 0, 1, 2, 3, 8, 9, 10 schedule) also experienced hepatic toxicity in the face of significant infection and capillary leak syndrome (R. Arceci M.D, personal communication, 2010). Both of these patients died as a complication of multi-organ failure. All fatal events on these 2 studies occurred

in patients who developed significant viral, bacterial, and/or fungal infections while neutropenic and who had preceding capillary leak syndrome. All patients were very heavily pre-treated for their leukemias, and 5 of the 6 patients that experienced severe hepatic toxicities had undergone prior stem cell transplantation between 4 and 12 months prior to study entry. Because of these serious adverse events (SAE) both studies were halted and amended to exclude patients with prior stem cell transplant, and to require that patients have normal bilirubin and no concomitant hepatic infections. Of note, no toxic deaths or hepatic SOS were observed on the Italian CLOF/CPM/ETOP Phase II study, although Grade 2 (n=6) and 3 (n=6) liver toxicities (transient and reversible transaminitis and/or hyperbilirubinemia) occurred in 12 of 25 patients.[58]

Accrual subsequently re-opened to both of these studies with stringent monitoring of patients and prolonged cohort windows to assess toxicity prior to accruing further patients. There has been no further hepatic toxicity noted in 4 additional patients enrolled on the amended clofarabine/cyclophosphamide study (Personal communication, R. Arceci M.D, 2010). CLO218 re-opened to enrollment at study sites in March 2008 under Amendment #3 and 15 patients were enrolled between June 2008 and June 2009. The protocol was amended a fourth time (A4) in July 2009 with a slight broadening of laboratory criteria, reduction in total number of patients to be enrolled in the phase II trial from 33 to 25 and a reduction in duration of follow-up from 2 years to 4 months. Two additional patients were enrolled under A4 for a total of 25 patients enrolled in the Phase II study (17 of which enrolled post A3) and a total of 50 patients across the entire study (25 on the Phase I and 25 on the Phase II portions, respectively). During the Phase II portion of the study (n=25), reported toxicities included ≥ Grade 3 AST (n=12), ≥ Grade 3 ALT (n=10), ≥ Grade 3 total bilirubin (n=6), ≥ Grade 3 lipase (n=8), ≥ Grade 3 amylase (n=3), ≥ Grade 3 pancreatitis (n=1), ≥ Grade 4 infections (n=9), and SOS (n=3). The median time for ANC recovery in patients achieving CR/CRp (n=7) was 14 days (range 11-47 days). A total of 24 Grade 3, 4, 5 events occurred in 10/17 patients enrolled in A3/A4 but no cases of SOS or severe hepatotoxicity. The majority of these toxicities were Grade 3 except for 1 Grade 4 hyperbilirubinemia; 1 Grade 4 AST elevation and 1 Grade 4 lipase elevation. Eleven of the 24 events recovered without sequelae with the remaining events still ongoing at the time of death. Further analyses of safety data from the CLO218 study reveal that the proportion of patients with at least one SAE was similar pre-A3 (94%) and post-A3 (100%). Febrile neutropenia, pyrexia, and neutropenia were the most commonly reported SAEs in both populations with similar incidence rates. SAEs of typhlitis, hypoxia and SOS were only reported in the pre-A3 study population, and have not been reported post-A3. The most commonly reported related AEs in the entire population were nausea, vomiting, febrile neutropenia and pyrexia, however, these were all reported with a greater frequency in the pre-A3 study population, compared to the post-A3 population. SAEs regardless of causality that were reported more commonly post-A3 relative to pre-A3 were hypotension (n=1), septic shock (n=2), ALT/AST increase (n=2), bacteremia (n=1), thrombocytopenia (n=1), cellulitis (n=1), exophthalmos (n=1), infection (n=1), leukopenia (n=1), nervous system disorder (n=1), pneumonia fungal (n=1), pneumothorax (n=1), sinusitis fungal (n=1), and blurred vision (n=1). This difference could be explained by the relatively low number of patients recruited post-A3. With the exception of exophthalmos (1 patient), nervous system disorder (1 patient), pneumothorax (1 patient) and vision blurred (1 patient) these are all either infection related events, possible complications of infection or adverse events that are expected with clofarabine. The significance of the events occurring in only one patient is difficult to determine. The reported SAEs of exophthalmos and blurred vision occurring in the same patient were attributed to central nervous system involvement of the leukemia, and not to study drug treatment.

The overall toxicities reported during the Phase II portion of CLO218 study were greater than what was identified during the Phase I portion, which raise concerns regarding the dose of clofarabine utilized in this HR trial. As well, the responses reported during the Phase I portion of CLO218 were seen at all dose levels without a clear dose/response effect. The outcome data from the Phase II portion of CLO218 were recently reported at the 2010 American Society of Hematology (ASH) meeting. Overall, 7 patients

achieved a CR (28%) and 4 a CRp (16%) providing an overall response rate of 44%. Additionally 3 patients (12%) achieved a partial response and 10 patients including 7/11 responders proceeded to SCT.[101]

2.3.2 Pilot Data on Adding Vincristine and PEG-Asparaginase to the Clofarabine/Etoposide/Cyclophosphamide Regimen

Taken together, the CLO218 and Italian studies of nearly identical CLOF/CPM/ETOP regimens provided promising early response data in relapsed and refractory ALL. Some concern, however, existed about eliminating vincristine and asparaginase during the Consolidation and Delayed Intensification phases as this has been demonstrated to be an effective element of therapy on prior studies. Therefore a pilot study was developed to test the 3-drug CLO218 regimen plus vincristine and pegaspargase (given as administered in the hABFM backbone) for safety in a Phase I trial. In order to obtain pilot safety data for this VHR B-ALL stratum, the COG ALL committee leadership has worked with Genzyme to design this single dose level pilot study (CLO08808) of the 5-drug regimen proposed for this study to enroll up to 12 children with first BM relapse of ALL with initial remission duration of at least 6 months. This pilot study opened to patient accrual in October 2009. Patients were required to meet strict liver function entry criteria due to prior concerns of hepatotoxicity. Patients who have undergone prior SCT were excluded. Patients received up to 2 cycles of the 5-drug regimen and then went off study to receive additional Consolidation therapies according to local physician preference. As of December 2010, 8 eligible patients have enrolled with 4 DLTs reported due to prolonged time to count recovery (n=2), Grade 4 lipase (n=1) and Grade 4 hyperbilirubinemia (n=1). The study has since been suspended to further enrollment. Of note, 1 of the DLTs occurred in a patient that had failed 2 Induction regimens (not the intended study population) and the other in a 23 year-old. It is important to note that the DLTs appeared to be predominately due to the CLOF/CPM/ETOP and not to the addition of pegaspargase or VCR.

Although it is anticipated that toxicities on the current study in a newly diagnosed population would be less than in the relapsed population on the CLO08808 study, the significant toxicities that emerged warranted reconsideration of the starting dose of CLOF. Because this 5-drug regimen was not tolerated in the CLO08808 pilot study, the CLOF dosing in 5-drug regimen of Experimental Arm 2 will be reduced to 30 mg/m^2/day for 5 days in a safety run-in phase of AALL1131. The current trial will include close monitoring for toxicity in the first 100 patients enrolled (20 on the Control Arm and 40 each on Experimental Arms 1 and 2; see Section 10.4).

2.3.3 Studies of Lower Dosages of Clofarabine

Four completed adult studies suggest that lower doses of CLOF may be efficacious: CLO141, UWCM-001, BIOV-121, and CLO243. The CLO141 utilized CLOF with intermediate dose cytarabine (1 g/m^2/day) for 5 days for the treatment of relapsed/refractory leukemias. The dose escalation phase for CLOF proceeded through 15, 22.5, 30, and 40 mg/m^2/day for 5 days. Thirty-two patients, median age 59 years (range 18-84 years), were enrolled, and the diagnoses included AML (n=25), myelodysplastic syndrome (MDS) (n=4), ALL (n=2), and blast phase chronic myeloid leukemia (CML) (n=1). Overall 12/32 (37.5%) patients obtained a CR/CRp. Although 9/23 (39%) patients treated at the Phase II dose of 40 mg/m^2/day for 5 days responded, 3/9 (33.3%) patients treated at lower doses (one each at 15, 22.5, and 30 mg/m^2/day for 5 days) also responded. Neither of the patients with ALL responded.[102]

The UWMC-001, BIOV-121, and CLO243 were open to untreated older patients with AML. Two consecutive studies, UWMC-001 and BIOV-121, enrolled 106 patients, median age 71 years (range 60-84 years), with AML to receive monotherapy with CLOF initially at 30 mg/m^2/day for 5 days (n=79), and subsequently at 20 mg/m^2/day for 5 days (n=27) in an effort to decrease toxicity. CR/CRp was obtained in 51/106 (48%) patients, with 16/29 (55%) treated at 30 mg/m^2/day for 5 days and 6/11 (55%) treated at 20 mg/m^2/day for 5 days responding on the UWMC-001 and 29/66 (49%) responding on the BIOV-121. Although no statistically significant differences in hematologic, liver, or renal toxicities were seen at the 2 dosing levels on UWMC-001, there appeared to be lower grades of liver and renal toxicities in the

20 mg/m^2/day for 5 days Cohort.[103] The CLO243 enrolled 112 evaluable patients, median age 71 years (range 60-88 years), with AML to receive monotherapy with CLOF at 30 mg/m^2/day for 5 days for Cycle 1, followed by CLOF 20 mg/m^2/day for 5 days for a maximum of 5 additional cycles. CR/CRp was obtained in 51/112 (46%) patients.[104]

These studies, predominantly in patients with AML, suggest that lower doses of CLOF are efficacious. Additionally, there is limited pharmacodynamic data suggesting that cellular CLOF triphosphate levels in leukemic blasts, including samples from patients with ALL, follow a dose dependent accumulation with CLOF dosages ranging from 4 to 22.5 mg/m^2, which was less evident at dosages ≥ 30 mg/m^2.[105] These data taken together suggest that it is reasonable to dose CLOF at 30 mg/m^2/day for 5 days on the present study.

2.3.4 Experimental Arm 2 Containing Clofarabine (**Amendment #2**):

Enrollment to the post-Induction Very High Risk (VHR) arm of AALL1131 was suspended September 14th 2012 due to increased toxicities observed during Part 2 of the Consolidation phase on Experimental Arm 2, which contained clofarabine (30 mg/m^2/day x 5 days in the 2nd half of Consolidation and 2nd half of Delayed Intensification [DI] in conjunction with etoposide [100 mg/m^2/day x 5] and cyclophosphamide [440 mg/m^2/day x 5]). Protocol specific toxicities were analyzed and are included in Table 1.

Table 1. Toxicities During Consolidation Part 2

Toxicity	Control Arm (N=26)	Experimental Arm 1 (N=49)	Experimental Arm 2 (N=50)	p-value
Gr4/5 Infection	1 Gr 4	1 Gr 4	12 Gr 4 (11) Gr 5(1)	0.0017
Gr3/4 ALT,AST,BILI*	3	1	1	0.18
Gr4 amylase/lipase*	0	1	4	0.27
Gr3/4 other non-hematologic*	2	7	16	0.0228
Gr3/4 Pancreatitis	0	0	5	0.0238
Gr3/4 Capillary leak Synd.	0	0	0	NA
Gr3/4 Acute Kidney Injury	0	0	2	0.3517
Other Gr3/4 AEs	13	37	134	-----

*toxicity did not return to Gr2 or less by the time D43 vincristine and asparaginase were scheduled to be administered during Consolidation Part 2.

The toxicity rate for Experimental Arm 2 significantly exceeded the 5% rate outlined in the safety monitoring section of the protocol (Section 10.4) for Grade 4/5 infection and Grade 3/4 pancreatitis when compared to both the Control Arm and Experimental Arm 1. Experimental Arm 2 was thus determined not feasible, and a reduction in the clofarabine dose to 20 mg/m^2/day x 5 days during both Consolidation and Delayed Intensification will occur and a new safety phase will start with careful monitoring of the first 40 patients randomized to each of the Experimental Arms (Arm 2 containing clofarabine at 20 mg/m^2/day x 5 days) and 20 patients randomized to the Control Arm. Enrollment on the VHR strata will be suspended temporarily after 100 patients are enrolled (20 to Control and 40 to each of Experimental Arms 1 and 2). After all patients have completed Consolidation and entered Interim Maintenance, the data will be reviewed. If the protocol defined safety criteria are met, then the VHR strata will reopen to accrual. If these criteria are not met, then Experimental Arm 2 will be closed permanently.

Duration of Consolidation Part 2 in days were reported for each of the 3 VHR arms and listed below in Table 2. Sites were queried as to the time of blood count recovery of granulocytes and platelets for patients randomized to Experimental Arm 2. There were significant delays observed for the 36 patients reported in both granulocytes (median of 38.5 days, range 11 to 122 days) and platelets (median of 42 days, range 17 to >132 days) with 6 patients receiving myeloid growth factor support to assist their neutrophil recovery. Due to the significant rate of infectious complications and delay in starting Interim Maintenance for patients in Experimental Arm 2 compared to Experimental Arm 1, the addition of myeloid growth factor support will be used for patients in Experimental Arm 2 after completion of the 5-day course of clofarabine, cyclophosphamide and etoposide. Additional supportive care guidelines can be found in Section 8.0.

Table 2.

AALL1131 VHR Consolidation Part II (mean duration in days ±std error)		
Control Arm (N=26)	**Experimental Arm 1 (N=49)**	**Experimental Arm 2 (N=50)**
40.0±8.5	37.1±8.6	51.4±23.2

Comparison	P-value
Control Arm vs. Experimental Arm 2	0.0697
Experimental Arm 1 vs. Experimental Arm 2	0.0022

2.3.5 Experimental Arm 2 Containing Clofarabine (**Amendment #3B**):

Enrollment to the post-Induction Very High Risk (VHR) arm of AALL1131 was temporarily suspended on May 5, 2014 after accrual of the initial 100 patients for the planned safety analysis. Details of the safety analysis are included below and the toxicities analyzed are included in Table 3

In Experimental Arm 2, three of the 39 evaluable subjects treated with the reduced clofarabine dose developed Grade 4 infections and one of these subjects later developed a Grade 5 toxicity (acute kidney injury) attributed to clofarabine. Additionally, four patients had prolonged cytopenias, including the one patient resulting in the Grade 5 acute kidney injury and one requiring removal from protocol therapy. This is in contrast to both the Control Arm (n=20) and Experimental Arm 1 (no clofarabine, n=47) where no Grade 4 or 5 infections have been reported. In Experimental Arm 2, there were four patients recording a length of phase >52 days to complete Consolidation Part 2 and begin Interim Maintenance (one of whom died of the Grade 5 acute kidney injury, one of whom never recovered counts, and two who recovered counts and continued on study) versus no patients with a length of phase >52 days in either the Control Arm or Experimental Arm 1. While this phase of therapy is scheduled to be 28 days in duration, a duration of up to 42-49 days is not uncommon; however, delays >50 days are rare. All of these toxicities occurred despite an increase in supportive care measures, which were added to the study in Amendment #2 and included: 1) Required use of myeloid growth factor in all patients in Experimental Arm 2 receiving clofarabine beginning after the last dose of clofarabine was administered during Consolidation and Delayed Intensification Part 2 and continuing until neutrophil count recovery; 2) Recommended hospital inpatient stay post clofarabine administration and until neutrophil count recovery and 3) Consideration for anti-fungal prophylaxis due to the increased incidence of fungal infections prior to Amendment #2.

Table 3. Toxicities During Consolidation Part 2

Toxicity	Control Arm (N=20)	Experimental Arm 1 (N=47)	Experimental Arm 2 (N=39)	p-value
Gr4/5 Infection	0	0	3 (7.7%)	
Gr3/4 ALT,AST,Bili, Gr4 amylase/lipase	0 (0%)	5 (10.6%)	0 (0%)	

Gr3/4 other non-hematologic*	1 (5.0%)	7 (14.9%)	12 (30.8%)	
Gr3/4 Pancreatitis	0 (0%)	1 (2.1%)	1 (2.6%)	
Gr3/4 Capillary leak Synd.	0 (0%)	0 (0%)	1 (2.6%)	
Gr3/4/5 Acute Kidney Injury	0 (0%)	0 (0%)	1 (2.6%)	
Other Gr3/4 AEs	6 (30.0%)	13 (27.7%)	17 (43.6%)	

*that do not return to Gr 2 or less by day 43 vincristine and asparaginase

Based on the events occurring in Experimental Arm 2 post-Amendment #2, it was determined that safe delivery of clofarabine in Experimental Arm 2 was not feasible and this Arm was permanently closed to accrual on September 12, 2014.

2.3.6 Results with Cyclophosphamide/ Etoposide in Relapsed B-ALL

The combination of ifosfamide and etoposide has yielded a 40% complete remission (CR) rate in children with refractory ALL.[63] Further, the combination of cyclophosphamide and etoposide has been well tolerated in newly diagnosed infants with ALL (CCG 1953, POG 9407, AALL0631) and has been a standard regimen in relapse B-ALL studies (AALL01P2, AALL02P2, AALL0433, ADVL04P2, AALL07P1). However, this combination has not been previously tested in newly diagnosed, non-infant, patients with B-ALL, particularly those identified as VHR with expected 4-year DFS < 80% and who are appropriate candidates for more intensive, and potentially more toxic, therapeutic strategies designed to improve DFS.

2.3.7 Induction Deaths **(Amendment #2)**:

As of January 22, 2013, 11 of the 410 (2.7%) non-Down Syndrome subjects that have completed Induction therapy have died of toxicity. This Induction death rate is not different from the rate of approximately 2% observed on other recent COG high risk B-ALL studies such as 1961 and AALL0232. One subject died secondary to chemotherapy induced hepatic failure, 1 subject died secondary to pancreatitis, and 9 subjects died of infectious complications, resulting in an Induction mortality rate of 2.7%. In 6 of the infectious deaths, fungal organisms were identified including: *Candida krusei, Candida parapsilosis*, *Trichosporon ashaii*, *Aspergillus* spp, Mucormycosis, and *Cunninghamella* spp. The COG Cancer Control Committee independently reviewed the Induction deaths to ascertain the attribution to invasive fungal infections (IFI). Through this review, they identified 2 of the 6 initially considered associated fungal infections as proven IFI directly attributable to the patient's death. Three cases of IFI were identified as probably or possibly related to death and the final associated IFI being uncertain to the attribution to death. Three of these Induction deaths were concurrent with bacterial infections that possibly, probably or definitely were the cause of the patient's death. Thus, the Cancer Control Committee concluded that these results do not appear to be greatly different from what is expected during Induction therapy regarding infectious complications in newly diagnosed children with B-ALL. In order to closely monitor Induction mortality, this amendment will include monitoring rules for Induction death and Induction deaths associated with fungal infections.

2.3.8 Rationale for the addition of Dasatinib therapy for Non-Down Syndrome (Non-DS) B-Acute Lymphoblastic Leukemia (B-ALL) Patients with a Predicted TKI-Sensitive Mutation **(Amendment #5A)**:

Recent studies have identified a phenotype of childhood B-ALL associated with very poor outcomes, alternatively referred to as "Ph-like" or "*BCR-ABL1*-like" because of its similarity to gene expression patterns seen in patients with the t(9;22) chromosomal translocation. [106,74,73] A more extensive molecular characterization of these cases has now demonstrated a very high frequency of *IKZF1* deletions, fusions of tyrosine kinase genes, fusions of *CRLF2 or EPOR* and mutations or fusions of *JAK1* and *JAK2, IL7R and SH2B3*.[76, 77] With the advent of TKI therapy for *BCR-ABL1* childhood ALL, the prognosis for these

patients has dramatically improved.[78, 79] Given the similarities in the underlying molecular events (specifically, gene fusions involving tyrosine kinases), some Ph-like patients with imatinib or dasatinib-sensitive kinase fusions have recently been treated with TKI therapies and demonstrated excellent responses.[107, 108] At present, the menu of tyrosine kinase fusion partners who have responded well to the addition of TKIs (*in vitro* or *in vivo*) includes: *ABL1*, *ABL2*, *CSF1R*, *PDGFRB* and *FGFR*.[80] This list is expected to grow as new fusions are identified and tested. To this end, a clinically-adaptable, multi-analyte low-density array (LDA) PCR screening assay to test diagnostic material from B-ALL patients has been developed. It is both highly sensitive and specific for identifying the Ph-like gene expression signature and with further downstream molecular testing, we can identify the presence of kinase alterations in those patients who are LDA positive. A recent comprehensive molecular analysis using this LDA assay on a cohort of 801 HR B-ALL patients from COG studies P9906 and AALL0232 was recently reported.[75] Given the inferior outcome of patients who express the Ph-like gene signature, HR B-ALL patients receiving Induction therapy on AALL1131 and identified as Ph-like (LDA card positive) with a predicted TKI-sensitive mutation will be non-randomly assigned to receive post-Induction therapy with dasatinib and the MBFM-IMHDM backbone. HR B-ALL patients receiving Induction therapy on AALL1131 and identified as Ph-like (LDA card positive) *without* kinase mutations will be assigned as High Risk or Very High Risk, based on the defined risk group criteria for post-Induction therapy. (Due to the rarity of Ph-like ALL in NCI standard risk patients, children initially receiving Induction therapy on AALL0932 will not undergo routine LDA testing and will not participate on the Dasatinib Arm of AALL1131). Patients with HR B-ALL identified as Ph-like with a predicted TKI-sensitive mutation who do not consent to non-random assignment to dasatinib therapy post-Induction on the MBFM-IMHDM backbone will be removed from AALL1131 post-Induction. Patients with HR B-ALL identified as Ph-like with predicted ruxolitinib-sensitive mutations will be eligible for participation on AALL1521 when open, and if they choose not to enroll on AALL1521, will remain on AALL1131 post-Induction and will be risk stratified according to their defined risk group criteria.

During the first five months after opening the AALL1131 dasatinib arm in August 2016, accrual to this arm was found to be significantly lower than originally projected. Additional testing revealed that several novel ABL-class fusions were missed by the PCR-based screening assays initially implemented. This lower than expected detection rate catalyzed development of additional technologies to improve the sensitivity of screening procedures. Since April 2017, all low density array (LDA) positive cases requiring downstream molecular testing have had the original multiplex RT-PCR performed in parallel with a type of targeted RNA sequencing-"Archer sequencing"; positive results have been confirmed using singleplex RT-PCR with bi-directional Sanger sequencing. The ALL committee anticipates that an unbiased RNA sequencing strategy will ultimately be used to screen for underlying Ph-like genomic lesions as this technology becomes available as a clinical (CAP/CLIA) test. Please see Appendix XII for further details.

2.3.9 Rationale for additional IT therapy for Non-Down Syndrome (Non-DS) B-Acute Lymphoblastic Leukemia (B-ALL) Patients with Central Nervous System 2 (CNS2) Disease **(Amendment #5A)**:

Results of COG AALL0232 and AALL0331 for patients with non-DS B-ALL demonstrate significantly inferior outcomes for patients with CNS2 and CNS3 disease compared to those with CNS1 status. The 5-year event free survival (EFS) for patients with CNS2 versus CNS3 and CNS1 treated on AALL0232/AALL0331 were 76 $\pm$2%, 76 $\pm$5.2% and 85 $\pm$0.6%, respectively ($p<0.001$). [*Personal communication, M. Devidas*] These differences in EFS are largely the result of CNS relapse rather than bone marrow relapse. The incidence of isolated and combined CNS relapse for patients with CNS1 status on AALL0232/AALL0331 was 2.9 $\pm$0.2% versus 7.8 $\pm$0.98% for CNS2 and 5.9 $\pm$2.2% for CNS3 ($p<0.001$). Additionally, there was no significant difference in the rate of bone marrow relapse based on CNS status (CNS1 versus CNS2/3; $p=0.1815$). No difference in EFS was seen between patients with CNS2 due to a traumatic lumbar puncture (TLP) versus CNS2 without a TLP ($p=0.333$). In multivariate

analysis comparing CNS1 to CNS2/CNS3, CNS status remained significant (HR 1.501, 95% CI 1.21 – 1.86; p=0.0002). When analyzing the NCI standard risk (SR) and high risk (HR) patients separately, CNS2/3 disease continued to predict worse outcome for both risk groups. SR patients with CNS1 status on AALL0331 had a 5-year EFS of 90 ±0.6% compared to 85 ±2% for CNS2 and 82 ±7% for CNS3 (p=0.0003) and HR patients on AALL0232 with CNS1 status had 5-year EFS of 77 ±1% compared to 67 ±3% for CNS2 and 71 ±7% for CNS3 (p<0.0001).

Systemic and intrathecal therapy for HR non-DS B-ALL patients with CNS1 or CNS2 on COG study AALL0232 was identical. Only patients with CNS3 disease received more intensive CNS-directed therapy during Induction with weekly intrathecal (IT) methotrexate on days 8, 15, 22 and 29 compared to patients with CNS1/2 who received IT methotrexate only on days 8 and 29. Patients with CNS3 disease did not receive IT therapy on days 15 and 22 of Consolidation but did receive cranial radiation (1800 cGy) during Delayed Intensification. The legacy POG protocols gave additional IT therapy to patients with CNS2 disease, legacy CCG protocols did not, with both demonstrating a modest increase in risk associated with CNS2 disease. The Dana Farber Cancer Institute ALL study DFCI 00-01 gives twice weekly IT cytarabine until the cerebral spinal fluid (CSF) clears for three consecutive lumbar punctures during Induction and the Berlin-Frankfurt-Munster (BFM) group includes two additional doses of IT methotrexate during Induction for CNS2/3 patients. It should be noted, however, that the BFM protocols use less overall IT therapy than the COG protocols. St. Jude Children's Research Hospital gives IT cytarabine day 1 (as does COG for all ALL patients) followed by twice weekly Intrathecal Triple Therapy (ITT) (cytarabine, hydrocortisone, methotrexate) in patients with CNS2/3 disease until the CSF is clear of blasts. When comparing outcomes at 5-years for patients with CNS2 disease enrolled on AALL0232 receiving HDMTX during Interim Maintenance 1 to those receiving Capizzi MTX there was no difference in event-free survival (66.7% vs. 67.4%, p=0.88) or overall survival (80.2% vs. 81.2%, p=0.98).

Given the recent finding that HR B-ALL patients with CNS2 disease have significantly inferior outcomes (< 70% 5-year EFS) compared to patients with CNS1 status, and the available safety data on the use of more frequent intrathecal therapy during Induction, we are proposing a modification in Induction on AALL1131 for patients with CNS2 disease such that they will receive twice weekly intrathecal therapy during Induction until 3 consecutive CSF samples after diagnosis are clear of blasts. Patients should receive additional IT Cytarabine on Day 4, 5 or 6 during Induction (depending on treatment schedule), IT Methotrexate on day 8, and then IT Cytarabine on day 11 or12. If the CSF at all three of these time points is negative for blasts, patients will receive their next IT therapy with methotrexate on Day 29. If the CSF remains positive after the initial LP, patients will continue IT Cytarabine twice weekly during Induction until the CSF is clear for three consecutive LPs. All patients will receive IT therapy with methotrexate on Day 29 at the end of Induction regardless of CSF evaluations.

2.3.10 Rational for Enhanced Supportive Care Guidelines for Patients with DS HR B-ALL **(Amendment #5A):**

Children with DS and B-ALL have historically experienced excessive treatment-related mortality (TRM), primarily from infection. An interim analysis on TRM in children with DS and newly diagnosed B-ALL enrolled on Children's Oncology Group (COG) trials for NCI standard risk (SR) (AALL0932) and high risk (HR) B-ALL (AALL1131) demonstrated that TRM continues to be higher on the current trials for patients with DS-ALL compared to non-DS patients.

As of 06/30/2015, 203 SR DS-ALL patients had completed Induction on AALL0932 with 146 receiving post-Induction treatment on AALL0932. Eighty-eight HR DS patients had completed Induction on AALL1131, with 80 receiving post-Induction treatment on AALL1131. An additional 26 SR DS patients with poor early response received post-Induction therapy on AALL1131. TRM on AALL0932 occurred

during Induction in 2/203 (1.0%) and post-Induction in 3/146 (2.1%), compared to 17/5528 (0.3%) and 12/3119 (0.4%) in non-DS SR patients (Fisher exact p=0.14 for Induction and p=0.03 for post-Induction). TRM on AALL1131 occurred during Induction in 4/88 (4.5%) and post-Induction in 5/106 (4.7%), compared to 34/2116 (1.6%) and 13/1258 (1.0%) in non-DS AALL1131 patients (p=0.06 for Induction and p=0.01 for post-Induction). Gram-negative organisms accounted for the majority of fatal bacterial infections in patients with HR DS-ALL.

Most of the toxic deaths occurred during intensive treatment phases due to infection in the context of profound neutropenia. Patients with HR B-ALL had a higher incidence of toxic death, notably in patients over 15 years of age. Based on this interim analysis, hospitalization and antimicrobial prophylaxis during intensive treatment phases may be considered in children with DS-ALL due to their increased risk of infection-related mortality.[109]

2.3.11 Rationale for the closure of the Very High Risk Randomization (**Amendment #6**)
With Amendment #6 the VHR randomization was closed. Planned interim analyses completed in spring 2017, showed that the interim monitoring boundary for futility was crossed [Hazard Ratio 0.606 (95% CI: 0.297 - 1.237)] concluding that the study would not be able to demonstrate that the VHR Experimental Arm 1 is superior to the Control Arm (see Section 10.4).

2.3.12 Eligible for future AALL1721 Study (**Amendment #6**)
NCI HR Patients with ALL and EOI MRD $\geq$ 0.01% continue to have a poor outcome, and those patients with EOC MRD $\geq$ 0.01% have survival rates < 50%. AALL1721, a Phase 2 study of CTL019, is expected to open in the first quarter of 2018. Eligibility for this study will include newly diagnosed NCI HR and Down syndrome HR patients with ALL who are not induction failures but have EOI MRD > 0.01% and EOC MRD $\geq$ 0.01%. Identification of these patients will be critical for enrollment on AALL1721. Treatment of NCI HR patients who have EOI MRD $\geq$ 0.01% (but do not have primary induction failure or hypodiploidy), will continue on AALL1131 Control Arm until the EOC MRD sample has been collected and processed. All VHR patients will go off protocol therapy after their EOC bone marrow is obtained on study.

2.3.13 Rationale for the closure of the High Risk Randomization (**Amendment #7A**)
A primary endpoint of this study is to determine if the administration of post-induction age adjusted ITT on an MBFM-IMHDM backbone will improve 5-year disease free survival (DFS) of children with HR B-ALL compared to age adjusted IT MTX. Interim monitoring revealed that a futility boundary was crossed, concluding the inability to show the superioiruty of the ITT regimen compared to IT methotrexate (see Section 10.4 for additional information). With Amendment #7A the HR experimental Arm B has been revised to prescribe single IT methotrexate therapy in place of ITTs. As outlined and approved with Amendment #6, the Down syndrome and dasatinib arms will remain open and additional changes have been made to implement AALL1131 as a screening protocol for HR Ph-like and Ph+ ALL patients until the next NCI HR frontline trial opens.

2.4 Correlative Studies

2.4.1 Minimal Residual Disease Determination at Serial Time Points during Therapy
Studies of MRD will be performed at the designated COG reference laboratories following completion of Consolidation therapy for subjects enrolled in the VHR B-ALL stratum of post-Induction therapy. The hypothesis is that the persistence of MRD following completion of Consolidation therapy will correlate with inferior DFS. We further hypothesize that the level of end-Consolidation MRD positivity will be reduced in one or both of the Experimental Arms as compared to the Control Arm.

Bone marrow MRD levels will be obtained at the start of Interim Maintenance I, when a required bone marrow aspirate to assess morphologic remission is obtained. These results will be made available to clinicians via remote data entry (RDE).

2.4.2 Host Polymorphisms

The emerging characterization of polymorphisms in genes encoding proteins involved in carcinogen and drug disposition and effects will potentially provide important insight into genetic susceptibility to childhood leukemia, toxicities experienced from therapy, and treatment outcome. Even though analysis of the genetic makeup of individuals reveals a remarkable similarity (>99%) within the human genome, subtle differences do exist which can lead to diversity in the risk of acquiring a particular disease and response to therapy, as measured either by toxicity or treatment failure. Such toxicities include, but are not limited to: Grade 2 or higher (CNS hemorrhage, pancreatitis, osteonecrosis, and seizures), Grade 3 or higher (GI bleed, encephalopathy, neuropathy, allergic reaction, ileus, mucositis/stomatitis, hyperbilirubinemia, and thrombosis) and all grades (transient ischemic attacks, strokes).

Approximately 60,000 single nucleotide polymorphisms (SNPs) exist in the coding regions of genes and these can result in proteins with altered function or stability. SNPs in promoter and intronic regions can also influence the expression of a particular gene product, and non-SNP polymorphisms are also common. Host polymorphisms in genes encoding enzymes, which function in drug detoxifying pathways (e.g. thiopurine methyltransferases, glutathione transferases, cytochrome P450 enzymes), DNA repair, DNA synthesis, and receptors have been hypothesized to influence host susceptibility to the development of malignancies, as well as affect drug response.[110-113] Specimens at the end of Induction will be collected from patients enrolled on this study via AALL08B1 (or APEC14B1 (*if available for ALL patients*) and banked. These specimens are available for use through the COG ALL Cell bank.

2.4.3 Incidence and Natural History of Osteonecrosis.

Please see Section 15.0 for details. Closed to accrual effective July 2016.

2.4.4 Longitudinal, Computerized Assessment of Neurocognitive Functioning.

Please see Section 16.0 for details

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

NOTE: if dasatinib is unavailable at your site, subjects are not eligible to enroll onto the post-Induction Ph-like with Predicted TKI-Sensitive Mutation (dasatinib arm) and will be removed from protocol therapy.

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via Patient Registry module in OPEN 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. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

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

Please see Appendix VII for detailed CTEP Registration Procedures for Investigators and Associates.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

IRB/REB approval documents may be submitted via the online portal via www.ctsu.org in the member's section, under the Regulatory Submission Portal where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org . For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

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. **IN ORDER TO ENROLL ONTO AALL1131: PATIENTS MUST EITHER:**

- **HAVE NCI HIGH RISK B-ALL AND BE ENROLLED IN COG APEC14B1 AND CONSENTED TO ELIGIBILITY SCREENING ON THE PART A CONSENT FORM. PATIENTS THAT BEGIN PROTOCOL THERAPY ON THIS STUDY (AALL1131) PRIOR TO ENROLLMENT ON AALL08B1 (OR APEC14B1) ARE INELIGIBLE**

Eligible patients on study will be asked to participate in the *Longitudinal, Computerized Assessment of Neurocognitive Functioning* (Neurocognitive study) ancillary studies as an **option** and not a requirement. Eligible patients will be consented for the simultaneous participation in the Neurocognitive study at the same time they are approached for consent to the post-Induction portion of the therapeutic trial.

3.1.4 Timing

Informed consent: Except for administration of intrathecal cytarabine or allowable steroid pretreatment (defined in Section 3.3), *informed consent/parental permission* MUST be signed before protocol therapy begins.

Study enrollment: Study enrollment (completion of forms in RDE) must take place no later than five (5) calendar days after beginning protocol therapy. If study enrollment takes place *before* starting protocol 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 below, 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 pretreatment as outlined below, must begin within 72 hours of the first dose of intrathecal chemotherapy.

3.1.5 Staged Consent

Informed consent for non Down syndrome patients will be in 2 stages. Informed consent that describes the first 4 weeks of Induction therapy will be obtained for all non Down syndrome patients before starting treatment. All non Down syndrome patients will receive a 4-drug Induction regimen that includes either dexamethasone for 14 days (for patients aged < 10 years) or prednisone for 28 days (for patients aged ≥ 10 years). At the end of Induction, after patients have been stratified into risk subgroups, a second informed consent that describes post-Induction therapy will be discussed with patients and their families. There are separate post-Induction consents for children with HR B-ALL and VHR B-ALL. Effective March 19, 2018 the HR randomization closed. Patients who meet criteria for HR randomization should not be approached for post-induction therapy on AALL1131. Patients in the VHR B-ALL subset with MRD ≥ 0.01% (excluding those with primary induction failure or hypodiploidy) will be approached with a post-Induction consent prior to beginning Consolidation therapy that describes VHR standard Consolidation therapy. Effective Amendment #6, EOI MRD negative NCI HR patients will go off-protocol therapy and should proceed to receive standard of care therapy. SR B-ALL patients on AALL0932 who meet criteria for HR B-ALL post-Induction are not eligible to continue on AALL0932, and due to the closure of the HR randomization, should not be approached for post-induction therapy on AALL1131. HR B-ALL patients receiving Induction therapy and randomization for the HR subgroup on AALL1131 and identified as Ph-like (LDA card positive) and subsequently confirmed to have a predicted

TKI sensitive mutation, will be approached with a post-Induction consent prior to beginning Consolidation therapy that describes a non-randomized regimen with dasatinib added to the MBFM-IMHDM backbone (Dasatinib Arm) of AALL1131. Patients who are identified to have a genetic lesion predicted to respond to ruxolitinib will be eligible for participation on AALL1521 when open at their institution or the successor trial, if applicable. The post-Induction informed consents for eligible non Down syndrome HR B-ALL patients will include the option of enrolling on the *Longitudinal, Computerized Assessment of Neurocognitive Functioning* ancillary studies.

Children with DS HR B-ALL will be presented with a single informed consent that describes their entire therapy on study at enrollment. DS SR B-ALL patients on AALL0932 who meet criteria for DS HR B-ALL post-Induction and, are not eligible to continue on that study will also be approached with a post-Induction consent prior to beginning Consolidation therapy, to continue post-Induction therapy on this study (AALL1131).

Summary of Required Consents for AALL1131

	Time Point for Obtaining Consent	Population for Consent*
Induction Consent	Prior to the start of Induction	• All HR- and VHR B-ALL without Down syndrome.
Post-Induction Consent	Prior to the start of Consolidation	• VHR B-ALL without Down syndrome (non-randomized)
		• Ph-like with predicted TKI-sensitive mutation without Down syndrome (non-randomized)
Informed consent	Prior to the start of Induction	• DS HR B-ALL (non-randomized)
Informed consent	Prior to the start of Consolidation	• DS HR B-ALL completing Induction therapy on AALL0932^ (non-randomized)
Neurocognitive study	Prior to the start of Consolidation (embedded in post-Induction consent)	• All HR- B-ALL without Down syndrome 6 - > 13 years old at time of ALL diagnosis.

** Each of these groups will sign a separate consent at the designated time points*
^Please note that DS SR B-ALL patients on AALL0932 who meet the criteria for DS HR B-ALL post-Induction are eligible to continue therapy on AALL1131 prior to the start of Consolidation.

3.1.6 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study. To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.1.7 Randomization

Randomizations for all non Down syndrome patients will take place after completion of Induction therapy and risk assignment, and prior to the beginning of Consolidation therapy via RDE. Randomization for all HR and VHR are closed effective March 19, 2018 and Frebruary 15, 2017, respectively.

3.1.7.1 HR B-ALL Patients

Randomization for post-Induction therapy for patients with HR B-ALL is closed effective March 19, 2018.

3.1.7.2 VHR B-ALL Patients

Effective Amendment #6, NCI HR patients completing Induction therapy who are **MRD positive**, excluding **hypodiploidy and induction failures,** will receive non-randomized Consolidation therapy (VHR Control arm) after risk assignment. Treatment assignment for these patients is accomplished by

going to the Callback application in the RDE system prior to the planned start of consolidation therapy. See experimental design.

NCI HR patients who otherwise meet criteria for the VHR arm and are EOI **MRD negative, induction failure, or hypodiploidy** will go off-protocol therapy at EOI and should proceed to receive standard of care therapy.

3.1.7.3 DS HR B-ALL Patients
Patients with DS HR B-ALL will receive non-randomized Induction and post-Induction treatment, after risk assignment. Treatment assignment for these patients is accomplished by going to the Callback application in the RDE system at enrollment onto study. See experimental design schema.

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy 7.12). 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

Patients must be enrolled on APEC14B1 and consented to Eligibility Screening on the Part A consent form prior to enrollment on AALL1131.

3.2.2 Age

Patients must be > 365 days and < 31 years of age

3.2.3 White Blood Cell Count (WBC) Criteria

- Age 1-9.99 years: WBC ≥ 50 000/μL
- Age 10-30.99 years: Any WBC
- Age 1-30.99 years: Any WBC with:
    a) Testicular leukemia
    b) CNS leukemia (CNS3)
    c) Steroid pretreatment (see Section 3.3)

3.2.4 Diagnosis

Patients must have newly diagnosed B lymphoblastic leukemia (2008 WHO classification) (also termed B-precursor acute lymphoblastic leukemia). Patients with Down syndrome are also eligible.

See the next page for organ function reuires for patients with Ph-like ALL and a predicted TKI-sensitive mutation.

3.2.5 Organ Function Requirements for Patients with Ph-like ALL and a Predicted TKI-Sensitive Mutation

Patients identified as Ph-like with a TKI-sensitive kinase mutation must have assessment of organ function performed within 3 days of study entry onto the dasatinib arm of AALL1131.

To be eligible for the Dasatinib Arm (For patients who are Ph-like with a predicted TKI-sensitive mutation), patients must have:

3.2.5.1 Adequate Renal Function Defined As

- Creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 years < 6 years	0.8	0.8
6 to < 10 years	1.0	1.0
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
> 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.[114]

3.2.5.2 Adequate Liver Function Defined As

- Direct bilirubin ≤3 x upper limit of normal (ULN) for age, and
- SGPT (ALT) ≤10x upper limit of normal (ULN) for age.

3.2.5.3 Adequate Cardiac Function** Defined As

- Shortening fraction ≥27% by echocardiogram, or - Ejection fraction ≥ 50% by gated radionuclide study.

  **** Patients must have an EKG fewer than 6 days prior to enrollment on the dasatinib arm.** Patients who have had cardiac assessments by echocardiogram or radionuclide scan at the beginning of Induction do not need to have these repeated prior to study entry.-QTc < 450 msec on baseline electrocardiogram as measured by the Frederica or Bazett formula
- No major conduction abnormality (unless a cardiac pacemaker is present)

3.2.5.4 Adequate Pulmonary Function Defined As

- No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% at sea level if there is clinical indication for determination.

3.2.5.5 Central Nervous System Function Defined As

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled. However, drugs that induce CYP3A4/5 (carbamazepine, oxcarbazepine, phenytoin, primidone, phenobarbital) should be avoided.

EXCLUSION CRITERIA

3.2.6 Prior Therapy

With the exception of steroid pretreatment (defined in Section 3.3) or the administration of intrathecal cytarabine, patients must not have received any prior cytotoxic chemotherapy for either the current

diagnosis of B-ALL or any cancer diagnosed prior to the initiation of protocol therapy on AALL1131. Patients cannot have secondary B-ALL that developed after treatment of a prior malignancy with cytotoxic chemotherapy.

Patients receiving prior steroid therapy may be eligible for AALL1131 as defined below (Section 3.3).

3.2.7 Post Induction

3.2.7.1
Patients with *BCR-ABL1* fusion are not eligible for post-Induction therapy on this study but may be eligible to enroll in a successor COG Ph+ ALL trial by Day 15 Induction.

3.2.7.2
DS HR B-ALL patients with Induction failure or *BCR-ABL1*

3.2.8
Female patients who are pregnant are ineligible since fetal toxicities and teratogenic effects have been noted for several of the study drugs.

3.2.9
Lactating females are not eligible unless they have agreed not to breastfeed their infant.

3.2.10
Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

3.2.11
Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation.

3.2.12
Eligibility criteria for the *Longitudinal, Computerized Assessment of Neurocognitive Functioning* study

- Patients must be aged 6 to 13 years at time of B-ALL diagnosis, enrolled on AALL1131
- Patients must be English-, French- or Spanish-speaking (languages in which the assessment is available)
- Patients must have no known history of neurodevelopmental disorder prior to diagnosis of B-ALL (e.g., Down syndrome, Fragile X, William's Syndrome, mental retardation)
- Patients must have no significant visual impairment that would prevent computer use and recognition of the visual test stimuli

3.2.13
Eligibility criteria for the NCI standard risk patients from AALL0932 enrolling on this study at the end of Induction.

3.2.14.1
Effective March 19, 2018, patients enrolled on AALL0932, without Down syndrome, meeting the following criteria will NOT be eligible to continue on AALL0932 or the **HR B-ALL stratum** of this study at the end of Induction:

a) Without favorable cytogenetics (no *ETV6-RUNX1* or double trisomies 4+10), with Day 8 PB MRD ≥ 1% and Day 29 BM MRD < 0.01%.
b) With favorable cytogenetics (*ETV6-RUNX1* or double trisomies 4+10), with any Day 8 PB MRD and Day 29 BM MRD ≥ 0.01%.

Both NCI SR and HR patients without Down syndrome and with testicular disease at diagnosis, who do not meet other VHR criteria.

3.2.14.2
Effective Amendment 6, patients enrolled on AALL0932, without Down syndrome, meeting the following criteria will NOT be eligible to continue on AALL0932 or the VHR stratum of AALL1131.

a) iAMP21
b) *MLL* rearrangement
c) Hypodiploidy (n< 44 chromosomes and/or a DNA index < 0.81)
d) Induction Failure (M3 BM at Day 29)
e) Without favorable cytogenetics (no *ETV6-RUNX1* or double trisomies 4+10), with Day 29 BM MRD ≥ 0.01%

3.2.14.3
Patients enrolled on AALL0932, with Down syndrome, meeting the following criteria will NOT be eligible to continue on AALL0932 but WILL BE eligible to enroll on the **DS HR B-ALL stratum** of this study at the end of Induction:

a) Day 29 MRD ≥ 0.01%
b) *MLL* rearrangement
c) Hypodiploidy (n< 45 chromosomes and/or DNA index < 0.81)

DS HR B-ALL patients initially enrolled on AALL0932 or this study who have Induction Failure (M3 BM Day 29) or Philadelphia chromosome (*BCR-ABL1*) will not be eligible for post-Induction therapy on either trial (AALL0932 or AALL1131).

REGULATORY REQUIREMENTS

3.2.15
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.16
All institutional, FDA, and NCI requirements for human studies must be met.

3.3 **Definitions**

INITIAL WBC: The first WBC at the treating COG institution, or the WBC prior to intravenous fluids, whichever occurred first. If prior therapy (i.e. steroids) has been administered and a CBC is available that was obtained within 72 hrs prior to steroid therapy, then this pre-steroid WBC 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.

STEROID PRETREATMENT:

1. For patients older than 10 years of age: the use of steroids prior to diagnosis will not affect their Induction therapy. Patients must meet all eligibility criteria (including an M3 bone marrow at diagnosis, or peripheral count of at least 1000/μL leukemic blasts for patients in whom there is a medical contraindication to a bone marrow aspirate). Post-Induction risk-assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29.

2. For patients younger than 10 years of age: If steroids are given for more than 24 hours in the 2 weeks prior to diagnosis and a CBC is obtained within 3 days prior to initiation of the steroid, the patient will be assigned to Induction based on NCI risk group using the pre-steroid WBC. Post-Induction risk assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29, except that SR patients in this group will not be eligible for the LR arm of the standard risk trial, AALL0932. If there is no pre-steroid CBC obtained, the patient will be assigned to receive HR Induction therapy on AALL1131. These patients are not eligible for AALL0932 but may be eligible for AALL1131. If steroids are given for less than 24 hours in the 2 weeks prior to diagnosis, Induction risk group will be based on NCI risk group using the initial WBC and patients will not be eligible for the LR arm.

3. For patients younger than 10 years of age: Any amount of steroid pretreatment at any time prior to 2 weeks before diagnosis will not affect initial Induction assignment as long as the patient meets all other eligibility criteria including the presence of an M3 marrow at diagnosis. The presenting WBC at the time of diagnosis will be used to assign the patient to SR or HR Induction therapy. Post-Induction risk assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29. SR patients in this group may be eligible for the LR arm of the SR B-ALL trial only if they did not receive steroids within the month prior to diagnosis.

4. Inhalational steroids and topical steroids are not considered as pretreatment.

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 < 5/μL WBCs and cytospin positive for blasts, or traumatic LP, ≥ 5/μL WBCs, cytospin positive for blasts, but negative by 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, after traumatic LP presence of ≥ 5/μL WBCs and cytospin positive for blasts and/or clinical signs of CNS leukemia:

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

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

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

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

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

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

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

BONE MARROW MRD STATUS (Day 29):
Positive: ≥ 0.01% detectable leukemia cells
Negative: < 0.01% detectable leukemia cells

UNFAVORABLE CHARACTERISTICS:
1) iAMP21 as identified by fluorescence in-situ hybridization (FISH).
2) *MLL* rearrangements as identified by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies.
3) HYPODIPLOIDY: Fewer than 44 chromosomes and/or DNA index < 0.81, or other clear evidence of a hypodiploid clone.
4) INDUCTION FAILURE: M3 BM on Day 29.
5) PHILADELPHIA CHROMOSOME LIKE (Ph-Like) ALL

Ph-like positive patients with a predicted TKI-Sensitive Mutation identified by Low Density Array (LDA) PCR and downstream molecular testing.

Patients enrolled on AALL1131 who are found to have Ph-Like ALL with *CRLF2*, *JAK1/2*, or other *JAK* pathway mutations (e.g., *EPOR* fusions, *SH2B3* deletions, *IL7RA* mutations), are eligible for a separate trial investigating the JAK inhibitor ruxolitinib (AALL1521). Patients who consent to AALL1521,will be

removed from AALL1131 post-Induction. Patients eligible for the AALL1521 study who decide to remain on AALL1131 will be considered HR or VHR based on their defined risk group criteria and may be eligible to participate in the relevant randomization questions post-Induction on AALL1131.

6) PHILADELPHIA CHROMOSOME POSITIVE (Ph+) ALL

   a) *BCR-ABL1* (formerly known as *BCR-ABL*) fusion determined by FISH or *BCR-ABL1* transcript detected via RT-PCR.
   b) t(9;22)(q34;q11) determined by cytogenetics

Patients enrolled on AALL1131 who are later found to have Ph+ ALL and meet eligibility criteria for the AALL1631 should be immediately taken off protocol therapy prior to Day 15 of Induction therapy if eligible to transfer to AALL1631. Otherwise, Ph+ ALL patients may continue on AALL1131 until the end of Induction therapy.

RELAPSE:
Any recurrence of disease whether in marrow or extramedullary. Relapse should be biopsy confirmed.

1) ISOLATED BONE MARROW RELAPSE:
   Patients with an M3 marrow at any point after achieving remission without involvement of the CNS and/or testicles.

2) COMBINED RELAPSE:
   M2 or M3 marrow at any point after achieving remission with concomitant CNS and/or testicular relapse.

3) CNS RELAPSE:
   Positive cytomorphology and WBC ≥ 5/μL OR clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome. If any CSF evaluation shows positive cytomorphology and WBC < 5/μL, a second CSF evaluation is required within 2-4 weeks. While identification of a leukemic clone in CSF by flow cytometry (TdT, CD19, CD10, etc) or FISH for diagnostic karyotypic abnormality may be useful, definitive evidence of CNS involvement (i.e. WBC ≥ 5/μL OR clinical signs of CNS leukemia) is required for the diagnosis of a CNS relapse.

4) TESTICULAR RELAPSE:
   Must be documented by testicular biopsy, if not associated with a marrow relapse.

DISEASE EVALUATION DURING FOLLOW-UP:
A disease evaluation is a procedure ordered with the intent to measure or assess the disease status of a patient. The most common evaluations are a bone marrow aspirate and/or biopsy and a lumbar puncture (LP). If a CBC has findings that raise suspicion for relapse, a bone marrow aspirate must be performed to confirm the relapse.

POST INDUCTION RISK GROUPS

HIGH RISK B-ALL (HR B-ALL) CRITERIA:
Effctive March 19, 2018, the following patients are not eligible to continue on AALL1131 for HR B-ALL post-induction therapy.

Patients with NCI HR B-ALL enrolled on this trial, without Down syndrome, who do not meet criteria for VHR stratum (see below). These will include patients with:

a) Age < 13 years at initial diagnosis with Day 29 BM MRD < 0.01% (unless other VHR features are present)

Patients enrolled on AALL0932, without Down syndrome, meeting the following criteria will NOT be eligible to continue on AALL0932 but WILL BE eligible to enroll on the HR B-ALL stratum of this study at the end of Induction:

a) Without favorable cytogenetics (no *ETV6-RUNX1* or double trisomies 4+10), with Day 8 PB MRD ≥ 1% and Day 29 BM MRD < 0.01%.

b) With favorable cytogenetics (*ETV6-RUNX1* or double trisomies 4+10), with any Day 8 PB MRD and Day 29 BM MRD ≥ 0.01%.

Both NCI SR and HR patients without Down syndrome and with testicular disease at diagnosis, who do not meet other VHR criteria.

Patients completing Induction therapy on AALL1131 with a predicted TKI-sensitive mutation will NOT be eligible to enroll on the HR B-ALL stratum.

VERY HIGH RISK B-ALL (VHR B-ALL) CRITERIA:

Patients with NCI HR-ALL enrolled on this trial, without Down syndrome, are classified as VHR B-ALL at end Induction if they have:

a) Age ≥ 13 years at diagnosis, regardless of other prognostic indicators

b) CNS3 leukemia at diagnosis

c) Day 29 BM MRD ≥ 0.01%

d) iAMP21

e) *MLL* rearrangement

f) Hypodiploidy (n< 44 chromosomes and/or a DNA index < 0.81)

g) Induction failure (M3 BM at Day 29)

Patients with NCI SR B-ALL, without Down syndrome, and CNS3 at diagnosis will be classified as VHR B-ALL at the end of Induction on this trial.

Patients enrolled on AALL0932, without Down syndrome, meeting the following criteria will NOT be eligible to continue on AALL0932 but WILL BE classified as VHR B-ALL at the end of Induction:

a) iAMP21

b) *MLL* rearrangement

c) Hypodiploidy (n< 44 chromosomes and/or a DNA index < 0.81)

d) Induction Failure (M3 BM at Day 29)

e) Without favorable cytogenetics (no *ETV6-RUNX1* or double trisomies 4+10), with Day 29 BM MRD ≥ 0.01%.

Patients completing Induction therapy on AALL1131 with a predicted TKI-sensitive mutation will NOT be eligible to enroll on the VHR B-ALL stratum.

Effective Amendment #6:

Patients with NCI HR-ALL enrolled on this trial, with or without Down syndrome, will be eligible to enroll on the VHR B-ALL stratum of this trial at end Induction if they have:

a) Day 29 BM MRD ≥ 0.01% without unfavorable features

b) Day 29 BM MRD ≥ 0.01% with iAMP21

c) Day 29 BM MRD ≥ 0.01% with *KMT2A* (*MLL)* rearrangement

d) Day 29 BM MRD ≥ 0.01% with *CNS3*

Patients completing Induction therapy on AALL1131 who are NOT EOI MRD positive will NOT be eligible to enroll on the VHR B-ALL stratum. Patients with induction failure or hypodiploidy will NOT be eligible to enroll on the VHR B-ALL stratum.

DASATINIB ARM CRITERIA:
Patients with NCI HR-ALL enrolled on this trial, without Down syndrome, will be eligible to enroll on the Dasatinib stratum of this trial at end Induction if they have:

a) Ph-like B-ALL (LDA positive) with a predicted TKI-sensitive mutation

Patients will receive non-randomized post-Induction treatment on the Dasatinib Arm after risk assignment. Treatment assignment for these patients is accomplished by going to the Callback application in the RDE system after the risk assignment has been completed.

NOTE: if dasatinib is unavailable at your site, subjects are not eligible to enroll onto the post-Induction Ph-like with Predicted TKI-Sensitive Mutation (dasatinib arm) and will be removed from protocol therapy.

DOWN SYNDROME HIGH RISK B-ALL (DS HR B-ALL) CRITERIA:
Patients enrolled on this trial, with NCI HR B-ALL and Down syndrome, are eligible to continue on the DS HR B-ALL stratum at end Induction regardless of features other than Induction Failure (M3 BM Day 29) or Philadelphia chromosome (*BCR-ABL1*) which will not be eligible for post-Induction therapy on AALL1131.

Patients enrolled on AALL0932, with Down syndrome, meeting the following criteria will NOT be eligible to continue on AALL0932 but WILL BE eligible to enroll on the DS HR B-ALL stratum this study at the end of Induction:

a) Day 29 MRD ≥ 0.01%

b) *MLL* rearrangement

c) Hypodiploidy (n< 44 chromosomes and/or DNA index < 0.81)

DS HR B-ALL patients initially enrolled on AALL0932 or this study who have Induction Failure (M3 BM Day 29) or Philadelphia chromosome (*BCR-ABL1*) will not be eligible for post-Induction therapy on either trial (AALL0932 or AALL1131).

For an overview of the classification system for B-ALL, see AALL08B1 or APEC14B1 (*if available for ALL patients)*.

4.0 TREATMENT PLAN

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

4.1 Overview of Treatment plan

At diagnosis, all patients will initially enroll on the AALL08B1 classification study or APEC14B1 **(***if available for ALL patients***)** and either the COG standard (AALL0932) or high-risk (AALL1131) B-ALL trials, on which they will receive a conventional 3- or 4-drug Induction according to NCI-risk group. At the end of a conventional 4-drug Induction on AALL1131, patients will be risk classified based on age, CNS or testicular disease status, sentinel cytogenetic lesions, and MRD response (see Section 3.3 for details) as High Risk (HR) or Very High Risk (VHR) for post-Induction therapy.

Down syndrome patients will be stratified separately at enrollment and will receive separate Induction and post-Induction therapy as detailed below (see Section 4.1.2).

Informed consent describing the first 4 weeks of Induction therapy is required for all non Down syndrome patients. At the end of Induction, after risk stratification, a second consent that describes post-Induction therapy must be obtained prior to the start of Consolidation. There will be separate post-Induction consents for the different risk groups eligible for this study. Effective March 19, 2018 the option t for HR B-ALL patients to consent for post-Induction therapy closed. Patients who are eligible for randomization on the HR arm should go off protocol therapy. With Amendment #6, the post-Induction consent for the VHR B-ALL patients will include only Consolidation therapy given on the Control Arm. The post-Induction consents for Ph-like B-ALL patients with a predicted TKI-sensitive mutation will include non-randomized assignment to dasatinib treatment and standard MBFM-IMHDM therapy (Dasatinib Arm) on AALL1131.

Effective March 19, 2018 all non Down SR B-ALL patients on AALL0932 who meet the criteria for HR B-ALL post-Induction should be removed from protocol therapy at the end of induction. NCI SR patients enrolled on AALL0932 who meet criteria for the VHR arm are not eligible to enroll on post-Induction therapy. These patients should continue to receive standard of care therapy.

For patients with Down syndrome and NCI HR B-ALL, informed consent that describes all therapy on this trial must be obtained prior to the start of Induction therapy. However, DS SR B-ALL patients on AALL0932 who meet the criteria for DS HR B-ALL post-Induction and are eligible to continue therapy on AALL1131 must be consented prior to the start of Consolidation.

4.1.1 Non-Down Syndrome Patients

Induction Therapy

NCI High risk ALL (HR B-ALL) patients without Down syndrome enrolled on this trial (AALL1131) receive a conventional 4-drug Induction with age based steroid therapy:

- Patients 1-9.99 years receive dexamethasone 10 mg/m^2/day x 14 days.
- Patients ≥ 10 years of age receive prednisone 60 mg/m^2/day x 28 days.

Effective March 19, 2018, NCI Standard risk B-ALL (SR B-ALL) patients on AALL0932 who would have received a conventional 3-drug Induction and have features of HR B-ALL post-Induction are no longer eligible to enroll on AALL1131.

All patients with CNS3 status or testicular leukemia at diagnosis and some patients with steroid pretreatment will receive a 4-drug Induction on this study regardless of their initial NCI risk status.

At the end of Induction, all eligible patients without Down syndrome are stratified into 3 risk groups:

1) High Risk (HR)
2) Very High Risk (VHR)
3) Ph-like (LDA positive) with a predicted TKI-sensitive mutation (Dasatinib Arm)

See Section 3.3 for defining criteria.

Post Induction Therapy

HIGH RISK (HR)
Patients who meet the HR criteria as outlined in Section 3.3 should be removed from protocol therapy at the end of Induction. HR B-ALL patients enrolled prior to the randomization closure should continue to receive standard therapy (Arm A):

Arm A (Standard Arm): Patients receive a modified MBFM-IMHDM therapy and age adjusted intrathecal methotrexate (IT MTX)

Arm B (Experimental Arm): Patients receive a modified MBFM-IMHDM therapy and age adjusted triple intrathecal therapy (ITT). **Closed effective March 19, 2018.**

Phases of Therapy:
Post-Induction therapy includes Consolidation, 1 Interim Maintenance phase with high dose methotrexate, 1 Delayed Intensification phase, and Maintenance therapy including prednisone and vincristine pulses given every 4 weeks for 2 years from the start of Interim Maintenance for female patients and 3 years from the start of Interim Maintenance for male patients. Pegaspargase will be administered by IV infusion.

Testicular Radiation Therapy:
Male patients with testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction will receive radiation to the testes (2400 cGy in 12 fractions) during Consolidation (see Section 14.0). A testicular biopsy should be performed if the clinical findings are equivocal. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

VERY HIGH RISK (VHR)
Effective Amendment #6, NCI HR patients completing Induction therapy who are **MRD positive**, excluding **hypodiploid and induction failures,** will receive non-randomized Consolidation therapy after risk assignment. Upon completion of Consolidation therapy and MRD assessment, EOC **MRD positive** patients will have the option to enroll on AALL1721. EOC **MRD positive** patients who choose not to enroll in AALL1721 and EOC **MRD negative** will go off-protocol therapy, and should continue to receive standard of care therapy. NCI SR patient classified as VHR post-Induction will not be eligible for AALL1131 and should proceed to receive standard of care therapy.

Patients who met the VHR criteria prior to Amendment #6 should continue to receive treatment on the Control Arm. Randomization on the VHR arm closed effective February 15, 2017.

Control Arm (Standard Arm): Patients receive an MBFM-IMHDM + CMTX therapy, including Interim Maintenance II with Capizzi methotrexate and pegaspargase.

Experimental Arm 1: **Permanently closed effective February 15, 2017.**

Experimental Arm 2: **Permanently closed as of Amendment #3B**

Testicular Radiation Therapy:
Male patients with testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction will receive radiation to the testes (2400 cGy in 12 fractions) during Consolidation (see Section 14.0). A testicular biopsy should be performed if the clinical findings are equivocal. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

Cranial Radiation Therapy:
Patients with CNS3 status at diagnosis receive cranial irradiation, 1800 cGy in 10 fractions, during the first cycle of Maintenance therapy (see Section 14.0). **No other non Down syndrome patients will receive cranial irradiation on this study**.

Option for Stem Cell Transplant:
Patients who have extreme hypodiploidy (n<44 chromosomes and/or a DNA index of < 0.81), or Induction Failure (M3 BM on Day 29 of Induction) will go off-protocol therapy at the end of Induction and continue to receve therapy at the discretion of treating physicians.

DASATINIB ARM
Patients who meet the Dasatinib Arm criteria as outlined in Section 3.3 are assigned at the end of Induction to the Dasatinib Arm:

Patients who are NCI High Risk and identified as Ph-like (LDA positive) with a predicted TKI-sensitive mutation are non-randomly assigned at the end of Induction to receive dasatinib therapy with standard MBFM-IMHDM treatment (Dasatinib Arm) on AALL1131.

NOTE: if dasatinib is unavailable at your site, subjects are not eligible to enroll onto the post-Induction Ph-like with Predicted TKI-Sensitive Mutation (dasatinib arm) and will be removed from protocol therapy.

Phases of Therapy:
Post-Induction therapy includes dasatinib continuously during Consolidation, Interim Maintenance 1 phase with high dose methotrexate, 1 Delayed Intensification phase, Interim Maintenance 2 with Capizzi methotrexate, and Maintenance therapy including prednisone and vincristine pulses given every 4 weeks for 2 years from the start of Interim Maintenance for female patients and 3 years from the start of Interim Maintenance for male patients.

Testicular Radiation Therapy:
Male patients with testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction will receive radiation to the testes (2400 cGy in 12 fractions) during Consolidation (see Section 14.0). A testicular biopsy should be performed if the clinical findings are equivocal. **Patients**

with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.

Cranial Radiation Therapy:
Patients with CNS3 status at diagnosis receive cranial irradiation, 1800 cGy in 10 fractions, during the first cycle of Maintenance therapy (see Section 14.0). No other non-Down syndrome patients will receive cranial irradiation on this study.

4.1.2 Patients with Down Syndrome

NCI HR B-ALL patients with Down syndrome (DS) and NCI SR B-ALL patients with DS and CNS3 disease or testicular disease or steroid pretreatment will be assigned to a separate stratum at the time of enrollment on this study and will receive a reduced intensity Induction and post-Induction therapy due to the higher risk of treatment-related morbidity and mortality. NCI SR-ALL patients with DS enrolled on the SR B-ALL trial (AALL0932) are eligible to transfer to this study for post-Induction therapy if they have Day 29 BM MRD ≥ 0.01%, hypodiploidy, or *MLL* rearrangement.

Induction Therapy.
NCI HR B-ALL patients with DS will start off receiving a 3-drug Induction with age based steroid therapy:

- Patients 1-9.99 years receive dexamethasone 6 mg/m^2/day x 28 days.
- Patients ≥ 10 years of age receive prednisone 60 mg/m^2/day x 28 days.

Response will be assessed by bone marrow morphology at Day 15:

- Patients with rapid early response (RER- M1 marrow at Day 15) will complete a 3-drug Induction, including a total of 28 days of dexamethasone for patients 1-9.99 years and 28 days of prednisone for patients ≥ 10 years of age.
- Patients with slow early response (SER- M2/M3 marrow at Day 15) will continue with a 4-drug Induction that includes a single "rescue" anthracycline dose (daunorubicin 50 mg/m^2) immediately after the Day 15 BM response is known, to complete a total of 28 days of dexamethasone for patients 1-9.99 years and 28 days of prednisone for patients ≥ 10 years of age. See experimental design schema.

Post Induction Therapy

Phases of Therapy:
Post-Induction therapy consists of MBFM-IMHDM therapy which includes Consolidation, 1 Interim Maintenance phase with intermediate dose methotrexate (ID MTX), 1 Delayed Intensification phase, and Maintenance. Modifications specific to DS patients will include:

1) Leucovorin rescue following intrathecal methotrexate in all phases prior to Maintenance, 2) Interim Maintenance with ID MTX beginning at a dose of 2000 mg/m^2 with early leucovorin rescue starting at hour 30. If this dose is tolerated, the dose will continue at 2000 mg/m^2 for the 2nd and subsequent courses with leucovorin rescue starting at hour 36. 3) Vincristine/prednisone pulses will be given every 12 weeks for all DS patients during Maintenance, and 4) Duration of Maintenance therapy will be 2 years from the start of Interim Maintenance for both boys and girls. Pegaspargase will be administered by IV infusion.

Testicular Radiation Therapy:
Male patients with Down syndrome and testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction will receive radiation to the testes (2400 cGy in 12 fractions) during Consolidation (see Section 14.0). A testicular biopsy should be performed if the clinical findings

are equivocal. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

Cranial Radiation Therapy:
Down syndrome patients with CNS3 status at diagnosis receive cranial irradiation, 1800 cGy in 10 fractions, during the first cycle of Maintenance therapy (see Section 14.0).

4.1.3 Incidence and Natural History of Osteonecrosis Ancillary Study (Osteonecrosis Study).
Closed to accrual July 2016

4.1.4 Longitudinal, Computerized Assessment of Neurocognitive Functioning Study (Neurocognitive Study).
Patients who meet the eligibility criteria outlined in Section 16.0 can participate in the neurocognitive study. These patients will have additional observations during Consolidation, Maintenance and End of therapy. For further information on evaluation schedule and specific test to be administered, please see Section 16.0.

4.1.5 Concomitant Therapy Restrictions

4.1.5.1 Cytochrome P450 Interactions with Antileukemic Drugs.
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.[115] Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsant. Azole antifungals (listed in the table below) and the macrolide group of antibiotics (listed in the table below) may have potent inhibitory effects on drug-metabolizing enzymes. 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 as alternative
Rifampin	Induction of drug metabolizing enzymes	DO NOT USE
Azole Antifungals (fluconazole, itraconazole*, posaconazole voriconazole, ketoconazole)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine*, anthracyclines, etoposide, steroids
Macrolide Antibiotics (erythromycin, clarithromycin, azithromycin, roxithromycin, telithromycin)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine, anthracyclines, etoposide, steroids

* Itraconazole should NOT be used in patients who are receiving vincristine due to a serious drug-drug interaction leading to severe neurotoxicity.[116, 117]

For a more complete list of CYP3A4/5 Inhibitors and Inducers, see Appendix X.

4.1.5.2 **Possible Drug Interactions with Dasatinib**
Dasatinib is metabolized primarily by the cytochrome P450 isoform CYP3A4/5. Potent inhibitors of CYP3A4/5 are likely to inhibit dasatinib metabolism and increase systemic exposure. Therefore, concomitant treatment with dasatinib and use of the following medications is discouraged: azole antifungals (eg, fluconazole, itraconazole, posaconazole, and voriconazole), cyclosporine, erythromycin, clarithromycin, HIV (human immunodeficiency virus) protease inhibitors, and nefazodone. The use of grapefruit juice is also discouraged.

It is also likely that inducers of CYP34A4/5, such as carbamazepine, dexamethasone, rifampin, phenobarbital, phenytoin, rifabutin and St. John‘s Wort will reduce the plasma exposure to dasatinib. Concomitant administration of these drugs is also discouraged, except for dexamethasone as prescribed in the treatment regimen, or stress doses of steroids.

Use of H2-blockers and proton pump inhibitors: Absorption of dasatinib is pH dependent, with increased absorption in more acidic conditions. As a result, agents that decrease the acidity of the stomach such as proton-pump inhibitors and H2-blockers are discouraged. Alternatively, use of antacids such as aluminum hydroxide/magnesium hydroxide 2 hours prior or 2 hours after dasatinib did not alter absorption. Therefore, consider the use of antacids instead or proton-pump inhibitors or H2-blockers.

4.1.5.3 Possible Drug Interactions with High or Intermediate Dose 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.

For COG Supportive Care Guidelines see:
https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines

4.2 **Induction (35 days) – All non-Down syndrome patients**
This therapy is for patients without Down syndrome. For patients with Down syndrome see Section 4.20.

PLEASE NOTE THAT STEROID THERAPY IS DEPENDENT ON AGE OF PATIENT:

- **Patients < 10 years old get a dexamethasone based Induction therapy.**
- **Patients ≥ 10 years old get a prednisone based Induction therapy.**

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at:
https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf
for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cytarabine: Intrathecal (IT)
All patients: Given at the time of diagnostic lumbar puncture (LP) OR on Day 1.May be given up to 72 hours prior to the start of protocol therapy for patient convenience.

Age-based dosing for Day 1 IT Cytarabine:

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

CNS2 patients Only: In addition to the initial dose (as above), patients will receive additional IT Cytarabine on either Day 4, 5 or 6 during Induction, IT Methotrexate on Day 8, and then receive IT Cytarabine on Days 11 or 12. If the CSF at all three of these time points is negative for blasts, patients will receive their next IT therapy with methotrexate on Day 29. If the CSF remains positive after the initial LP, patients will continue IT Cytarabine twice weekly during Induction until the CSF is clear for three consecutive LPs. All patients will receive IT therapy with methotrexate on Day 8 and 29 at the end of Induction regardless of CSF evaluations.

Age-based dosing for additional IT Cytarabine for **CNS2 patients Only (Days 4, 5 or 6 and Days 11 or 12)** and additional IT Cytarabine until clear:

Age (yrs)	Dose
1 – 1.99	20 mg
2 – 2.99	30 mg
≥ 3	40 mg

For IT administration use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may be given IV) – Patients < 10 years ONLY
Days 1-14 (do not taper)
Dose: 5 mg/m^2/dose BID (i.e., total daily dose: 10 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m^2/day, divided BID) may be used temporarily as needed.

PrednisONE: PO (may be given IV^) – Patients ≥ 10 years ONLY
Days 1-28 (do not taper)
Dose: 30 mg/m^2/dose BID (Total daily dose: 60 mg/m^2/day divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given, at 80 % of the oral dose.

DAUNOrubicin: IV push/infusion over 1-15 minutes
Days 1, 8, 15 and 22
Dose: 25 mg/m^2/dose

The reconstituted solution or the commercially available solution (5 mg/mL) can be administered (undiluted or diluted) 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 a rapidly infusing solution of D_5W or 0.9% NaCl, infused into a large vein or central venous access device. Protect from sun light.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DAUNOrubicin is available in a liposomal formulation (DAUNOrubicin citrate, DaunXome®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours
Day 4*
Dose: 2500 International Units/m^2/dose

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

***PLEASE NOTE: DUE TO THE NEED FOR DAY 8 EARLY RESPONSE ASSESSMENT, PEGASPARGASE MUST BE ADMINISTERED ON DAY 4.**

Special precautions:
1. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.

2. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Methotrexate: Intrathecal (IT)
Days 8 and 29 for CNS 1 and CNS2 (CNS3 also on Days 15 & 22)
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Disease Evaluations During Induction

- Day 29: Bone marrow sample will be obtained for morphology and a 2 mL aliquot will be shipped to a COG-Approved ALL Flow Cytometry Laboratory for MRD determination.

Research Studies (for patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for ALL patients)*)

- Day 29: 5 mL of peripheral blood will be obtained and shipped to the COG ALL Molecular Reference Laboratory for studies of genomic variation and cell banking. ***This specimen is very important and should be obtained on all patients that have provided consent.***

NOTE: IF THE DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY AND RESULTS AVAILABLE FOR RISK STRATIFICATION, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

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

Following completion of Induction, based upon the patient's age, CNS or testicular disease status, sentinel cytogenetic lesions, and Day 29 MRD results, patients will be classified as HR B-ALL or VHR B-ALL or Ph-like:

Effective March 19, 2018 for HR B-ALL patients:

- For HR B-ALL enrolled prior to the closure of the HR randomization, Consolidation (Section 4.3) starts on Day 36 or when blood count parameters are met (whichever occurs later).

For VHR B-ALL patients:
Effective Amendment #6, patients completing Induction therapy who meet criteria for the VHR arm and are EOI MRD negative should go off protocol therapy and proceed to receive standard of care therapy.

NCI HR patients who are EOI MRD positive (excluding hypodiploid and induction failures) should continue on to Consolidation therapy. Consolidation Part 1 (Section 4.8) starts on Day 36 or when peripheral counts recover (whichever occurs later).

For patients with Ph-like B-ALL and a predicted TKI-sensitive mutation:
For all Ph-like B-ALL patients, Consolidation Part 1 (Section 4.15) starts on Day 36 or when peripheral counts recover (whichever occurs later).

NOTE: if dasatinib is unavailable at your site, subjects are not eligible to enroll onto the post-Induction Ph-like with Predicted TKI-Sensitive Mutation (dasatinib arm) and will be removed from protocol therapy.

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

4.2.1 INDUCTION

This Induction therapy is for all patients **without** Down syndrome. **For patients with Down syndrome see Section 4.20.1**

Patient name or initials _____ DOB _____

Induction is 5 weeks (35 days). This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Cytarabine (IT ARAC)	IT	At LP or Day1: 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*	**Note age-based dosing**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. BM eval[1] d. PB sample[1] e. CSF cell count, cytospin[2] f. Bilirubin, ALT & Creatinine g. Echocardiogram h. TPMT and NUDT15 genotype[#] i. Pregnancy test [1]See Section 7.0 for further details [2] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Cytarabine (IT ARAC)	IT	CNS2 ONLY: Age (yrs) / Dose 1-1.99 / 20 mg 2-2.99 / 30 mg ≥ 3 / 40 mg	**CNS2:** twice weekly[†]	[†]The initial dose is followed by 2x weekly IT ARAC except on Days 8 & 29 when IT MTX is administered. **Note:** IT therapy is administered until 3 consecutive CSF samples are clear of blasts.	
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	Days 1, 8, 15 &22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX) **Patients < 10 years ONLY**	PO (may be given IV)	5 mg/m^2/dose BID	Days 1-14	Total daily dose: 10 mg/m^2/day, divided BID See Section 4.2 for admin guidelines	
PrediniSONE (PRED) **Patients ≥ 10 years ONLY**	PO (may be given IV)	30 mg/m^2/dose BID	Days 1-28	Total daily dose: 60 mg/m^2/day, divided BID See Section 4.2 for admin guidelines **Note**: IV methylprednisolone may be substituted for oral prediniSONE at 80% of the oral dose	
DAUNOrubicin (DAUN)	IV push/infusion over 1-15 min	25 mg/m^2/dose	Days 1, 8, 15 & 22	See Section 4.2 for admin guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 4	**Note: pegaspargase must be administered on Day 4.** 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** also on Days 15 & 22	See Section 4.2 for admin guidelines **Note age-based dosing** **Note:** All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation.	

Ht_____cm **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Day	IT ARAC ____mg	IT ARAC ____mg	VCR ____mg	DEX ____mg ____mg **Patients < 10 yrs ONLY**	PRED ____mg ____mg **Patients ≥ 10 yrs ONLY**	DAUN _____mg	PEG-ASP _____IU	IT MTX ____mg	Studies	Comments
				Enter calculated dose above and actual dose administered below								♦Note any additional IT ARAC doses here.
		-2/-1/0/LP*	_____mg								(a, b, c, e, f, g, i)[@]	
		1			_____mg	____mg ____mg	____mg ____mg	_____mg				
		2										
		3										
		4♦		_____mg♦					_____IU		e♦	
		–										
		8			_____mg			_____mg		_____mg	a[%], b, e	
		9										
		10										
		11♦		_____mg♦							e♦	
		12										
		13										
		14										
		15^♦		_____mg♦	_____mg			_____mg		_____mg^	a[%], b, e^♦, h	
		–										
		22^			_____mg			_____mg		_____mg^	a[%], b, e^	
		–										
		28										
		29								_____mg	a[%], b, c**, d[#], e, f	
		36	**VHR EOI MRD positive (excluding hypodiploid and induction failures), begin next course Consolidation (based upon Day 29 evaluation results for risk stratification and treatment randomization) on Day 36 or when blood count parameters are met (whichever occurs later). VHR EOI MRD negative patients go off-protocol therapy and proceed to receive standard of care therapy.**								

*On Day 1 **OR** at the time of diagnostic lumbar puncture (LP) if ≤ than 72 hours from the start of protocol therapy. ^ CNS3 patients only @ Baseline

[%] **Note**: Height (Ht) is only required at the beginning of this course. [#] TPMT and NUDT15 genotype (TPMT highly recommended for all subjects; NUDT15 is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects (See Section 5.9)

♦**CNS2 patients only: administer IT therapy twice weekly until 3 consecutive CSF are clear of blasts. Day 8 & 29 IT therapy will remain IT MTX for all patients.**

Note: CNS2 patients receive IT ARAC on Days 4, 5, or 6 and 11 or 12, etc., depending on treatment schedule. Log additional IT-ARAC doses in the comments section.

****NOTE: IF THE DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY. THESE SAMPLES ARE ABSOLUTELY ESSENTIAL.**

[#]Day 29 PB specimen should be shipped to the COG ALL Molecular Reference Laboratory for all patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for ALL patients)*. ***This specimen is very important***.

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

4.3 Consolidation (56 days) – HR B-ALL Patients enrolled prior to March 19, 2018

CONSENT TO POST-INDUCTION THERAPY (AND RANDOMIZATION FOR HR B-ALL PATIENTS) MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END-INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF PROTOCOL THERAPY.

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) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should not be interrupted for fever, if there are no signs of serious infection. Therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 chemotherapy until ANC ≥ 750/μL and platelets ≥ 75 000/μL.

Testicular Radiation Therapy

Patients with testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 14.0). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at:
https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf
for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cyclophosphamide: IV over 30-60 minutes
Days 1 and 29
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Mercaptopurine: PO
Days 1-14 and 29-42
Dose: 60 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details. Do not escalate or reduce dose based on blood counts during this cycle.

Methotrexate: Intrathecal (IT)
Days 1, 8, 15 and 22
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours
Days 15 and 43
Dose: 2500 International Units/m^2/dose

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

Special precautions:
1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).

2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Disease Evaluation during Consolidation

- Patients with Induction Day 29 MRD ≥ 0.01% are required to have a Consolidation Day 56 (or IM Day 1 for convenience) BM examination to evaluate remission status.

Osteonecrosis Study (for those enrolled prior to July 2016)

For non DS patients enrolled on the optional osteonecrosis study, blood draws for asparaginase (ASNase) levels, anti-ASNase antibodies and serum albumin are due on Days 1 and 22 of Consolidation. The first MRI evaluation time point can occur anytime on or after Day 57 of Consolidation and within 4 weeks of starting Interim Maintenance. See Section 15.0 & Appendix V for details of evaluation schedule and blood draws.

Neurocognitive Study

For non DS patients enrolled on the optional neurocognitive study, the first evaluation time point can occur anytime from Day 15 of Consolidation but prior to the start of Interim Maintenance I. See Section 16.0 for details of evaluation schedule.

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

Following completion of Consolidation, the next course (Interim Maintenance with HD MTX, Section 4.4) starts on Day 57 or when blood count parameters are met (whichever occurs later).

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

4.3.1 **CONSOLIDATION (56 days)** – HR B-ALL Patients enrolled prior to March 19, 2018

_____ 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 & platelets ≥ 75 000/µL (whichever occurs later). This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Days 1 & 29	See Section 4.3 for admin guidelines	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin ALT, & Creatinine, e. BM Evaluation f. Osteonecrosis study (optional) g. Neurocognitive study (optional) ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cytarabine (ARAC)	IV over 1-30 mins or SubQ	75 mg/m^2/dose	Days 1-4, 8-11, 29-32 & 36-39		
Mercaptopurine (MP)	PO	60 mg/m^2/dose*	Days 1-14 & 29-42	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.3 for admin 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, 8, 15 & 22	See Section 4.3 for admin guidelines **Note age-based dosing**	
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 15, 22, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Days 15 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Patients with testicular disease at diagnosis & continued clinical evidence of testicular disease at end-Induction will receive testicular XRT. See Section 4.3 & Section 14.0 for additional details.

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	CPM mg	ARAC mg	MP mg	IT MTX mg	VCR mg	PEG-ASP IU	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		1	___mg	___mg	___mg	___mg			a, b, c, d, f*	
		2		↓	↓					
		3		↓	↓					
		4		↓	↓					
		8		___mg	↓	___mg			b, c	
		9		↓	↓					
		10		↓	↓					
		11		↓	↓					
		14			↓					
		15				mg	mg	IU	b, c, g**	
		22				___mg	___mg		b, c, f*	
		29^	___mg	___mg	___mg				b	
		30		↓	↓					
		31		↓	↓					
		32		↓	↓					
		33			↓					
		34			↓					
		35			↓					
		36		___mg	↓				b	
		37		↓	↓					
		38		↓	↓					
		39		↓	↓					
		40			↓					
		41			↓					
		42			↓					
		43					___mg	___IU	b	
		50					___mg		b	
		56							e+, f*	

Begin next course (Interim Maintenance, Section 4.4) on Day 57 or when blood count parameters are met (whichever occurs later).

* For patients enrolled on this study prior to July 2016, blood draws for ASNase levels, anti-ASNase antibodies and serum albumin are due on Days 1 & 22. The first MRI evaluation can be done anytime on or after Day 57 of Consolidation, & within 4 weeks of starting IM. See Section 15.0 & Appendix V for details.

**For patients enrolled on this study, evaluations can be done anytime from Day 15 of Consolidation, but prior to start of IM. See Section 16.0 for details.

^Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL to begin Day 29 therapy.

+For patients with Induction Day 29 MRD ≥ 0.01%.

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

4.4 Interim Maintenance with HD MTX (63 days) – HR B-ALL Patients enrolled prior to March 19, 2018

Criteria to Start Interim Maintenance
Begin IM on Day 57 of Consolidation or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later.

Interruption and/or Modification of Therapy
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.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

High Dose Methotrexate: IV over 24 hours
Days 1, 15, 29, and 43
Dose: 5000 mg/m^2/dose (no maximum dose)

ANC must be ≥ 750/µL and platelets must be ≥ 75 000/µL prior to each dose of HD MTX.

Leucovorin: PO/IV
Days 3-4, 17-18, 31-32, and 45-46.
Dose: 15 mg/m^2/dose x minimum of 3 doses given at 42, 48 and 54 hours after the start of HD MTX infusion.

See next page for HD MTX/LCV rescue and infusion guidelines.

Methotrexate: Intrathecal (IT)
Days 1 and 29
Age-based dosing:

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

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Mercaptopurine: PO
Days 1-56
Dose: 25 mg/m^2/dose once daily

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ 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 II for details. Do not escalate or reduce dose based on blood counts during this cycle. Mercaptopurine should be held for ANC < 750/µL or platelets < 75 000/µL. 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 (see Section 5.9).

HD MTX/LCV Rescue and Infusion Guidelines
See Section 5.8.1 for further details.

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

Hold trimethoprim/sulfamethoxazole (TMP-SMX), 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 medications until MTX level is less than 0.1 µM.*

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. An acetate or bicarbonate bolus (0.5- 1 mEq/kg over 15 minutes) may be given to raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Recommend hydration and alkalinization throughout HD MTX infusion, and for a minimum of 54 hours after the MTX bolus is started for patients who meet expected clearance parameters. In patients with delayed MTX clearance, continue hydration and leucovorin as instructed (Appendix IV-A) until the plasma MTX concentration is below 0.1 µM.

Hour 0: MTX 500 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the 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 and Appendix IV-A)

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 5.8.1.1). 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 5.8.1.1.

If the 24 hour level is ≥ 150 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table in Section 5.8.1.1.

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 5.8.1.1.

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

Following completion of Interim Maintenance with HD MTX, the next course (Delayed Intensification, Section 4.5) starts on Day 64 or when blood count parameters are met (whichever occurs later).

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

4.4.1 **INTERIM MAINTENANCE with HD MTX (63 days)** – HR B-ALL Patients enrolled prior to March 19, 2018	_____ Patient name or initials _____ DOB

Begin Interim Maintenance when peripheral counts recover with an ANC ≥ 750/µL & platelets ≥ 75 000/µL. See Section 4.5 for therapy interruption guidelines. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 15, 29, & 43	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt. Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT & Creatinine ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High Dose Methotrexate (HD MTX)	IV over 24 hours	5000 mg/m² (no max dose)	Days 1, 15, 29, & 43	See Section 4.4 & Appendix IV-A for admin guidelines.	
Leucovorin (LCV)	PO/IV	15 mg/m²/dose	Days 3-4, 17-18, 31-32, & 45-46	42, 48, and 54 hours after the start of HD MTX infusion. See Section 5.8.1.1 and Appendix IV-A for admin 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	See Section 4.4 for admin guidelines **Note age-based dosing** When IT therapy and HD MTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).	
Mercaptopurine (MP)	PO	25 mg/m²/dose	Days 1-56	See Section 4.4 for admin guidelines	

Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR ___mg	HD MTX ___mg	LCV ___mg	IT MTX ___mg	MP ___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							

		15	___mg	___mg				b, d	
		16							
		17			___mg*				
		18							

		29	___mg	___mg		___mg		b, c, d	
		30							
		31			___mg*				
		32							

		43	mg	mg				b, d	
		44							
		45			___mg*				
		46							

		56							
		64	**Begin next course (Delayed Intensification, Section 4.5) on Day 64 or when blood count parameters are met (whichever occurs later).**						

*Please document the number of doses of leucovorin administered

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

4.5 Delayed Intensification (56 days) – HR B-ALL Patients enrolled prior to March 19, 2018

Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL prior to starting therapy on Days 1 and 29. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Otherwise, therapy should not be interrupted for uncomplicated myelosuppression or fever.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may give IV)
Days 1-7 and 15-21
Dose: 5 mg/m^2/dose BID (i.e., total daily dose: 10 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m^2/day, divided BID) may be used temporarily as needed.

DOXOrubicin: IV push/infusion over 1-15 minutes
Days 1, 8 and 15
Dose: 25 mg/m^2/dose

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 or central venous access device.

Special precautions: Medication errors have occurred due to confusion between DOXOrubicin and DAUNOrubicin. DOXOrubicin is available in a liposomal formulation (DOXOrubicin liposomal, Doxil®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intrathecal (IT)
Days 1, 29 and 36
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Pegaspargase: IV over 1-2 hours
Day 4 and 43
Dose: 2500 International Units/m^2/dose

Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.

Special precautions:

1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Cyclophosphamide: IV over 30-60 minutes
Day 29 ONLY
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: PO
Days 29-42.
Dose: 60 mg/m^2/dose/once daily

Administer at the same time every day Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix III for details.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, blood draws for dexamethasone (DEX) and asparaginase (ASNase) levels, anti-ASNase antibodies and serum albumin are due on Day 8 of Delayed Intensification. See Section 15.0 & Appendix V for details of evaluation schedule.

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

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

The Therapy Delivery Maps (TDMs) for Delayed Intensification are on the next 2 pages.

4.5.1a **DELAYED INTENSIFICATION –** HR B-ALL Patients enrolled prior to March 19, 2018.

_____ _____
Patient name or initials DOB

To begin Delayed Intensification therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL. See Section 4.5 for therapy interruption guidelines. This Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF Cell count, cytospin! d. Bilirubin, ALT &, Creatinine e. Echocardiogram [1] f. Osteonecrosis study (optional) ! Obtain with each IT admin. [1] Obtain prior to first doxorubicin dose. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (may give IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID. See Section 4.5 for admin. Guidelines	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m^2/dose	Days 1, 8 & 15	See Section 4.5 for admin guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	See Section 4.5 for admin. guidelines **Note age-based dosing**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Days 4 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29	See Section 4.5 for admin. guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m^2/dose	Days 29-42	See Section 4.5 for admin. guidelines	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	IT MTX ____mg	PEG-ASP ____IU	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	____mg	____mg ____mg	____mg	____mg		a, b, c, d, e#	
		2		____mg ____mg					
		3		____mg ____mg					
		4		____mg ____mg			____IU		
		5		____mg ____mg					
		6		____mg ____mg					
		7		____mg ____mg					
		8	____mg		____mg			b, f*	

		15	____mg	____mg ____mg	____mg			b	
		16		____mg ____mg					
		17		____mg ____mg					
		18		____mg ____mg					
		19		____mg ____mg					
		20		____mg ____mg					
		21		____mg ____mg					

		This therapy delivery map continues on the next page.							

[#] For patients transferred from AALL0932 only, collect prior to first doxorubicin dose.

[*] For patients enrolled on this study prior to July 2016, blood draws for DEX and ASNase levels, anti-ASNase antibodies and serum albumin are due on Day 8. See Section 15.0 & Appendix V for details

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

4.5.1b **DELAYED INTENSIFICATION** – HR B-ALL Patients enrolled prior to March 19, 2018.

_____ _____
Patient name or initials DOB

To begin Delayed Intensification therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL. See Section 4.5 for therapy interruption guidelines. This Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht b. CBC/diff/platelets c. CSF Cell count, cytospin! d. Bilirubin, ALT & Creatinine ! Obtain with each IT administration **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	10 mg/m²/day, divided BID. See Section 4.5 for administration guidelines	
DOXOrubicin (DOXO)	IV Push/infusion over 1-15 min	25 mg/m²/dose	Days 1, 8 & 15	See Section 4.5 for administration guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	See Section 4.5 for administration guidelines **Note age-based dosing**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m²/dose	Days 4 **&** 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m²/dose	Day 29	See Section 4.5 for administration guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42	See Section 4.5 for administration guidelines	

Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR ____mg	IT MTX ____mg	PEG-ASP _____IU	CPM ____mg	ARAC ____mg	TG ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29^		____mg		____mg	____mg	____mg	b, c, d	
		30					____mg	____mg		
		31					____mg	____mg		
		32					____mg	____mg		
		33						____mg		
		34						____mg		
		35						____mg		
		36		____mg			____mg	____mg	b, c	
		37					____mg	____mg		
		38					____mg	____mg		
		39					____mg	____mg		
		40						____mg		
		41						____mg		
		42						____mg		
		43	____mg		_____IU				b	

		50	____mg						b	
		57	**Begin next course (Maintenance, Section 4.6) on Day 57 or when blood count parameters are met (whichever occurs later).**							

^ Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL to begin Day 29 therapy.

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

4.6 Maintenance – HR B-ALL Patients enrolled prior to March 19, 2018

Maintenance begins on Day 57 of DI, or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and prednisone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12-week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance. Therapy may be stopped on anniversary date if the prednisone is completed for the 5-day prednisone pulse. If anniversary date falls during 5-day prednisone pulse, complete that 5-day pulse. Otherwise continue current cycle through prednisone administration.

The administration schedule below describes one 12-week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intrathecal (IT)
Days 1 and 29 **(first 4 cycles only)**
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

PredniSONE: PO (may give IV^)
Days 1-5, 29-33 and 57-61
Dose: 20 mg/m^2/dose BID (i.e. total daily dose: 40 mg/m^2/day divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Methotrexate: PO
Days 8, 15, 22, 36, 43, 50, 57, 64, 71 and 78. **Omit on days when IT MTX is given.**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. **See Section 5.9 for dose modifications during Maintenance**.

Mercaptopurine: PO
Days 1-84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ 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 II for details. **See Section 5.9 for dose modifications during Maintenance**.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, evaluations are due on Day 1 of Cycle 1 (within 4 weeks of starting Maintenance), and at the end of therapy (within 4 weeks of the completion of protocol therapy). See Section 15.0 for details of evaluation schedule.

Neurocognitive Study.
For non DS patients enrolled on this study evaluations are due on Day 84 (or within 1 month afterwards) of Cycle 2, 4, 6, 10 (boys only) & 1 year post therapy. See Section 16.0 for details.

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

Repeat above cycle for a total of four (4) cycles. Then proceed to additional 12-week Maintenance cycles (Section 4.7) until End of Therapy.

The therapy delivery map (TDM) for Maintenance Cycles 1-4 is on the next page.

4.6.1 **Maintenance –** HR B-ALL Patients enrolled prior to March 19, 2018 **(Cycles 1-4)**	_____ Patient name or initials	_____ DOB

Maintenance begins on Day 57 of DI or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Section 4.6 and 5.9 for details. 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: 2 mg**	a. Hx, PE, Wt., Ht b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, & Creatinine e. Osteonecrosis study (optional) f. Neurocognitive study (optional) ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1 &29 **(first 4 cycles only)**	See Section 4.6 for administration guidelines **Note age-based dosing**	
PrediniSONE (PRED)	PO (may be given IV)	20 mg/m²/dose BID	Days 1-5, 29-33 & 57-61	Total daily dose: 40 mg/m²/day, divided BID See Section 4.6 for admin guidelines **Note**: IV methylprednisolone may be substituted for prednisone at 80% of the oral dose	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day^	Days 1-84	^see Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.6 & Appendix II for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m²/dose/week	Days 8, 15, 22, 36, 43, 50, 57, 64, 71 & 78	**Omit on days when IT MTX is given.**	

Enter Cycle #_____ Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR mg	IT MTX mg	PRED mg mg	MP mg	PO 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							
		8					_____mg		
		15					_____mg		
-		22					_____mg		
		29	_____mg	_____mg	_____mg _____mg			a%, b, c	
		30			↓	↓			
		31							
		32							
		33							
		36					_____mg		
		43					_____mg		
		50					_____mg		
		57	_____mg		_____mg _____mg		_____mg	a%, b	
		58			↓	↓			
		59							
		60							
		61							
-		64					_____mg		
		71					_____mg		
		78					_____mg		
		84						f**	
		85	**Begin next cycle on Day 85 and repeat for a total of four (4) Cycles. Repeat Cycles 2 to 4 based on dose modifications for low counts or low platelets (see Section 5.9). Maintenance continues after Cycle 4 (see Section 4.6)**						

%**Note:** Height (Ht) is only required at the beginning of each cycle #**Omit on Day 29when IT MTX is given**

*For patients enrolled on this study prior to July 2016, evaluations are due on Day 1 of Cycle 1 (within 4 weeks of starting Maintenance), and at the end of therapy (within 4 weeks of the completion of protocol therapy). See Section 15.0 for details.

**For patients enrolled on this study evaluations are due on Day 84 of Cycle 2, 4, 6, 10 (boys only) & 1 year post therapy. See Section 16.0 for details.

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

4.7 Maintenance Continued after Cycle 4 – HR B-ALL Patients enrolled prior to March 19, 2018

Maintenance continues based on the dose modifications for low ANC or low platelets (see Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and prednisone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12-week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance. Therapy may be stopped on anniversary date if the prednisone is completed for the 5-day prednisone pulse. If anniversary date falls during 5-day prednisone pulse, complete that 5-day pulse. Otherwise continue current cycle through prednisone administration.

The administration schedule below describes one 12-week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intrathecal (IT)
Day 1 ONLY **(Cycle 5 and later)**
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

PredniSONE: PO (may give IV^)
Days 1-5, 29-33 and 57-61
Dose: 20 mg/m^2/dose BID (i.e. total daily dose: 40 mg/m^2/day divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit on days when IT MTX is given.**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. **See Section 5.9 for dose modifications during Maintenance**.

Mercaptopurine: PO
Days 1-84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ 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 II for details. **See Section 5.9 for dose modifications during Maintenance**.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, evaluations are due on Day 1 of Cycle 1 (within 4 weeks of starting Maintenance), and at the end of therapy (within 4 weeks of the completion of protocol therapy). See Section 15.0 for details of evaluation schedule.

Neurocognitive Study.
For non DS patients enrolled on this study evaluations are due on Day 84 (or within 1 month afterwards) of Cycle 2, 4, 6, 10 (boys only) & 1 year post therapy. See Section 16.0 for details.

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

The therapy delivery map (TDM) for Maintenance continued after Cycle 4 is on the next page.

4.7.1 **Maintenance Continued after Cycle 4** – HR B-ALL Patients enrolled prior to March 19, 2018

_____ _____
Patient name or initials DOB

Maintenance continues based on dose modifications for low ANC or low platelets (see Section 5.9). This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m^2/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT, & Creatinine e. Osteonecrosis study (optional) f. Neurocognitive study (optional)
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 **(Cycle 5 and later)**	See Section 4.7 for administration guidelines **Note age-based dosing**	! Obtain with each IT administration
PrediniSONE (PRED)	PO (may be given IV)	20 mg/m^2/dose BID	Days 1-5, 29-33 & 57-61	Total daily dose: 40 mg/m^2/day, divided BID See Section 4.7 for admin guidelines **Note**: IV methylprednisolone may be substituted for prednisone at 80% of the oral dose	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-84	*see Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.7 & Appendix II for administration guidelines	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit on days when IT MTX is given.**	

Enter Cycle # _____ Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Day	VCR _____ mg	IT MTX _____ mg	PRED _____ mg _____ mg	MP _____ mg	PO 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			↓	↓			
		…				↓			
		8				↓	_____mg		
		…				↓			
		15				↓	_____mg		
		…				↓			
-		22				↓	_____mg		
		…				↓			
		29	_____mg		_____mg _____mg	↓	_____mg	a%, b	
		30			↓	↓			
		31			↓	↓			
		32			↓	↓			
		33			↓	↓			
		36				↓	_____mg		
		…				↓			
		43				↓	_____mg		
		…				↓			
		50				↓	_____mg		
		…				↓			
		57	_____mg		_____mg _____mg	↓	_____mg	a%, b	
		58			↓	↓			
		59			↓	↓			
		60			↓	↓			
		61			↓	↓			
		…				↓			
-		64				↓	_____mg		
		…				↓			
		71				↓	_____mg		
		…				↓			
		78				↓	_____mg		
		…				↓			
		84				↓		f**	
		85	**Repeat next cycles based on dose modifications for low counts or low platelets until 2 yrs (females) or 3 yrs (males) from start of IM**						

%**Note:** Height (Ht) is only required at the beginning of each cycle. #**Omit on Day 1 when IT MTX is given**

* For patients enrolled on this study prior to July 2016, evaluations are due on Day 1 of Cycle 1 (within 4 weeks of starting Maintenance), and at the end of therapy (within 4 weeks of the completion of protocol therapy). See Section 15.0 for details.

**For patients enrolled on this study evaluations are due on Day 84 of Cycle 2, 4, 6, 10 (boys only) & 1 year post therapy. See Section 16.0 for details.

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

4.8 Consolidation Part 1 (Day 1-28) – VHR B-ALL Patients (All Arms)
EFFECTIVE AMENDMENT #6:

- VHR PATIENTS RECEIVING THERAPY PRIOR TO AMENDMENT #6 MAY CONTINUE ON THE CONTROL ARM.

- VHR PATIENTS COMPLETING INDUCTION THERAPY WHO ARE **MRD NEGATIVE** AND OTHERWISE MEET CRITERIA FOR THE VHR ARM SHOULD GO OFF-PROTOCOL PROTOCOL THERAPY AND SHOULD PROCEED TO RECEIVE STANDARD OF CARE THERAPY.

- VHR PATIENTS COMPLETING INDUCTION THERAPY WHO ARE **EOI MRD POSITIVE** (EXCLUDING HYPODIPLOID AND INDUCTION FAILURES) ARE ELIGIBLE TO CONTINUE ON TO CONSOLIDATION THERAPY. Upon completion of Consolidation therapy and EOC MRD assessment, VHR patients go off-protocol therapy.

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END-INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF PROTOCOL THERAPY.

This therapy is common for all VHR B-ALL patients. Patients receive a standard MBFM-IMHDM +CMTX therapy, including IM II with Capizzi methotrexate and asparaginase.

Criteria to start Consolidation:
Start Consolidation Part 1 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) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should not be interrupted for fever, if there are no signs of serious infection.

Note: Patients who are VHR based on having Induction Failure (M3 Day 29 marrow) should begin Consolidation therapy as soon as possible, irrespective of hematologic values provided there is no active infection or life threatening organ malfunction.

Testicular Radiation Therapy
Patients with testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 14.0). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cyclophosphamide: IV over 30-60 minutes
Day 1
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Cytarabine: IV over 1-30 minutes or Subcutaneous
Days 1-4, and 8-11
Dose: 75 mg/m^2/dose

Mercaptopurine: PO
Days 1-14
Dose: 60 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details. Do not escalate or reduce dose based on blood counts during this cycle.

Methotrexate: Intrathecal (IT)
Days 1, 8, 15 and 22 (**Omit Days 15 and 22 for CNS3 patients)**
Age-based dosing:

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

Note: For patients with M3 marrow on Day 29, who begin Consolidation prior to Day 36 Induction; adjust IT MTX so that there is a minimum of 4 days between each intrathecal therapy.

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours
Day 15
Dose: 2500 International Units/m^2/dose

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

Special precautions:

1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, blood draws for asparaginase (ASNase) levels, anti-ASNase antibodies and serum albumin are due on Days 1 and 22 of Consolidation. See Section 15.0 & Appendix V for details of evaluation schedule.

Neurocognitive Study
For non DS patients enrolled on the optional neurocognitive study, the first evaluation time point can occur anytime from Day 15 of Consolidation but prior to the start of Interim Maintenance I. See Section 16.0 for details of evaluation schedule.

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

Following completion of Consolidation Part 1 (Day 1-28), therapy continues for Consolidation Part 2 (Days 29-57). Upon completion of Consolidation Part 2 and EOC MRD assessment, VHR patients go off-protocol therapy.

For patients on the Control Arm, see Section 4.9.

The therapy delivery map (TDM) for Consolidation Part 1 (Day 1-28) is on the next page.

4.8.1 Consolidation Part 1 (Day 1-28) – VHR B-ALL Patients (All Arms)

Patient name or initials _____ DOB _____

Start Consolidation Part 1 on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL & platelets ≥ 75 000/µL (whichever occurs later**). Patients with Induction Failure (M3 Day 29 marrow) should begin Consolidation therapy as soon as possible irrespective of hematologic values provided there is no active infection or life threatening organ malfunction.** This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Cyclophosphamide (CPM)	IV over 30 min-60 mins	1000 mg/m^2/dose	Day 1	See Section 4.8 for admin guidelines	a Hx, PE, Wt., Ht. b CBC/diff/platelets c CSF cell count, cytospin! d Bilirubin, ALT, AST, Lipase & Creatinine e Osteonecrosis study(optional) f. Neurocognitive study (optional) g. Performance status ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cytarabine (ARAC)	IV over 1-30 mins or SubQ	75 mg/m^2/dose	Days 1-4, & 8-11		
Mercaptopurine (MP)	PO	60 mg/m^2/dose*	Days 1-14	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.8 for admin 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, 8, 15 & 22	See Section 4.8 for admin guidelines ^For patients with M3 marrow on Day 29, who begin Consolidation prior to Day 36 Induction; adjust IT MTX so that there is a minimum of 4 days between each intrathecal therapy. **Note age-based dosing** **Omit Days 15 & 22 for CNS3 pts**	
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 15 & 22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 15	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Patients with testicular disease at diagnosis & continued clinical evidence of testicular disease at end-Induction will receive testicular XRT. See Section 4.8 & Section 14.0 for additional details.

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	CPM mg	ARAC mg	MP mg	VCR mg	IT MTX mg	PEG-ASP IU	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		1	mg	mg	mg		mg^		a, b, c, d+, e*, g%	
		2		↓	↓					
		3		↓	↓					
		4		↓	↓					
		8		mg	↓		mg		c	
		9		↓	↓					
		10		↓	↓					
		11		↓	↓					
		14			↓					
		15#				mg	mg#	IU	c#, f**	
		22#				mg	mg#		c#, e	
		28	Continue Consolidation Part 2 (Days 29-57) based on treatment arm patient is randomized to.							

^For patients with M3 marrow on Day 29 who begin Consolidation prior to Day 36 Induction, adjust IT MTX so that there is a minimum of 4 days between each IT therapy.

+ Obtain AST and Lipase on Day 1 ONLY.

*For patients enrolled on this study, blood draws for ASNase levels, anti-ASNase antibodies and serum albumin are due on Days 1 and 22. See Section 15.0 & for Appendix V for details.

** For patients enrolled on this study, evaluations can be done anytime from Day 15 of Consolidation, but prior to start of IM I. See Section 16.0 for details

% Perform prior to Day 1 therapy. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

Omit Days 15 & 22 for CNS3 pts

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

4.9 Consolidation Part 2 (Day 29-57) – VHR B-ALL Patients (Control Arm)

EFFECTIVE AMENDMENT #6:

- VHR PATIENTS RECEIVING THERAPY ON STUDY PRIOR TO AMENDMENT #6 MAY CONTINUE ON THE CONTROL ARM.

- VHR PATIENTS COMPLETING INDUCTION THERAPY WHO ARE **MRD NEGATIVE** AND OTHERWISE MEET CRITERIA FOR THE VHR ARM SHOULD GO OFF-PROTOCOL THERAPY AND SHOULD PROCEED TO RECEIVE STANDARD OF CARE THERAPY.

- VHR PATIENTS COMPLETING INDUCTION THERAPY WHO ARE **EOI MRD POSITIVE** (EXCLUDING HYPODIPLOID AND INDUCTION FAILURES) ARE ELIGIBLE TO CONTINUE ON CONSOLIDATION THERAPY. Upon completion of Consolidation therapy and EOC MRD assessment, VHR patients go off-protocol therapy.

This therapy is for VHR B-ALL patients on the Control Arm. Patients receive a standard MBFM-IMHDM + CMTX therapy including IM II with Capizzi methotrexate and pegaspargase.

Criteria to begin Day 29 of Consolidation Therapy:
Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL to continue therapy on Day 29. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Otherwise, therapy should not be interrupted for uncomplicated myelosuppression or fever.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cyclophosphamide: IV over 30-60 minutes
Day 29
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Mercaptopurine: PO
Days 29-42
Dose: 60 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details. Do not escalate or reduce dose based on blood counts during this cycle.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours
Day 43
Dose: 2500 International Units/m^2/dose

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

Special precautions:
1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, the first MRI evaluation time point can occur anytime on or after Day 57 of Consolidation and within 4 weeks of starting Interim Maintenance I. See Section 15.0 for details of evaluation schedule.

Neurocognitive Study
For non DS patients enrolled on the optional neurocognitive study, the first evaluation time point can occur anytime from Day 15 of Consolidation but prior to the start of Interim Maintenance I. See Section 16.0 for details of evaluation schedule.

Disease Evaluation during Consolidation

- Patients with EOI MRD ≥ 0.01% will have an end of Consolidation (or IM Day1 for convenience) BM for MRD testing. Send BM to the Eastern or Western ALL Flow Cytometry Reference Laboratory (see Section 7.4 for shipping requirements and addresses). Please note that decentralized testing does not apply to this specimen. Patients with EOC MRD ≥ 0.01% who are not M2/M3 may be eligible for AALL1721 (when available).
- Patients with induction Day 29 M2/M3 marrow will have a consolidation Day 29 BM examination to evaluate remission status. If still M2/M3 patient should continue on therapy and be evaluated at the end of Consolidation therapy (or IM Day 1 for convenience). If still not M1, patients are off-protocol therapy.

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

Patients enrolled after Amendment #6, go off study following the completion of Consolidation Part 2 (Days 29-57).

Patients receiving therapy on-study prior to Amendment #6: Following completion of Consolidation Part 2 (Day 29-57), the next course (Interim Maintenance I with HD MTX, Section 4.10) starts on Day 57 or when blood count parameters are met (whichever occurs later).

The therapy delivery map (TDM) for Consolidation (Day 29-57) is on the next page.

4.9.1 **Consolidation Part 2 (Day 29-57) –** VHR B-ALL Patients **(Control Arm)**

Patient name or initials _____ DOB _____

Consolidation Part 2 (Day 29-57) starts when ANC ≥ 750/µL & platelets ≥ 75 000/µL. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29	See Section 4.9 for admin guidelines	a) Hx, PE, Wt., Ht. b) CBC/diff/platelets c) CSF cell count, cytospin! d) Bilirubin, ALT & Creatinine e) BM evaluation f) Osteonecrosis study (optional) g) Neurocognitive study (optional) ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cytarabine (ARAC)	IV over 1-30 mins or SubQ	75 mg/m^2/dose	Days 29-32, & 36-39		
Mercaptopurine (MP)	PO	60 mg/m^2/dose*	Days 29-42	*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.9 for admin guidelines	
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	CPM mg	ARAC mg	MP mg	VCR mg	PEG-ASP IU	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		29^	____mg	____mg	____mg			b, d, e#	
		30		↓	↓				
		31							
		32							

		36		____mg				b, d	
		37		↓					
		38							
		39							

		42			↓				
		43				____mg	____IU	b, d	

		50				____mg			

		56						e$, f*, g**	
		57	Begin Next course (Interim Maintenance I, Section 4.10) on Day 57 or when blood count parameters are met (whichever occurs later).						

^ Hold Day 29 chemotherapy until ANC ≥ 750/µL & platelets ≥ 75 000/µL

#For patients with Induction Day 29 M2/M3 marrow only.

$ For patients enrolled after Amendment #6, send a 2 mL aliquot of the Consolidation Day 56 or IM Day 1 BM sample to the Eastern or Western ALL Flow Cytometry Reference Lab for MRD (see Section 7.4 for shipping information). This specimen does not apply to patients enrolled prior to Amendment #6.

* For patients enrolled on this study, the first MRI evaluation can be done anytime on or after Day 57 of Consolidation, and within 4 weeks of starting IM I. See Section 15.0 for details.

** For patients enrolled on this study, evaluations can be done anytime from Day 15 of Consolidation, but prior to start of IM I. See Section 16.0 for details

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

4.10 Interim Maintenance I with HD MTX (63 days) – VHR B-ALL Patients (All Arms)

EFFECTIVE AMENDMENT #6:

- VHR PATIENTS RECEIVING THERAPY ON STUDY PRIOR TO AMENDMENT #6 MAY CONTINUE ON THE CONTROL ARM.
- PATIENTS COMPLETING INDUCTION THERAPY WHO OTHERWISE MEET CRITERIA FOR THE VHR ARM SHOULD GO OFF-PROTOCOL THERAPY AS OUTLINED IN SECTION 4.1.1 AND SHOULD PROCEED TO RECEIVE STANDARD OF CARE THERAPY.

This therapy is common for all VHR B-ALL patients. Patients receive a standard MBFM-IMHDM therapy with HD MTX. Interim Maintenance I lasts 63 days.

Criteria to Start Interim Maintenance I

Begin IM I on Day 57 of Consolidation or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later.

Interruption and/or Modification of Therapy

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.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

High Dose Methotrexate: IV over 24 hours
Days 1, 15, 29, and 43
Dose: 5000 mg/m^2/dose (no maximum dose)

ANC must be ≥ 750/µL and platelets must be ≥ 75 000/µL prior to each dose of HD MTX.

Leucovorin: PO/IV
Days 3-4, 17-18, 31-32, and 45-46.
Dose: 15 mg/m^2/dose for a minimum of 3 doses given at 42, 48 and 54 hours after the start of HD MTX infusion.

See next page for HD MTX/LCV rescue and infusion guidelines.

Mercaptopurine: PO
Days 1-56
Dose: 25 mg/m^2/dose once daily

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ 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 II for details. Do not escalate or reduce dose based on blood counts during this cycle. Mercaptopurine should be held for ANC < 750/µL or platelets < 75 000/µL. 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 (see Section 5.9).

Methotrexate: Intrathecal (IT)
Days 1 and 29
Age-based dosing:

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

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies

HD MTX/LCV Rescue and Infusion Guidelines
See Section 5.8.1 for further details.

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

Hold trimethoprim/sulfamethoxazole (TMP-SMX), 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 medications until MTX level is less than 0.1 µM.*

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. An acetate or bicarbonate bolus (0.5- 1 mEq/kg over 15 minutes) may be given to

raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Recommend hydration for a minimum of 54 hours after the MTX bolus is started for patients who meet expected clearance parameters. In patients with delayed MTX clearance, continue hydration and leucovorin as instructed (Appendix IV-A) until the plasma MTX concentration is below 0.1 µM.

Hour 0: MTX 500 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the 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 and Appendix IIV-A)

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 5.8.1.1.

If the 24 hour level is ≥ 150 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table in Section 5.8.1.1.

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 5.8.1.1.

Disease Evaluation:
Day 1: Bone marrow examination for morphologic remission.

Please note: for patients who will go off study post-Consolidation, bone marrow samples for MRD determination may be collected at count recovery also.

Following completion of Interim Maintenance, the next course (Delayed Intensification [Day 1-28], Section 4.11) starts on Day 64 or when blood count parameters are met (whichever occurs later).

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

4.10.1 **INTERIM MAINTENANCE I with HD MTX (63 days) –** VHR B-ALL **(All Arms)**	_____ Patient name or initials	_____ DOB

Begin Interim Maintenance I when peripheral counts recover with an ANC ≥ 750/µL & platelets ≥ 75 000/µL. See Section 4.10 for therapy interruption guidelines. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 15, 29, & 43	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt. Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT & Creatinine. e. BM evaluation ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
High Dose Methotrexate (HD MTX)	IV over 24 hours	5000 mg/m² (no max dose)	Days 1, 15, 29, & 43	See Section 4.10 & Appendix IV-A for admin guidelines	
Leucovorin (LCV)	PO/IV	15 mg/m²/dose	Days 3-4, 17-18, 31-32, & 45-46	42, 48 and 54 hours after the start of HD MTX infusion. See Section 5.8.1.1 and Appendix IV-A for admin guidelines	
Mercaptopurine (MP)	PO	25 mg/m²/dose	Days 1-56	See Section 4.10 for admin 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	See Section 4.10 for admin guidelines **Note age-based dosing** When IT therapy and HD MTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).	

Ht_____ cm Wt_____ kg BSA _____ m²

Date Due	Date Given	Day	VCR ___ mg	HD MTX ___ mg	LCV ___ mg	IT MTX ___ mg	MP ___ mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	mg	mg		mg	___mg	a, b, c, d, e*	
		2							
		3			___mg**				
		4							
		15	mg	mg				b, d	
		16							
		17			___mg**				
		18							
		29	___mg	___mg		___mg		b, c, d	
		30							
		31			___mg**				
		32							
		43	mg	mg				b, d	
		44							
		45			___mg**				
		46							
		56							
		64	**Begin next course (Delayed Intensification [Day 1-28], Section 4.11) on Day 64 or when blood count parameters are met (whichever occurs later).**						

**Please document the number of doses of leucovorin administered.

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

4.11 Delayed Intensification Part 1 (Day 1-28) – VHR B-ALL Patients (All Arms)

EFFECTIVE AMENDMENT #6:

- VHR PATIENTS RECEIVING THERAPY STUDY PRIOR TO AMENDMENT #6 MAY CONTINUE ON THE CONTROL ARM.
- PATIENTS COMPLETING INDUCTION THERAPY WHO OTHERWISE MEET CRITERIA FOR THE VHR ARM SHOULD GO OFF-PROTOCOL THERAPY AS OUTLINED IN SECTION 4.1.1 AND SHOULD PROCEED TO RECEIVE STANDARD OF CARE THERAPY.

This therapy is common for all VHR B-ALL patients. Patients receive a standard MBFM-IMHDM therapy including a 2nd IM phase with Capizzi MTX and pegaspargase.

Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL prior to starting therapy on Day 1. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Otherwise, therapy should not be interrupted for uncomplicated myelosuppression or fever.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may give IV)
Days 1-7 and 15-21
Dose: 5 mg/m^2/dose BID (i.e., Total daily dose: 10 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m^2/day, divided BID) may be used temporarily as needed.

DOXOrubicin: IV push/infusion over 1-15 minutes
Days 1, 8 and 15.
Dose: 25 mg/m^2/dose

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 or central venous access device.

Special precautions: Medication errors have occurred due to confusion between DOXOrubicin and DAUNOrubicin. DOXOrubicin is available in a liposomal formulation (DOXOrubicin liposomal, Doxil®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intrathecal (IT)
Day 1
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Pegaspargase: IV over 1-2 hours
Day 4
Dose: 2500 International Units/m^2/dose

Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.

Special precautions:
1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, blood draws for dexamethasone (DEX) and asparaginase (ASNase) levels, anti-ASNase antibodies and serum albumin are due on Day 8 of Delayed Intensification. See Section 15.0 & Appendix V for details of evaluation schedule.

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

Following completion of Delayed Intensification Part 1 (Day 1-28), therapy continues for Delayed Intensification Part 2 (Days 29-57) based on treatment arm patient is randomized to.

For patients randomized to Control Arm, see Section 4.11.

The Therapy Delivery Map (TDM) for Delayed Intensification Part 1 (Day 1-28) is on the next page.

4.11.1 **Delayed Intensification Part 1 (Day 1-28) –** VHR B-ALL Patients **(All Arms)**	_____ Patient name or initials	_____ DOB

To begin DI Part 1 therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL on Day 1. See Section 4.11 for therapy interruption guidelines. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 1, 8, & 15	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF Cell count, cytospin! d. Bilirubin, ALT & Creatinine e. Echocardiogram ^ f Osteonecrosis study (optional) ! Obtain with each IT admin. ^ Obtain prior to first doxorubicin dose **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO (may give IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID. See Section 4.11 for admin. Guidelines	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m^2/dose	Days 1, 8 & 15	See Section 4.11 for admin. 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	Day 1	See Section 4.11 for admin. guidelines **Note age-based dosing**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 4	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	VCR ____mg	DEX ____mg ____mg	DOXO ____mg	IT MTX ____mg	PEG-ASP ____IU	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	____mg	____mg ____mg	____mg	____mg		a, b, c, d, e^	
		2		____mg ____mg					
		3		____mg ____mg					
		4		mg mg			IU		
		5		mg mg					
		6		mg mg					
		7		____mg ____mg					
		8	____mg		____mg			b, f*	

		15	____mg	____mg ____mg	____mg			b	
		16		____mg ____mg					
		17		____mg ____mg					
		18		____mg ____mg					
		19		____mg ____mg					
		20		____mg ____mg					
		21		____mg ____mg					
		22						b	

		28	Continue Delayed Intensification Part 2 (Days 29-57) based on treatment arm patient is randomized to.						

^ Prior to doxorubicin dose for patients transferred from AALL0932 study.

* For patients enrolled on this study, blood draws for DEX and ASNase levels, anti-ASNase antibodies and serum albumin are due on Day 8. See Section 15.0 & Appendix V for details.

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

4.12 Delayed Intensification Part 2 (Day 29-57) – VHR B-ALL Patients (Control Arm)

EFFECTIVE AMENDMENT #6:

- VHR PATIENTS RECEIVING THERAPY STUDY PRIOR TO AMENDMENT #6 MAY CONTINUE ON THE CONTROL ARM.
- PATIENTS COMPLETING INDUCTION THERAPY WHO OTHERWISE MEET CRITERIA FOR THE VHR ARM SHOULD GO OFF-PROTOCOL THERAPY AS OUTLINED IN SECTION 4.1.1 AND SHOULD PROCEED TO RECEIVE STANDARD OF CARE THERAPY.

This therapy is for VHR B-ALL patients on the Control Arm. Patients receive a standard MBFM-IMHDM therapy including a 2nd IM phase with Capizzi MTX and pegaspargase.

Criteria to begin Day 29 of Delayed Intensification Therapy:
Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL to continue therapy on Day 29. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Otherwise, therapy should not be interrupted for uncomplicated myelosuppression or fever.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cyclophosphamide: IV over 30-60 minutes
Day 29
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Thioguanine: PO
Days 29-42.
Dose: 60 mg/m^2/dose/once daily

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix III for details.

Methotrexate: Intrathecal (IT)
Days 29 and 36
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours
Day 43
Dose: 2500 International Units/m^2/dose

Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.

Special precautions:
1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

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

Following completion of Delayed Intensification Part 2 (Day 29-57), the next course (Interim Maintenance II with Capizzi methotrexate, Section 4.13) starts on Day 57 or when blood count parameters are met (whichever occurs later).

The therapy delivery map (TDM) for Delayed Intensification Part 2 (Day 29-57) is on the next page.

4.12.1 **Delayed Intensification Part 2 (Day 29-57) –** VHR B-ALL Patients **(Control Arm)**	_____ Patient name or initials	_____ DOB

To continue DI Part 2 therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL on Day 29. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29	See Section 4.12 for admin guidelines	a) Hx, PE, Wt., Ht. b) CBC/diff/platelets c) CSF cell count, cytospin!
Cytarabine (ARAC)	IV over 1-30 mins or SubQ	75 mg/m^2/dose	Days 29-32, & 36-39		
Thioguanine (TG)	PO	60 mg/m^2/dose	Days 29-42	See Section 4.12 for admin. guidelines	d) Bilirubin, ALT & Creatinine
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 29 & 36	See Section 4.12 for admin. guidelines **Note age-based dosing**	! Obtain with each IT administration
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	CPM ___mg	ARAC ___mg	TG ___mg	IT MTX ___mg	VCR ___mg	PEG-ASP IU	Studies	Comments
			Enter calculated dose above and actual dose administered below							
		29^	___mg	___mg	___mg	___mg			a%, b, c, d	
		30		↓	↓					
		31								
		32								

		36		___mg		___mg			a%, b, c	
		37		↓						
		38								
		39								

		42			↓					
		43					___mg	IU	b	

		50					___mg		b	

		57	Begin Next course (Interim Maintenance II, Section 4.13) on Day 57 or when blood count parameters are met (whichever occurs later).							

^ Hold Day 29 chemotherapy until ANC ≥ 750/µL & platelets ≥ 75 000/µL

%**Note:** Height (Ht) is only required at the beginning of each course.

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

4.13 Interim Maintenance II with Capizzi MTX (56 days) – VHR B-ALL Patients (All Arms)

EFFECTIVE AMENDMENT #6:

- VHR PATIENTS RECEIVING THERAPY STUDY PRIOR TO AMENDMENT #6 MAY CONTINUE ON THE CONTROL ARM.

- PATIENTS COMPLETING INDUCTION THERAPY WHO OTHERWISE MEET CRITERIA FOR THE VHR ARM SHOULD GO OFF-PROTOCOL THERAPY AS OUTLINED IN SECTION 4.1.1 AND SHOULD PROCEED TO RECEIVE STANDARD OF CARE THERAPY.

This therapy is common for all VHR B-ALL patients, irrespective of treatment randomization assignment. Patients receive standard MBFM therapy with Capizzi style methotrexate. Interim Maintenance II lasts 56 days.

Criteria to Start Interim Maintenance II
Begin IM II on Day 57 of Delayed Intensification or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later.

Interruption and/or Modification of Therapy
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 prior to each 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) In 4 days, if ANC ≥ 500/µL and platelets ≥ 50 000/µL, give same dose of methotrexate as previous cycle.
   2) In 4 days, if ANC is still < 500/µL or platelets < 50 000/µL, give VCR (and IT MTX if Day 31) and pegaspargase (if due) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.
      a. If after 7 days, ANC ≥ 500/µL and platelets ≥ 50 000/µL, reduce dose of MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.
      b. If after 7 days ANC is still < 500/µL or platelets < 50 000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50 000/µL. When ANC ≥ 500/µL and platelets ≥ 50 000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A-C.

B) If ANC ≥ 500/µL but < 750/µL and/or platelets ≥ 50 000/µL but < 75 000/µL, give same dose of MTX as previously (i.e. no escalation).

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

D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A-C.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

Special precautions: FOR INTRAVENOUS USE ONLY.

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: IV over 2-5 minutes (undiluted) or over 10-15 minutes (diluted).
Days 1, 11, 21, 31 and 41

Starting dose of 100 mg/m^2 and then **escalate by 50 mg/m^2/dose**

Methotrexate: Intrathecal (IT)
Days 1 and 31
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Pegaspargase: IV over 1-2 hours
Days 2 and 22
Dose: 2500 International Units/m^2/dose

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

Special precautions:
1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, blood draws for plasma methotrexate (MTX) and asparaginase (ASNase) levels, anti-ASNase antibodies and serum albumin are due on Day 22 of Interim Maintenance II prior to PEG-ASP administration. See Section 15.0 & Appendix V for details of evaluation schedule.

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

Following completion of Interim Maintenance II, the next course (Maintenance, Section 4.14) starts on Day 57 or when blood count parameters are met (whichever occurs later).

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

4.13.1 **INTERIM MAINTENANCE II with Capizzi MTX (56 days)** – VHR B-ALL **(All Arms)**	Patient name or initials _____ DOB _____

Begin Interim Maintenance II when peripheral counts recover with an ANC ≥ 750/µL & platelets ≥ 75 000/µL. See Section 4.13 for therapy interruption guidelines. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT & Creatinine e. Osteonecrosis study (optional) ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Methotrexate (MTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m². **escalate by 50 mg/m²/dose**	Days 1, 11, 21, 31 & 41	See Section 4.13 for admin guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m²/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1-1.99 / 8 mg 2-2.99 / 10 mg 3-8.99 / 12 mg ≥ 9 / 15 mg	Days 1 & 31	See Section 4.13 for admin guidelines **Note age-based dosing**	

Therapy Delivery Map Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR ____mg	IV MTX ____mg *(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		e*	

		31	____mg	____mg		____mg	b, c, d	

		41	____mg	____mg			b, d	

		57	**Begin next course (Maintenance, Section 4.14) on Day 57 or when blood count parameters are met (whichever occurs later).**					

* For patients enrolled on this study, blood draws for MTX and ASNase levels, anti-ASNase antibodies and serum albumin are due on Day 22 prior to PEG-ASP administration. See Section 15.0 & Appendix V for details.

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

4.14 Maintenance – VHR B-ALL Patients (All Arms)

EFFECTIVE AMENDMENT #6:

- VHR PATIENTS RECEIVING THERAPY STUDY PRIOR TO AMENDMENT #6 MAY CONTINUE ON THE CONTROL ARM.

- PATIENTS COMPLETING INDUCTION THERAPY WHO OTHERWISE MEET CRITERIA FOR THE VHR ARM SHOULD GO OFF-PROTOCOL THERAPY AS OUTLINED IN SECTION 4.1.1 AND SHOULD PROCEED TO RECEIVE STANDARD OF CARE THERAPY.

This therapy is common for all VHR B-ALL patients. Patients receive standard Maintenance therapy.

Criteria to begin Maintenance
Maintenance begins on Day 57 of IM II, or when peripheral counts recover to ANC ≥ 750/μL and platelets ≥ 75 000/μL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate and vincristine will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12-week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance I. Therapy may be stopped on anniversary date if the 5-day prednisone is completed for the cycle (i.e. complete all 5 days of prednisone before ending therapy). Otherwise continue current cycle through prednisone administration.

The administration schedule below describes one 12-week cycle of Maintenance therapy.

CNS Radiation Therapy
Patients with CNS3 disease at diagnosis will receive cranial irradiation, 1800cGy in 10 fractions, during the first 4 weeks of Maintenance therapy and should be completed by Day 29 of Maintenance therapy. See Section 14.0 for details of cranial irradiation.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

PredniSONE: PO (may give IV^)
Days 1-5, 29-33 & 57-61
Dose: 20 mg/m^2/dose BID (i.e., Total daily dose: 40 mg/m^2/day, divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit on days when IT MTX is given.**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration.

Mercaptopurine: PO
Days 1-84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ 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 II for details. **See Section 5.7 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1 **(also Day 29 of Cycles 1 and 2, for patients who did NOT receive CNS radiation)**
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Osteonecrosis Study (for those enrolled prior to July 2016)
For non DS patients enrolled on the optional osteonecrosis study, evaluations are due on Day 1 of Cycle 1 (within 4 weeks of starting Maintenance), and at the end of therapy (within 4 weeks of the completion protocol therapy). See Section 15.0 for details of evaluation schedule.

Neurocognitive Study
For non DS patients enrolled on the optional neurocognitive study, evaluations are due on Day 84 (or within 1 month afterwards) of Cycle 2, 4, 6, 10 (boys only) and 1 year post therapy. See Section 16.0 for details of evaluation schedule.

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

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

4.14.1 **Maintenance** – VHR B-ALL Patients (**All Arms**)

Patient name or initials _____ DOB _____

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL (whichever occurs later) for Cycle 1. F
subsequent cycles, follow dose modifications for low counts and platelets. See Section 4.14 and 5.9 for details. 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: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[1] d. Bilirubin, ALT & Creatinine e. Osteonecrosis study (optional) f. Neurocognitive study (optional) [1] Obtain with each IT administration
PrednISONE (PRED)	PO (may be given IV)	20 mg/m²/dose BID	Days 1-5, 29-33 & 57-61	Total daily dose: 40 mg/m²/day, divided BID See Section 4.14 for admin guidelines Note: IV methylprednisolone may be substituted for prednisone at 80% of the oral dose	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day*	Days 1-84	See Section 4.14 & Appendix II for administration guidelines *See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status	
Methotrexate (MTX)	PO	20 mg/m²/dose/week	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit on days when IT MTX is given.**	
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 **Also Day 29 of Cycles 1 & 2 for patients who did NOT receive CNS radiation.**	See Section 4.14 for administration guidelines **Note age-based dosing**	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
For patients with CNS3 disease cranial XRT (See Section 4.14 & 14.0) should begin during the first 4 weeks of Maintenance therapy and should be completed by Day 29.					

Enter Cycle #_____ Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR mg	PRED mg mg	MP mg	IT MTX mg	PO 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							
		8					_____mg		
		15					_____mg		
-		22					_____mg		
		29	_____mg	_____mg _____mg		_____mg#	_____mg##	a%, b, c#	
		30		↓	↓				
		31							
		32							
		33							
		36					_____mg		
		43					_____mg		
		50					_____mg		
		57	_____mg	_____mg _____mg			_____mg	a%, b	
		58		↓	↓				
		59							
		60							
		61							
-		64					_____mg		
		71					_____mg		
		78			↓		_____mg		
		84						f**	
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs (females) or 3 yrs (males) from start of IM I**						

%**Note:** Height (Ht) is only required at the beginning of each course.

Cycle 1 & 2 ONLY for patients who did NOT receive CNS radiation.

##**Omit on days when IT MTX is given**

*For patients enrolled on this study, evaluations are due on Day 1 of Cycle 1 (within 4 weeks of starting Maintenance), and at the end of therapy (within 4 weeks of completing protocol therapy). See Section 15.0 for details of evaluation schedule.

**For patients enrolled on this study, evaluations are due on Day 84 of Cycle 2, 4, 6, 10 (boys only) and 1 year post-therapy. See Section 16.0 for details of evaluation schedule.

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

4.15 Consolidation (56 days) –Ph-like with Predicted TKI-Sensitive Mutation (Dasatinib Arm)

NOTE: IF DASATINIB IS UNAVAILABLE AT YOUR SITE, SUBJECTS ARE NOT ELIGIBLE TO ENROLL ONTO THE POST-INDUCTION PH-LIKE WITH PREDICTED TKI-SENSITIVE MUTATION (DASATINIB ARM) AND WILL BE REMOVED FROM PROTOCOL THERAPY.

PATIENTS MUST MEET ORGAN FUNCTION REQUIREMENTS IN SECTION 3.2.5. CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END-INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALL-BACK PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF PROTOCOL THERAPY.

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) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should not be interrupted for fever, if there are no signs of serious infection. Therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75 000/µL.

Testicular Radiation Therapy

Patients with testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 14.0). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **vincristine, which is capped at a maximum dose of 2 mg**
- **dasatinib, which is capped at a maximum of 140 mg/day**

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Dasatinib: PO
Days 1-56
Dose: 60 mg/m^2/dose. Rounded to the nearest 5 mg, up to a maximum of 140 mg/day (refer to Appendix I)

Administer continuously once daily. **Dasatinib treatment shall continue without planned interruption until the completion of maintenance therapy. Hold drug only for toxicity** (Refer to Section 5.6 for dose modifications).

Administration in young children: Swallowing the tablets whole is preferable due to differences in PK between the tablet and oral suspension. If absolutely necessary to permit administration in young children, the intact tablets may be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. **PLEASE NOTE**: THE DASATINIB TABLETS SHOULD NOT BE CRUSHED. See Section 6.5 for complete administration instructions.

Cyclophosphamide: IV over 30-60 minutes
Days 1 and 29
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Mercaptopurine: PO
Days 1-14 and 29-42
Dose: 60 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

*See Section 5.9. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details. Do not escalate or reduce dose based on blood counts during this cycle.

Methotrexate: Intrathecal (IT)
Days 1, 8, 15 and 22 (**Omit Days 15 and 22 for CNS3 patients)**
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours
Days 15 and 43
Dose: 2500 International Units/m^2/dose

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

Special precautions:

4. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
5. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
6. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Disease Evaluation during Consolidation

- Patients with Induction Day 29 MRD ≥ 0.01% are required to have a Consolidation Day 56 (or IM Day 1 for convenience) BM examination to evaluate remission status.

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

Following completion of Consolidation, the next course (Interim Maintenance with HD MTX, Section 4.16) starts on Day 57 or when blood count parameters are met (whichever occurs later).

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

4.15.1 **CONSOLIDATION (56 days)** – Ph-like B-ALL Patients with predicted TKI-sensitive mutation assigned to **Dasatinib Arm**

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 & platelets ≥ 75 000/µL (whichever occurs later).
This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dasatinib	PO	60 mg/m^2/dose	Days 1-56		a) Hx, PE, Wt., Ht. b) CBC/diff/platelets c) CSF cell count, cytospin! d) Bilirubin ALT, & Creatinine, e) BM Evaluation f) EKG (& echocardiogram if cardiopulmonary symptoms of unknown cause) g) Performance Status ! Obtain with each IT administration See Section 7.1d for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Days 1 & 29	See Section 4.15 for admin guidelines	
Cytarabine (ARAC)	IV over 1-30 mins or SubQ	75 mg/m^2/dose	Days 1-4, 8-11, 29-32 & 36-39		
Mercaptopurine (MP)	PO	60 mg/m^2/dose*	Days 1-14 & 29-42	See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.15 for admin 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, 8, 15 & 22	See Section 4.15 for admin guidelines **Note age-based dosing** **Omit Days 15 & 22 for CNS3**	
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 15, 22, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Days 15 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Patients with testicular disease at diagnosis & continued clinical evidence of testicular disease at end-Induction will receive testicular XRT. See Section 4.15 & Section 14.0 for additional details.

Ht____ cm Wt____ kg BSA____ m^2

Date Due	Date Given	Day	Dasatinib	CPM ___mg	ARAC ___mg	MP ___mg	IT MTX ___mg	VCR ___mg	PEG-ASP ___IU	Studies	Comments
				Enter calculated dose above and actual dose administered below							
		-6 to 1								f++	
		1	___mg	mg	___mg	___mg	mg			a, b, c, d, h%	
		2									
		3									
		4									
		8			___mg		___mg			b, c	
		9									
		10									
		11									
		14									
		15#					mg#	mg	IU	b, c	
		22#					mg#	___mg		b, c,	
		29^		mg	___mg	___mg				b	
		30									
		31									
		32									
		33									
		34									
		35									
		36			___mg					b	
		37									
		38									
		39									
		40									
		41									
		42									
		43						mg	IU	b	
		50						___mg		b	
		56								e$	
	Begin next course (Interim Maintenance with HD MTX, Section 4.16) on Day 57 or when blood count parameters are met (whichever occurs later).										

^Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL to begin Day 29 therapy. $For patients with Induction Day 29 MRD ≥ 0.01%.
#Omit Days 15 & 22 for CNS3 pts only ++ To be performed within 6 days of starting treatment with Dasatinib. %Perform prior to Day 1 therapy.
Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

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

4.16 Interim Maintenance with HD MTX (63 days) – Ph-like with Predicted TKI-Sensitive Mutation (Dasatinib Arm)

Criteria to Start Interim Maintenance
Begin IM on Day 57 of Consolidation or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later.

Interruption and/or Modification of Therapy
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.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **vincristine, which is capped at a maximum dose of 2 mg**
- **dasatinib, which is capped at a maximum of 140 mg/day**

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Dasatinib: PO
Days 1-63
Dose: 60 mg/m^2/dose. Rounded to the nearest 5 mg, up to a maximum of 140 mg/day (refer to Appendix I)

Administer continuously once daily. **Dasatinib treatment shall continue without planned interruption until the completion of maintenance therapy. Hold drug only for toxicity** (Refer to Section 5.6 for dose modifications).

Administration in young children: Swallowing the tablets whole is preferable due to differences in PK between the tablet and oral suspension. If absolutely necessary to permit administration in young children, the intact tablets may be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. **PLEASE NOTE**: THE DASATINIB TABLETS SHOULD NOT BE CRUSHED. See Section 6.5 for complete administration instructions.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

High Dose Methotrexate: IV over 24 hours
Days 1, 15, 29, and 43
Dose: 5000 mg/m^2/dose (no maximum dose)

ANC must be ≥ 750/µL and platelets must be ≥ 75 000/µL prior to each dose of HD MTX.

Leucovorin: PO/IV
Days 3-4, 17-18, 31-32, and 45-46
Dose: 15 mg/m^2/dose x minimum of 3 doses given at 42, 48 and 54 hours after the start of HD MTX infusion.

See next page for HD MTX/LCV rescue and infusion guidelines.

Methotrexate: Intrathecal (IT)
Days 1 and 29
Age-based dosing:

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

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Mercaptopurine: PO
Days 1-56
Dose: 25 mg/m^2/dose once daily

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 175 mg/m^2/week as possible. See Appendix II for details. Do not escalate or reduce dose based on blood counts during this cycle. Mercaptopurine should be held for ANC < 750/µL or platelets < 75 000/µL. 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 (see Section 5.9).

HD MTX/LCV Rescue and Infusion Guidelines
See Section 5.8.1 for further details.

When IT therapy and HD MTX are scheduled for the same day, deliver the IT therapy within 6 hours of

the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).

Hold trimethoprim/sulfamethoxazole (TMP-SMX), 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 medications until MTX level is less than 0.1 µM.*

Recommended Prehydration with D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. An acetate or bicarbonate bolus (0.5- 1 mEq/kg over 15 minutes) may be given to raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Recommend hydration for a minimum of 54 hours after the MTX bolus is started for patients who meet expected clearance parameters. In patients with delayed MTX clearance, continue hydration and leucovorin as instructed (Appendix IV-A) until the plasma MTX concentration is below 0.1 µM.

Hour 0: MTX 500 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the 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 and Appendix IV-A)

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 5.8.1.1). 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 5.8.1.1.

If the 24 hour level is ≥ 150 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table in Section 5.8.1.1.

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 5.8.1.1.

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

Following completion of Interim Maintenance with HD MTX, the next course (Delayed Intensification, Section 4.17) starts on Day 64 or when blood count parameters are met (whichever occurs later).

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

4.16.1 **INTERIM MAINTENANCE I with HD MTX (63 days)** – Ph-like B-ALL Patients with predicted TKI-sensitive mutationassigned to **Dasatinib Arm**	_____ Patient name or initials _____ DOB

Begin Interim Maintenance when peripheral counts recover with an ANC ≥ 750/µL & platelets ≥ 75 000/µL. See Section 4.16 for therapy interruption guidelines. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dasatinib IND	PO	60 mg/m^2/dose	1-63		a) Hx, PE, Wt. Ht. b) CBC/diff/platelets c) CSF cell count, cytospin! d) Bilirubin, ALT & Creatinine e) BM evaluation ! Obtain with each IT administration See Section 7.1d for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 1, 15, 29, & 43	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
High Dose Methotrexate (HD MTX)	IV over 24 hours	5000 mg/m^2 (no max dose)	Days 1, 15, 29, & 43	See Section 4.16 & Appendix IV-A for admin guidelines.	
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	Days 3-4, 17-18, 31-32, & 45-46	42, 48, and 54 hours after the start of HD MTX infusion. See Section 5.8.1.1 and Appendix IV-A for admin 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	See Section 4.16 for admin guidelines **Note age-based dosing** When IT therapy and HD MTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).	
Mercaptopurine (MP)	PO	25 mg/m^2/dose	Days 1-56	See Section 4.16 for admin guidelines	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	Dasatinib	VCR ___mg	HD MTX ___mg	LCV ___mg	IT MTX ___mg	MP ___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				___mg**				
		4								

		15		___mg	___mg				b, d	
		16								
		17				___mg**				
		18								

		29		mg	mg		mg		b, c, d	
		30								
		31				___mg**				
		32								

		43		mg	mg				b, d	
		44								
		45				___mg**				
		46								

		56								
		63								
		64	**Begin next course (Delayed Intensification, Section 4.17) on Day 64 or when blood count parameters are met (whichever occurs later).**							

*A bone marrow aspirate for morphology is required.
**Please document the number of doses of leucovorin administered

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

4.17 Delayed Intensification (1-56 days) – Ph-like with Predicted TKI-Sensitive Mutation (Dasatinib Arm)

Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL prior to starting therapy on Days 1 and 29. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Otherwise, therapy should not be interrupted for uncomplicated myelosuppression or fever.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **vincristine, which is capped at a maximum dose of 2 mg**
- **dasatinib, which is capped at a maximum of 140 mg/day**

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Dasatinib: PO
Days 1-56
Dose: 60 mg/m^2/dose. Rounded to the nearest 5 mg, up to a maximum of 140 mg/day (refer to Appendix I)

Administer continuously once daily. **Dasatinib treatment shall continue without planned interruption until the completion of maintenance therapy. Hold drug only for toxicity** (Refer to Section 5.6 for dose modifications).

Administration in young children: Swallowing the tablets whole is preferable due to differences in PK between the tablet and oral suspension. If absolutely necessary to permit administration in young children, the intact tablets may be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. **PLEASE NOTE**: THE DASATINIB TABLETS SHOULD NOT BE CRUSHED. See Section 6.5 for complete administration instructions.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may give IV)
Days 1-7 and 15-21
Dose: 5 mg/m^2/dose BID (i.e., total daily dose: 10 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m^2/day, divided BID) may be used temporarily as needed.

DOXOrubicin: IV push/infusion over 1-15 minutes
Days 1, 8 and 15.
Dose: 25 mg/m^2/dose

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 or central venous access device.

Special precautions: Medication errors have occurred due to confusion between DOXOrubicin and DAUNOrubicin. DOXOrubicin is available in a liposomal formulation (DOXOrubicin liposomal, Doxil®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intrathecal (IT)
Days 1, 29 and 36
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Pegaspargase: IV over 1-2 hours
Day 4 and 43
Dose: 2500 International Units/m^2/dose

Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.

Special precautions:

4. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
5. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
6. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to

treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Cyclophosphamide: IV over 30-60 minutes
Day 29 ONLY
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Thioguanine: PO
Days 29-42.
Dose: 60 mg/m^2/dose/once daily

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix III for details.

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

Following completion of Delayed Intensification 1, the next course (Interim Maintenance II, Section 4.18) starts on Day 57 or when blood count parameters are met (whichever occurs later).

The Therapy Delivery Maps (TDMs) for Delayed Intensification are on the next 2 pages.

4.17.1a **DELAYED INTENSIFICATION Day 1-28**– Ph-like B-ALL Patients with predicted TKI-sensitive mutationassigned to **Dasatinib Arm**

_____ _____
Patient name or initials DOB

To begin Delayed Intensification therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL. See Section 4.17 for therapy interruption guidelines. This Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dasatinib	PO	60 mg/m^2/dose	1-28		a) Hx, PE, Wt., Ht. b) CBC/diff/platelets c) CSF Cell count, cytospin! d) Bilirubin, ALT &, Creatinine e) Echocardiogram ! Obtain with each IT admin. See Section 7.1d for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 1, 8, & 15	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX)	PO (may give IV)	5 mg/m^2/dose BID	Days 1-7 & 15-21	Total daily dose: 10 mg/m^2/day, divided BID. See Section 4.17 for admin. Guidelines	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m^2/dose	Days 1, 8 & 15	See Section 4.17 for admin 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	Day 1	See Section 4.17 for admin. guidelines **Note age-based dosing**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 4	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	Dasatinib	VCR mg	DEX mg	DEX mg	DOXO mg	IT MTX mg	PEG-ASP IU	Studies	Comments
				Enter calculated dose above and actual dose administered below							
		1	____mg	mg	mg	mg	mg	mg		a, b, c, d, e	
		2			mg	mg					
		3			mg	mg					
		4			mg	mg			IU		
		5			mg	mg					
		6			mg	mg					
		7			mg	mg					
		8		mg			mg			b	

		15		mg	mg	mg	mg			b	
		16			mg	mg					
		17			mg	mg					
		18			mg	mg					
		19			mg	mg					
		20			mg	mg					
		21			mg	mg					

		28		**This therapy delivery map continues on the next page.**							

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

4.17.1b **DELAYED INTENSIFICATION Day 29-57–** Ph-like B-ALL Patients with predicted TKI-sensitive mutationassigned to **Dasatinib Arm**

_____ Patient name or initials

_____ DOB

To begin Delayed Intensification therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL. See Section 4.17 for therapy interruption guidelines. This Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dasatinib	PO	60 mg/m^2/dose	Days 29-56		a) Hx, PE, Wt., Ht b) CBC/diff/platelets c) CSF Cell count, cytospin! d) Bilirubin, ALT & Creatinine ! Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Day 29	See Section 4.17 for administration guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m^2/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m^2/dose	Days 29-42	See Section 4.17 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 29 & 36	See Section 4.17 for administration guidelines **Note age-based dosing**	
VinCRIStine (VCR)	IV push over 1 minute$^+$	1.5 mg/m^2/dose	Days 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	Dasatinib	VCR mg	IT MTX mg	PEG-ASP IU	CPM mg	ARAC mg	TG mg	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		29^	____mg		____mg		____mg	____mg	____mg	b, c, d	
		30	↓					↓	↓		
		31									
		32									
		33									
		34									
		35									
		36			____mg			____mg		b, c	
		37						↓			
		38									
		39									
		40									
		41									
		42							↓		
		43		____mg		____IU				b	

		50		____mg						b	
		--									
		56	↓								
		57	**Begin next course (Interim Maintenance II, Section 4.18) on Day 57 or when blood count parameters are met (whichever occurs later).**								

^ Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL to begin Day 29 therapy.

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

4.18 Interim Maintenance II with Capizzi MTX (56 days) – Ph-like with Predicted TKI-Sensitive Mutation (Dasatinib Arm)

This therapy is common for all Ph-like B-ALL patients with kinase mutations assigned to treatment on the Dasatinib Arm. Patients receive standard MBFM therapy with Capizzi style methotrexate. Interim Maintenance II lasts 56 days.

Criteria to Start Interim Maintenance II

Begin IM II on Day 57 of Delayed Intensification or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later.

Interruption and/or Modification of Therapy

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 prior to each 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) In 4 days, if ANC ≥ 500/µL and platelets ≥ 50 000/µL, give same dose of methotrexate as previous cycle.
   2) In 4 days, if ANC is still < 500/µL or platelets < 50 000/µL, give VCR (and IT MTX if Day 31) and pegaspargase (if due) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.
      a. If after 7 days, ANC ≥ 500/µL and platelets ≥ 50 000/µL, reduce dose of MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.
      b. If after 7 days ANC is still < 500/µL or platelets < 50 000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50 000/µL. When ANC ≥ 500/µL and platelets ≥ 50 000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A-C.

B) If ANC ≥ 500/µL but < 750/µL and/or platelets ≥ 50 000/µL but < 75 000/µL, give same dose of MTX as previously (i.e. no escalation).

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

D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A-C.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **vincristine, which is capped at a maximum dose of 2 mg**
- **dasatinib, which is capped at a maximum of 140 mg/day**

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Dasatinib: PO
Days 1-56
Dose: 60 mg/m^2/dose. Rounded to the nearest 5 mg, up to a maximum of 140 mg/day (refer to Appendix I)

Administer continuously once daily. **Dasatinib treatment shall continue without planned interruption until the completion of maintenance therapy. Hold drug only for toxicity** (Refer to Section 5.6 for dose modifications).

Administration in young children: Swallowing the tablets whole is preferable due to differences in PK between the tablet and oral suspension. If absolutely necessary to permit administration in young children, the intact tablets may be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. **PLEASE NOTE**: THE DASATINIB TABLETS SHOULD NOT BE CRUSHED. See Section 6.5 for complete administration instructions.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: IV over 2-5 minutes (undiluted) or over 10-15 minutes (diluted).
Days 1, 11, 21, 31 and 41

Starting dose of 100 mg/m^2 and then **escalate by 50 mg/m^2/dose**

Methotrexate: Intrathecal (IT)
Days 1 and 31
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Pegaspargase: IV over 1-2 hours
Days 2 and 22
Dose: 2500 International Units/m^2/dose

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

Special precautions:

1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

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

Following completion of Interim Maintenance II, the next course (Maintenance, Section 4.19) starts on Day 57 or when blood count parameters are met (whichever occurs later).

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

4.18.1 **INTERIM MAINTENANCE II with Capizzi MTX (56 days)** – Ph-like B-ALL with predicted TKI-sensitive mutation **(Dasatinib Arm)**	_____ Patient name or initials _____ DOB

Begin Interim Maintenance II when peripheral counts recover with an ANC ≥ 750/µL & platelets ≥ 75 000/µL. See Section 4.18 for therapy interruption guidelines. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dasatinib	PO	60 mg/m^2/dose	1-56		a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin! d. Bilirubin, ALT & Creatinine ! Obtain with each IT administration See Section 7.1d for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 1, 11, 21, 31 & 41	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Methotrexate (MTX)	IV push over 2-5 mins or IV infusion over 10-15 mins	Starting dose is 100 mg/m^2. **escalate by 50 mg/m^2/dose**	Days 1, 11, 21, 31 & 41	See Section 4.18 for admin guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Days 2 & 22	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) / Dose 1-1.99 / 8 mg 2-2.99 / 10 mg 3-8.99 / 12 mg ≥ 9 / 15 mg	Days 1 & 31	See Section 4.18 for admin guidelines **Note age-based dosing**	

Therapy Delivery Map Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	Dasatinib	VCR ____mg	IV MTX ____mg *(escalating dose)*	PEG-ASP ____IU	IT MTX _____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below						
		1	____mg ▼	____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	**Begin next course (Maintenance, Section 4.19) 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.

4.19 Maintenance – Ph-like with Predicted TKI-Sensitive Mutation (Dasatinib Arm)

Maintenance begins on Day 57 of IM II, or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and dexamethasone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12-week cycles repeated until total duration of therapy is 2 years for female patients and 3 years for male patients from the start of Interim Maintenance I. Therapy may be stopped on anniversary date if the 5-day prednisone is completed for the cycle (i.e. complete all 5 days of prednisone before ending therapy). Otherwise continue current cycle through prednisone administration.

The administration schedule below describes one 12-week cycle of Maintenance therapy.

CNS Radiation Therapy

Patients with CNS3 disease at diagnosis will receive cranial irradiation, 1800cGy in 10 fractions, during the first 4 weeks of Maintenance therapy and should be completed by Day 29 of Maintenance therapy. See Section 14.0 for details of cranial irradiation.

Dosing should be based on actual BSA. There is no maximum dosing, except for:

- **vincristine, which is capped at a maximum dose of 2 mg**
- **dasatinib, which is capped at a maximum of 140 mg/day**

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Dasatinib: PO
Days 1-84
Dose: 60 mg/m^2/dose. Rounded to the nearest 5 mg, up to a maximum of 140 mg/day (refer to Appendix I)

Administer continuously once daily. **Dasatinib treatment shall continue without planned interruption until the completion of maintenance therapy. Hold drug only for toxicity** (Refer to Section 5.6 for dose modifications).

Administration in young children: Swallowing the tablets whole is preferable due to differences in PK between the tablet and oral suspension. If absolutely necessary to permit administration in young children, the intact tablets may be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. **PLEASE NOTE**: THE DASATINIB TABLETS SHOULD NOT BE CRUSHED. See Section 6.5 for complete administration instructions.

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

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

by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

PredniSONE: PO (may give IV^)
Days 1-5, 29-33 & 57-61
Dose: 20 mg/m^2/dose BID (i.e., Total daily dose: 40 mg/m^2/day, divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. Omit on days when IT MTX is given.
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration.

Mercaptopurine: PO
Days 1-84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible. See Appendix II for details. **See Section 5.9 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1 **(also Day 29 of Cycles 1 and 2, for patients who did NOT receive CNS radiation)**
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

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

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

4.19.1 **Maintenance –** Ph-like B-ALL Patients with predicted TKI-sensitive mutation assigned to **Dasatinib Arm**	_____ Patient name or initials	_____ DOB

Maintenance begins on Day 57 of IM II or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Section 4.19 and 5.9 for details.

This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dasatinib	PO	60 mg/m^2/dose	1-84		a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[!] d. Bilirubin, ALT & Creatinine [!] Obtain with each IT administration See Section 7.1d for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 min[+]	1.5 mg/m^2/dose	Days 1, 29 & 57	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
PrednISONE (PRED)	PO (may be given IV)	20 mg/m^2/dose BID	Days 1-5, 29-33 & 57-61	Total daily dose: 40 mg/m^2/day, divided BID See Section 4.19 for admin guidelines Note: IV methylprednisolone may be substituted for prednisone at 80% of the oral dose	
Mercaptopurine (MP)	PO	75 mg/m^2/dose/day*	Days 1-84	See Section 4.19 & Appendix II for administration guidelines *See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status	
Methotrexate (MTX)	PO	20 mg/m^2/dose/week	Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 & 78	**Omit on days when IT MTX is given.**	
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 **Also Day 29 of Cycles 1 & 2 for patients who did NOT receive CNS radiation**.	See Section 4.19 for administration guidelines **Note age-based dosing**	
For patients with CNS3 disease cranial XRT (See Section 4.19 & 14.0) should begin during the first 4 weeks of Maintenance therapy and should be completed by Day 29.					

Enter Cycle # **Ht** **cm** **Wt** **kg** **BSA** **m^2**

Date Due	Date Given	Day	Dasatinib	VCR mg	PRED mg mg	MP mg	IT MTX mg	PO MTX mg	Studies	Comments
			Enter calculated dose above and actual dose administered below.							
		1	_____mg	_____mg	____mg ____mg	_____mg	_____mg		a[%], b, c, d,	
		2								
		3								
		4								
		5								
		8						_____mg		
		15						_____mg		
-		22						_____mg		
		29		_____mg	____mg ____mg		_____mg[#]	_____mg[##]	a[%], b, c[#]	
		30								
		31								
		32								
		33								
		36						_____mg		
		43						_____mg		
		50						_____mg		
		57		_____mg	____mg ____mg			_____mg	a[%], b	
		58								
		59								
		60								
		61								
-		64						_____mg		
		71						_____mg		
		78						_____mg		
		84								
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs (females) or 3 yrs (males) from start of IM I**							

[%]**Note:** Height (Ht) is only required at the beginning of each cycle

[##]**Omit on Day 29 when IT MTX is given**

[#] **Cycle 1 & 2 ONLY for patients who did NOT receive CNS radiation.**

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

4.20 Induction (Day 1-14) - DS HR B-ALL Patients (All)

This therapy is common to all DS HR B-ALL patients for the first 14 days of Induction therapy.

It is important to note that Induction therapy has been separated for convenience into 2 halves to delineate treatment after Day 15 BM examination which will determine further Induction therapy for rapid early responders (RER) with an M1 Day 15 BM and slow early responders (SER) with an M2/M3 Day 15 BM. Rapid early responders complete a 3-drug Induction, including a total of 28 days of dexamethasone for patients < 10 years and 28 days of prednisone for patients ≥ 10 years of age (see Section 4.21); while slow early responders continue Induction with a 4-drug Induction that includes a one time "rescue" anthracycline dose to complete a total of 28 days of dexamethasone for patients < 10 years and 28 days of prednisone for patients ≥ 10 years of age (see Section 4.22).

Steroids continue without interruption. Do not hold therapy while awaiting Day 15 BM results.

PLEASE NOTE THAT STEROID THERAPY IS DEPENDENT ON AGE OF PATIENT:

- **Patients < 10 years old get a dexamethasone based Induction therapy for 28 days.**
- **Patient's ≥ 10 years old get a prednisone based Induction therapy for 28 days.**

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cytarabine: Intrathecal (IT)
Given at the time of diagnostic lumbar puncture (LP) OR on Day 1.May be given up to 72 hours prior to the start of protocol therapy for patient convenience .
Age-based dosing:

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

For IT administration use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8
Dose: 1.5 mg/m^2/dose (maximum 2 mg)

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may be given IV) – Patients < 10 years ONLY
Days 1-14 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/day, divided BID) may be used temporarily as needed.

PredniSONE: PO (may give IV^) – Patients ≥ 10 years ONLY
Days 1-14 (do not taper)
Dose: 30 mg/m^2/dose BID (Total daily dose: 60 mg/m^2/day divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Pegaspargase: IV over 1-2 hours.
Day 4
Dose: 2500 International Units/m^2/dose

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

Special precautions:
1 Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
2 Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Methotrexate: Intrathecal (IT)
Day 8
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO
Days 10-11
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture.

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE GUIDELINES.

Patients will complete Induction therapy based upon the patient's Day 15 BM morphology.

For patients determined to be RER: see Section 4.21
For patients determined to be SER: see Section 4.22

The therapy delivery map (TDM) for Induction (Day 1-14) is on the next page.

4.20.1 Induction—DS HR B-ALL Patients (Day 1-14)

Leucovorin rescue will be given after each IT MTX

_____ Patient name or initials _____ DOB

See Section 4.20 for full treatment details. 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 LP OR Day 1	See Section 4.20 for administration guidelines **Note age-based dosing**	**a.** Hx, PE, Wt ., Ht. b. CBC/diff/platelets c. BM eval[1] d. PB sample[1] e. CSF cell count, cytospin[2] f. Bilirubin, ALT & Creatinine g. Varicella titer h. IgG i. Echocardiogram j. Pregnancy test [1]See Section 7.1c for further details [2] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	Days 1 & 8	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Dexamethasone (DEX) **(For patients < 10 years ONLY)**	PO (may give IV)	3 mg/m^2/dose BID	Days 1-14 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.20 for admin guidelines	
PredniSONE (PRED) **(For patients ≥ 10 years ONLY)**	PO (may give IV)	30 mg/m^2/dose BID (may be given IV)	Days 1-14 (do not taper)	Total daily dose: 60 mg/m^2/day, divided BID Note: IV methylprednisolone may be substituted for predniSONE at 80% of the dose. See Section 4.20 for admin guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Day 4	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl **Note: pegaspargase must be administered on Day 4**	
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 8	See Section 4.20 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m^2/dose q12 hrs x 2doses	Days 10-11	48 & 60 hrs after each IT MTX. See Section 4.20 for administration guidelines	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	IT ARAC ____mg	VCR ____mg	DEX (BID Dosing) ____mg ____mg **(Pts < 10years only)**	PRED (BID Dosing) ____mg ____mg **(Pts≥10years only)**	PEG-ASP ____IU	IT MTX ____mg	LCV ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		-2/-1/0/LP*	____mg							(a[%], b, c, e, f, g, h, i[+], j) [@]	
		1		____mg	____mg ____mg	____mg ____mg					
		2									
		3									
		4					____IU				

		8		____mg				____mg		a[%], b, e	
		9									
		10							____mg		
		11							____mg		

		14									
		Continue Induction based on Day 15 BM response (RER: Section 4.21 SER: Section 4.22)									

[%]**Note:** Height (Ht) is only required at the beginning of each course. [+]Must be done prior to Day 15, if unable to obtain at baseline.

[@] Baseline

***** *On Day 1* ***OR*** *at the time of diagnostic LP if ≤ 72 hrs from the start of protocol therapy*

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

4.21 Induction (Day 15-29) - DS HR B-ALL Patients (RER)

This therapy is for rapid early responders (RER - M1 Day 15 BM). Patients will complete a 3-drug Induction, including a total of 28 days of dexamethasone for patients < 10 years and 28 days of prednisone for patients ≥ 10 years of age.

PLEASE NOTE THAT STEROID THERAPY IS DEPENDENT ON AGE OF PATIENT:

- **Patients < 10 years old get a dexamethasone based Induction therapy.**
- **Patients ≥ 10 years old get a prednisone based Induction therapy.**

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may be given IV) – Patients < 10 years ONLY
Days 15-28 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/day, divided BID) may be used temporarily as needed.

PredniSONE: PO (may give IV^) – Patients ≥ 10 years ONLY
Days 15-28 (do not taper)
Dose: 30 mg/m^2/dose BID (Total daily dose: 60 mg/m^2/day divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Methotrexate: Intrathecal (IT)
Day 29 (CNS3 also on Days 15 and 22)
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO
Days 31-32 (CNS3 also on Days 17-18 and 24-25)
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture.
Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Disease Evaluations During Induction (Day 15-29)

- Day 15: Bone marrow sample will be obtained for morphology the results of which will determine therapy for the rest of Induction.
    - RER: M1 Marrow.
    - SER: M2/M3 Marrow.
- Day 29: Bone marrow sample will be obtained for morphology and a 2 mL aliquot will be shipped to a COG ALL Flow Cytometry Approved Reference Laboratory for MRD determination.

Research Studies (for patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for ALL*))

- Day 29: 5 mL of peripheral blood will be obtained and shipped to the COG ALL Molecular Reference Laboratory for studies of genomic variation and cell banking. ***This specimen is very important and should be obtained on all patients that have provided consent.***

NOTE: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG ALL FLOW CYTOMETRY APPROVED REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY

SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE GUIDELINES.

Following Induction therapy, begin next course, Consolidation (Section 4.23) on Day 36 or when blood count parameters are met (whichever occurs later).

The therapy delivery map (TDM) for Induction (Day 15-29) is on the next page.

4.21.1 **Induction (Day 15-29) — DS HR-ALL (RER)** Leucovorin rescue will be given after each IT MTX	_____ Patient name or initials _____ DOB

See Section 4.21 for full treatment details. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 15 & 22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	**a.** Hx, PE, Wt., Ht. b. CBC/diff/platelets c. BM eval[1] d. PB sample[1] e. CSF cell count, cytospin[2] f. TPMT and NUDT15 genotype[#]
Dexamethasone (DEX) **(For patients < 10 years ONLY)**	PO (may give IV)	3 mg/m^2/dose BID	Days 15-28 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.21 for admin guidelines	
PrediniSONE (PRED) **(For patients ≥ 10 years ONLY)**	PO (may give IV)	30 mg/m^2/dose BID	Days 15-28 (do not taper)	Total daily dose: 60 mg/m^2/day, divided BID Note: IV methylprednisolone may be substituted for prednisone at 80% of the dose See Section 4.21 for admin guidelines	[1]See Section 7.1cc for further details [2] Obtain with each IT administration
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 29 **CNS3 also Days 15 & 22**	See Section 4.21 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m^2/dose q12 hrs x 2 doses	Days 31-32 CNS3 also Days 17-18 & 24-25	48 & 60 hrs after each IT MTX. See Section 4.21 for administration guidelines	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	VCR ____mg	DEX (BID Dosing) ____mg ____mg **pts <10 years only**	PRED (BID Dosing) ____mg ____mg **Pts ≥ 10 years only**	IT MTX _____mg	LCV _____mg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		15	_____mg	____mg ____mg	____mg ____mg	_____mg^		a%, b, c#, e^, f	
		16							
		17					_____mg^		
		18					_____mg^		

		22	____mg			_____mg^		a%, b, e^	
		23							
		24					_____mg^		
		25					_____mg^		

		28							
		29				_____mg		a%, b, c$, d**, e	
		30							
		31					_____mg		
		32					_____mg		

		36	**Begin Consolidation (Section 4.23) on Day 36 or when blood count parameters are met (whichever occurs later).**						

^CNS3 patients only **% Note:** Height (Ht) is only required at the beginning of each course.

[#] TPMT and NUDT15 genotype (TPMT highly recommended for all subjects; NUDT15 is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects (See Section 5.9)

[#] Day 15 BM sample is **important** for response evaluation.

Day 29 PB sample should be shipped to the COG ALL Molecular Reference Laboratory for all patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for ALL*). ***This specimen is very important.*

[$]NOTE: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG ALL FLOW CYTOMETRY APPROVED REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

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

4.22 Induction (Day 15-29) - DS HR-ALL Patients (SER)

This therapy is for slow early responders (SER - M2/M3 Day 15 BM). Patients continue Induction with a 4-drug Induction that includes a one time "rescue" anthracycline dose and a total of 28 days of dexamethasone for patients < 10 years and 28 days of prednisone for patients ≥ 10 years of age.

PLEASE NOTE THAT STEROID THERAPY IS DEPENDENT ON AGE OF PATIENT:

- **Patients < 10 years old get a dexamethasone based Induction therapy.**
- **Patients ≥ 10 years old get a prednisone based Induction therapy.**

Myeloid Growth Factor Support: for example filgrastim (G-CSF) **5 mcg/kg/dose SubQ/IV** starting 24 hours after daunorubicin until ANC is ≥ 750/µL on 2 consecutive days after the expected nadir. Myeloid growth factor support need not be limited to filgrastim; pegfilgrastim is also permitted according to the institution's standard guidelines. Discontinue at least 48 hours before the next chemotherapy course.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DAUNOrubicin: IV push/infusion over 1-15 minutes
Day 15*
Dose: 50 mg/m^2/dose

*Please note: Daunorubin should be given as soon as Day 15 BM response is known (i.e. Day 15 or subsequently)

The reconstituted solution or the commercially available solution (5 mg/mL) can be administered (undiluted or diluted) 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 administer through the tubing of a rapidly infusing solution of D_5W or 0.9% NaCl, infused into a large vein or central venous access device. Protect from sun light.

Special precautions: Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DAUNOrubicin is available in a liposomal formulation (DAUNOrubicin citrate,

DaunXome®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may be given IV) – Patients < 10 years ONLY
Days 15-28 (do not taper)
Dose: 3 mg/m^2/dose BID (i.e., total daily dose: 6 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m^2/day) may be used temporarily as needed.

PrednisONE: PO (may give IV^) – Patients ≥ 10 years ONLY
Days 15-28 (do not taper)
Dose: 30 mg/m^2/dose BID (Total daily dose: 60 mg/m^2/day divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Methotrexate: Intrathecal (IT)
Day 29 (CNS3 also Days 15 and 22)
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO
Days 31-32 (CNS3 also Days 17-18 and 24-25)
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture.
Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Disease Evaluations During Induction (Day 15-29)

- Day 15: Bone marrow sample will be obtained for morphology the results of which will determine therapy for the rest of Induction.
    - RER: M1 Marrow
    - SER: M2/M3 Marrow
- Day 29: Bone marrow sample will be obtained for morphology and a 2 mL aliquot will be shipped to a COG ALL Flow Cytometry Approved Reference Laboratory for MRD determination.

Research Studies (for patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for ALL patients*))

- Day 29: 5 mL of peripheral blood will be obtained and shipped to the COG ALL Molecular Reference Laboratory for studies of genomic variation and cell banking. ***This specimen is very important and should be obtained on all patients that have provided consent.***

NOTE: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG ALL FLOW CYTOMETRY APPROVED REFERENCE LABORATORY AND RESULTS AVAILABLE FOR RISK STRATIFICATION, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

SEE SECTION 5.0 FOR DOSE MODIFICATIONS AND TOXICITIES. SEE SECTION 8.0 FOR SUPPORTIVE CARE GUIDELINES.

Following Induction therapy, begin next course, Consolidation (Section 4.23) on Day 36 or when blood count parameters are met (whichever occurs later).

The therapy delivery map (TDM) for Induction (Day 15-29) is on the next page.

4.22.1 **Induction (Day 15-29) — DS HR-ALL Patients (SER)**
Leucovorin rescue will be given after each IT MTX

_____ Patient name or initials _____ DOB

See Section 4.22 for full treatment details. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	Days 15 & 22	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt , Ht. b. CBC/diff/platelets c. BM eval[1] d. CSF cell count, cytospin[2] e PB sample[1] f TPMT and NUDT15 genotype (optional) [1]See Section 7.1c for further details [2] Obtain with each IT administration **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX) **(For patients < 10 years ONLY)**	PO (may give IV)	3 mg/m^2/dose BID	Days 15-28 (do not taper)	Total daily dose: 6 mg/m^2/day, divided BID See Section 4.22 for admin. guidelines	
PrediniSONE (PRED) **(For patients ≥ 10 years ONLY)**	PO (may give IV)	30 mg/m^2/dose BID	Days 15-28 (do not taper)	Total daily dose: 60 mg/m^2/day, divided BID Note: IV methylprednisolone may be substituted for predniSONE at 80% of the oral dose See Section 4.22 for admin. guidelines	
DAUNOrubicin (DAUN)	IV push/infusion over 1-15 min	50 mg/m^2/dose	Day 15*	**Please note**: Give one time daunorubicin dose as soon as Day 15 BM response is known.	
Start myeloid growth factor support, for example filgrastim (G-CSF) **5mcg/kg/dose SubQ/IV** starting 24 hours after daunorubicin dose; continue until ANC is ≥ 750/µL on 2 consecutive days after the expected nadir. Discontinue at least 48 hours before the next chemotherapy course.					
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 29 **CNS3 also Days 15 & 22**	See Section 4.22 for administration guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m^2/dose q12 hrs x 2 doses	Days 31-32 **CNS3 also Days 17-18 & 24-25**	48 & 60 hrs after each IT MTX. See Section 4.22 for administration guidelines	

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	VCR ____mg	DAUN ____mg	Myeloid growth factor used: _____ mcg	DEX (BID Dosing) ____mg ____mg **pts <10 years only**	PRED (BID Dosing) ____mg ____mg **Pts ≥ 10 years only**	IT MTX _____mg	LCV ____mg	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		15	____mg	____mg* X 1 dose	Start Date: __/__/__	____mg ____mg	____mg ____mg	____mg^		a%, b, c#, d^, f	
		16									
		17							____mg^		
		18							____mg^		

		22	____mg					____mg^		a%, b, d^	
		23									
		24							____mg^		
		25							____mg^		

		28									
		29						____mg		a%, b, c$, d, e**	

		31			Stop Date: __/__/__				____mg		
		32							____mg		

		36	**Begin Consolidation (Section 4.23) on Day 36 or when blood count parameters are met (whichever occurs later).**								

^CNS3 patients only

% **Note:** Height (Ht) is only required at the beginning of each course.

Day 15 BM sample is **important** for response evaluation.

***Please note that Daunorubicin is to be given as soon as Day 15 BM response is known. Enter date given: ___/___/___**

Day 29 PB sample should be shipped to the COG ALL Molecular Reference Laboratory for all patients that consented to studies of genomic variation on AALL08B1 or APEC14B1 (*if available for ALL*). ***This specimen is very important.* $**NOTE: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG ALL FLOW CYTOMETRY APPROVED REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.**

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

4.23 Consolidation (56 days) – DS HR B-ALL Patients (All Patients).

FOR PATIENTS WITH DS SR B-ALL ON AALL0932 WHO ARE ELIGIBLE TO CONTINUE POST-INDUCTION THERAPY ON AALL1131, CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY.

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 severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should not be interrupted for fever, if there are no signs of serious infection. Therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 chemotherapy until ANC ≥ 750/μL and platelets ≥ 75 000/μL.

Testicular Radiation Therapy
Patients with Down syndrome and testicular disease at diagnosis and continued clinical evidence of testicular disease at the end of Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see Section 14.0). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cyclophosphamide: IV over 30-60 minutes
Days 1 and 29
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Mercaptopurine: PO
Days 1-14 and 29-42
Dose: 60 mg/m^2/dose once daily

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix II for details. Do not escalate or reduce dose based on blood counts during this cycle.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hour
Days 15 and 43
Dose: 2500 International Units/m^2/dose

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

Special precautions:
1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Methotrexate: Intrathecal (IT)
Days 1, 8, 15 and 22(**Omit Days 15 and 22 for CNS3 patients**)
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO
Days 3-4, 10-11, 17-18 and 24-25
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture.

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Disease Evaluation during Consolidation

- Patients with Induction Day 29 MRD ≥ 0.01% are required to have a Consolidation Day 56 (or IM Day 1 for convenience) BM examination to evaluate remission status.
- Patients with EOI MRD ≥ 0.01% will have an end of Consolidation (or IM Day1 for convenience) BM for MRD testing. Send BM to the Eastern or Western ALL Flow Cytometry Reference Laboratory (see Section 7.4 for shipping requirements and addresses). Please note that decentralized testing does not apply to this specimen. Patients with EOC MRD ≥ 0.01% who are not M2/M3 may be eligible for AALL1721 (when available).

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

Following completion of Consolidation, the next course (Interim Maintenance with ID MTX, (Section 4.24) starts on Day 57 or when blood count parameters are met (whichever occurs later).

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

4.23.1 CONSOLIDATION (56 days) – DS HR B-ALL Patients (All Patients)

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 & platelets ≥ 75 000/µL (whichever occurs later). This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m^2/dose	Days 1 & 29	See Section 4.23 for admin guidelines	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[!] d. Bilirubin, ALT, Creatinine e. IgG f. BM Evaluation[+] ! Obtain with each IT administration [!]See Section 7.1c for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cytarabine (ARAC)	IV over 1-30 mins or SubQ	75 mg/m^2/dose	Days 1-4, 8-11, 29-32 & 36-39		
Mercaptopurine (MP)	PO	60 mg/m^2/dose	Days 1-14 & 29-42	See Section 4.23 for admin guidelines	
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	Days 15, 22, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m^2/dose	Days 15 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1, 8, 15 & 22 **Omit Days 15 & 22 for CNS3 pts only**	See Section 4.23 for admin guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m^2/dose	Days 3-4, 10-11, 17-18 and 24-25	48 & 60 hrs after each IT MTX	

Patients with testicular disease at diagnosis & continued clinical evidence of testicular disease at end-Induction will receive testicular XRT. See Sections 4.28 & 14.0 for additional details.

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Day	CPM mg	ARAC mg	MP mg	VCR mg	PEG-ASP IU	IT MTX mg	LCV mg	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		1	___mg	___mg	___mg			___mg		a, b, c, d, e	
		2		↓	↓						
		3		↓	↓				___mg		
		4		↓	↓				___mg		
		--									
		8		___mg	↓			___mg		b, c	
		9		↓	↓						
		10		↓	↓				___mg		
		11		↓	↓				___mg		
		--									
		14			↓						
		15				___mg	___IU	___mg*		b, c*	
		16									
		17							___mg*		
		18							___mg*		
		--									
		22				___mg		___mg*		b, c*	
		23									
		24							___mg*		
		25							___mg*		
		--									
		29^	___mg	___mg	___mg					b, e	
		30		↓	↓						
		31		↓	↓						
		32		↓	↓						
		33			↓						
		34			↓						
		35			↓						
		36		___mg	↓					b	
		37		↓	↓						
		38		↓	↓						
		39		↓	↓						
		40		↓	↓						
		41			↓						
		42			↓						
		43				___mg	___IU			b	
		--									
		50				___mg				b	
		--									
		56								f[+]	
		57	**Begin next course (Interim Maintenance, Section 4.24) on Day 57 or when blood count parameters are met (whichever occurs later).**								

*Omit for CNS3 patients only. ^ Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL to begin Day 29 therapy

+For patients with Induction Day 29 MRD ≥ 0.01%, send a 2 mL aliquot of the Consolidation Day 56 or IM Day 1 BM sample to a COG ALL Flow Cytometry Approved Reference Lab for MRD (see Section 7.4 for shipping requirements and addresses) This specimen does not apply to patients enrolled prior to Amendment #6.

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

4.24 Interim Maintenance with ID MTX (63 days) - DS HR B-ALL Patients (All Patients)

Criteria to Start Interim Maintenance
Begin IM on Day 57 of Consolidation or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later.

Interruption and/or Modification of Therapy
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.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Intermediate Dose Methotrexate: IV over 24 hours
Days 1, 15, 29, and 43
Dose: 2000 mg/m^2/dose

ANC must be ≥ 750/µL and platelets must be ≥ 75 000/µL prior to each dose of ID MTX.

Leucovorin: PO/IV
Days 2-3, 17-18, 31-32, and 45-46.
Dose: 15 mg/m^2/dose for a minimum of 5 doses given at 30, 36, 42, 48 and 54 hours after the start of ID MTX infusion. If tolerated (see below), subsequent cycles of ID MTX should be followed by leucovorin 15 mg/m^2 x minimum 4 doses given at 36, 42, 48 and 54 hours after the start of ID MTX infusion.

See next page for ID MTX/LCV rescue and infusion guidelines. **Please note that the dose of MTX and leucovorin rescue for DS patients are different from those of non-DS patients.**

Mercaptopurine: PO
Days 1-56
Dose: 25 mg/m^2/dose once daily

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ 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 II for details. Do not escalate or reduce dose based on blood counts during this cycle. Mercaptopurine should be held for ANC < 750/µL or platelets < 75 000/µL. Restart mercaptopurine at full dose with next cycle of ID MTX when ANC is ≥ 750/µL and platelets are ≥ 75 000/µL. Do not make up missed doses (see Section 5.9).

Methotrexate: Intrathecal (IT)
Days 1 and 29
Age-based dosing:

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

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

ID MTX/LCV rescue and Infusion Guidelines
See Section 5.8.1 for further details.

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

Hold trimethoprim/sulfamethoxazole (TMP-SMX), any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors, or aspirin-containing medications on the day of ID MTX infusion and for at least 72 hours after the start of the ID MTX infusion and until the MTX level is less than 0.2 µM. *In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 µM.*

Recommended Prehydration with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. An acetate or bicarbonate bolus (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. Recommend hydration for a minimum of 54 hours after the MTX bolus is started for patients who meet expected clearance parameters. In patients with delayed MTX clearance, continue

hydration and leucovorin as instructed (Appendix IV-B) until the plasma MTX concentration is below 0.1 µM.

Dose of 2000 mg/m^2:

Hour 0: MTX 200 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 1800 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the ID MTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Leucovorin rescue: 15 mg/m^2 PO/IV q 6h beginning **30 hrs** after the start of the infusion for a minimum of 5 doses if 48 hr plasma MTX is < 0.2 µM. If the first cycle of ID MTX is tolerated, defined as no delayed clearance, no treatment delay due to myelosuppression, no mucositis of Grade 2 or higher, and no nephrotoxicity (pre-treatment serum creatinine >1.5x baseline or GFR creatinine clearance < 65 mL/minute/1.73 m^2), subsequent cycles of ID MTX should be followed by leucovorin 15 mg/m^2 PO/IV q 6hrs beginning **36 hrs** after the start of the infusion for a minimum of 4 doses if 48 hour plasma MTX is < 0.2 µM.

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

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 table in Section 5.8.1.2).

If the 24 hour level is < 60 µM draw the next level at hour 42 and refer to table in Section 5.8.1.2.

If the 24 hour level is ≥ 60 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to table in Section 5.8.1.2.

If the 42 and 48 hour levels are ≤ 1 and 0.2 µM, respectively, continue Leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose (see above for initial leucovorin guidelines). No additional levels are needed, nor is additional leucovorin. If levels exceed these values, see Section 5.8.1.2.

Following completion of Interim Maintenance, the next course (Delayed Intensification, Section 4.25) starts on Day 64 or when blood count parameters are met (whichever occurs later).

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

4.24.1 **INTERIM MAINTENANCE with ID MTX (63 days) – DS HR B-ALL Patients (All Patients)**	_____ Patient name or initials	_____ DOB

Begin Interim Maintenance when peripheral counts recover with an ANC ≥ 750/µL & platelets ≥ 75 000/µL. See Section 4.24 for therapy interruption guidelines. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 15, 29, & 43	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht. b. CBC/diff/platelets c. CSF cell count, cytospin[!] d. Bilirubin, ALT & Creatinine e. IgG ! Obtain with each IT administration [!]See Section 7.1c for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intermediate Dose Methotrexate (ID MTX)	IV over 24 hours	2000 mg/m²/dose	Days 1, 15, 29, & 43	See Section 4.24 & Appendix IV-B for admin guidelines	
Leucovorin (LCV)	PO/IV	15 mg/m²/dose	Days 2-3, 17-18, 31-32, and 45-46.	30, 36, 42, 48 and 54 hours after the start of ID MTX infusion. If tolerated, subsequent courses should be administered 36, 42, 48, and 54 hrs after the start of ID MTX infusion. See Section 5.8.1.2 &Appendix IV-B for admin guidelines.	
Mercaptopurine (MP)	PO	25 mg/m²/dose	Days 1-56	See Section 4.24 for admin 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	See Section 4.24 for admin guidelines **Note age-based dosing** When IT therapy and ID MTX are scheduled for the same day, deliver the IT therapy within 6 hours of the beginning of the IV MTX infusion (hour -6 to +6, with 0 being the start of the MTX bolus).	

Ht_____ cm Wt_____ kg BSA_____ m²

Date Due	Date Given	Day	VCR mg	ID MTX mg	LCV 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, e	
		2							
		3			____mg*				
		4							

		15	____mg	____mg				b, d	
		16							
		17			____mg*				
		18							

		29	____mg	____mg			____mg	b, c, d	
		30							
		31			____mg*				
		32							

		43	____mg	____mg				b, d	
		44							
		45			____mg*				
		46							

		56							

		64	**Begin next course (Delayed Intensification, Section 4.25) on Day 64 or when blood count parameters are met (whichever occurs later).**						

*Please document the number of doses of leucovorin administered.

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

4.25 Delayed Intensification - DS HR B-ALL Patients (All Patients)

Patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL prior to starting therapy on Days 1 and 29. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Otherwise, therapy should not be interrupted for uncomplicated myelosuppression or fever.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

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

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may give IV)
Days 1-7 and 15-21
Dose: 5 mg/m^2/dose BID (i.e., total daily dose: 10 mg/m^2/day, divided BID)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m^2/day, divided BID) may be used temporarily as needed.

DOXOrubicin: IV push/infusion over 1-15 minutes
Days 1, 8 and 15.
Dose: 25 mg/m^2/dose

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 infused into a large vein or central venous access device.

Special precautions: Medication errors have occurred due to confusion between DOXOrubicin and DAUNOrubicin. DOXOrubicin is available in a liposomal formulation (DOXOrubicin liposomal, Doxil®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours
Day 4 and 43
Dose: 2500 International Units/m^2/dose

Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl.

Special precautions:
1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy (see Section 5.1).
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

Cyclophosphamide: IV over 30-60 minutes
Day 29 ONLY
Dose: 1000 mg/m^2/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: PO
Days 29-42.
Dose: 60 mg/m^2/dose/once daily

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m^2/week as possible. See Appendix III for details.

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

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: Intrathecal (IT)
Days 1, 29 and 36
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO
Days 3-4, 31-32 and 38-39
Dose: 5 mg/m^2/dose x 2 doses given 48 and 60 hours after the lumbar puncture.

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy **EXCEPT Maintenance**. The first dose to be given 48 hours after the lumbar puncture and the second dose to be given approximately 60 hours after the lumbar puncture

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

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

Following completion of Delayed Intensification, the next course (Maintenance, Section 4.26) starts on Day 57 or when blood count parameters are met (whichever occurs later).

The Therapy Delivery Maps (TDMs) for Delayed Intensification are on the next 2 pages.

4.25.1a **DELAYED INTENSIFICATION -** DS HR B-ALL Patients **(All Patients)**	_____ Patient name or initials _____ DOB

To begin Delayed Intensification therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL. See Section 4.25 for therapy interruption guidelines. This Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a Hx, PE, Wt. b CBC/diff/platelets c CSF Cell count, cytospin!
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. See Section 4.25 for admin. guidelines	d Bilirubin, ALT & Creatinine, e. IgG
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m²/dose	Days 1, 8 & 15		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m²/dose	Days 4 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m²/dose	Day 29	See Section 4.25 for admin. guidelines	! Obtain with each IT admin.
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		[1]See Section 7.1c for further details
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42	See Section 4.25 for admin. guidelines	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	See Section 4.25 for admin. guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m²/dose	Days 3-4, 31-32, & 38-39	48 & 60 hrs after each IT MTX	

Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR mg	DEX mg	mg	DOXO mg	PEG-ASP IU	IT MTX mg	LCV mg	Studies	Comments
			Enter calculated dose above and actual dose administered below								
		1	mg	mg	mg	mg		mg		a, b, c, d, e	
		2		mg	mg						
		3		mg	mg				mg		
		4		mg	mg		IU		mg		
		5		mg	mg						
		6		mg	mg						
		7		mg	mg						
		8	mg			mg				b	

		15	mg	mg	mg	mg				b	
		16		mg	mg						
		17		mg	mg						
		18		mg	mg						
		19		mg	mg						
		20		mg	mg						
		21		mg	mg						

		This therapy delivery map continues on the next page.									

4.25.1b **DELAYED INTENSIFICATION -** DS HR B-ALL Patients **(All Patients)**

_____ Patient name or initials

_____ DOB

To begin Delayed Intensification therapy patients should have ANC ≥ 750/µL and platelets ≥ 75 000/µL. See Section 4.25for therapy interruption guidelines. This Therapy Delivery Map is on **two (2)** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	Days 1, 8, 15, 43 & 50	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a Hx, PE, Wt. b CBC/diff/platelets c CSF[!] Cell count, cytospin d Bilirubin, ALT & Creatinine e. IgG ! Obtain with each IT administration [!]See Section 7.1c for further details **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	10 mg/m²/day, divided BID. See Section 4.25for admin. Guidelines	
DOXOrubicin (DOXO)	IV push/infusion over 1-15 min	25 mg/m²/dose	Days 1, 8 & 15		
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International Units/m²/dose	Days 4 & 43	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cyclophosphamide (CPM)	IV over 30-60 min	1000 mg/m²/dose	Day 29	See Section 4.25for admin. guidelines	
Cytarabine (ARAC)	IV over 1-30 min or SubQ	75 mg/m²/dose	Days 29-32 & 36-39		
Thioguanine (TG)	PO	60 mg/m²/dose	Days 29-42	See Section 4.25 for admin. guidelines	
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg	Days 1, 29 & 36	See Section 4.25 for admin. guidelines **Note age-based dosing**	
Leucovorin (LCV)	PO	5 mg/m²/dose	Days 3-4, 31-32, & 38-39	48 & 60 hrs after each IT MTX	

Ht_____cm Wt_____kg BSA_____m²

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

		50	____mg								
		57	**Begin next course (Maintenance, Section 4.26) on Day 57 or when blood count parameters are met (whichever occurs later).**								

^Hold Day 29 therapy until ANC ≥ 750/µL and platelets ≥ 75 000/µL

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

4.26 Maintenance - DS HR B-ALL Patients (All Patients)

Maintenance begins on Day 57 of DI, or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only. For subsequent Maintenance cycles, please follow the dose modifications for low ANC or low platelets (Section 5.9). Only oral mercaptopurine and methotrexate will be interrupted for myelosuppression as outlined in Section 5.9. Intrathecal methotrexate, vincristine and prednisone will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12-week cycles repeated until total duration of therapy is 2 years from the start of Interim Maintenance for both male and female patients. Therapy may be stopped on anniversary date if the prednisone is completed for the 5-day prednisone pulse. If anniversary date falls during 5-day prednisone pulse, complete that 5-day pulse. Otherwise continue current cycle through prednisone administration.

The administration schedule below describes one 12-week cycle of Maintenance therapy.

CNS Radiation Therapy

Patients with CNS3 disease at diagnosis will receive cranial irradiation, 1800cGy in 10 fractions, during the first 4 weeks of Maintenance therapy, and should be completed by Day 29 of Maintenance. See Section 14.0 for details of cranial irradiation.

Dosing should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day 1
Dose: 1.5 mg/m^2/dose (maximum dose: 2 mg)

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

PredniSONE: PO (may give IV^)
Days 1-5
Dose: 20 mg/m^2/dose BID (i.e. total daily dose: 40 mg/m^2/day divided BID)

^**Note**: If a patient in unable to take predniSONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Methotrexate: PO
Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit on days when IT MTX is given.**
Dose: 20 mg/m^2/dose weekly

Administer the tablets on an empty stomach (at least 1 hour before or 2 hours after food or milk). Food or milk delays absorption and decreases the peak concentration. **See Section 5.9 for dose modifications during Maintenance**.

Mercaptopurine: PO
Days 1-84
Dose: 75 mg/m^2/dose once daily*

*See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status (if status is known)

It is strongly recommended that mercaptopurine be taken at the same time each day. Tablets are scored and doses can be rounded to half tablet.

The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ 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 II for details. **See Section 5.9 for dose modifications during Maintenance**.

Methotrexate: Intrathecal (IT)
Day 1 **(also Day 29 of Cycle 1 through 4, for patients who did NOT receive CNS radiation)**
Age-based dosing:

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

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

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

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

4.26.1 **Maintenance -** DS HR B-ALL Patients **(All Patients)**

Patient name or initials _____ DOB _____

Maintenance begins on Day 57 of DI or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75 000/µL, (whichever occurs later) for Cycle 1. For subsequent cycles, follow dose modifications for low counts and platelets. See Section 4.26 and 5.9 for details. This Therapy Delivery Map is on **one (1)** page.

DRUG	ROUTE	DOSAGE	DAY	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose	Day 1	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	a. Hx, PE, Wt., Ht b. CBC/diff/platelets c. CSF cell count, cytospin[!] d. Bilirubin, ALT & Creatinine e. IgG [!] Obtain with each IT administration See Section 7.1c for further details
Prednisone (PRED)	PO^ (may be given IV)	20 mg/m²/dose BID	Days 1-5 (do not taper)	Total daily dose: 40 mg/m²/day, divided BID See Section 4.26 for administration guidelines ^IV methylprednisolone may be substituted for prednisone at 80% of the oral dose	
Mercaptopurine (MP)	PO	75 mg/m²/dose/day†	Days 1-84	†See Section 5.9 for suggested starting dose based on TPMT and NUDT15 status See Section 4.26 & Appendix II for administration guidelines	
Methotrexate (MTX)	PO	20 mg/m²/dose/week	Days 8, 15, 22, 29**, 36, 43, 50, 57, 64, 71 & 78	****Omit on days when IT MTX is given.**	
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 **Also on Day 29 of Cycles 1 to 4, for patients who did NOT receive CXRT.**	See Section 4.26 for administration guidelines **Note age-based dosing**	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Patients with CNS3 disease receive cranial XRT, during the first 4 weeks of Maintenance. See Section 4.26 & 14.0 for details.

Enter Cycle #_____ Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	VCR mg	PRED mg mg	MP mg	IT MTX mg	PO 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							

		8					mg		

		15					mg		

		22					mg		

		29				mg*	mg**	a%, b, c*	

		36					mg		

		43					mg		

		50					mg		

		57					mg	a%, b, e	

		64					mg		

		71					mg		

		78					mg		

		84							
		85	**Repeat next cycle based on dose modifications for low counts or low platelets until 2 yrs from start of IM for both males and females**						

***During Cycles 1 to 4 ONLY for patients who did NOT receive CNS radiation** ****Omit on days when IT MTX is given.**

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

5.0 DOSE MODIFICATION FOR TOXICITIES

Notify the Study Co-Chairs 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 as defined by CTCAE v4.0 (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: Premedication with antihistamines to decrease the risk of overt allergy symptoms has been discouraged in the past since anti-histamine use may mask the appearance of systemic allergy and fail to alert the provider of the presence of asparaginase neutralizing antibodies, which render asparaginase therapy ineffective. Asparaginase activity assays are now commercially available so that in the face of premedication; if allergy is suspected, or; if a provider seeks to monitor asparaginase therapy, a sample can be sent to determine activity and evaluate the patient for the presence of neutralizing antibodies. In the event of severe systemic or recurrent local allergic reaction, or if activity level is not detectable in an appropriately drawn sample, *Erwinia chrysanthemi* asparaginase (Erwinaze®), which is FDA-approved for this indication, should be substituted.

Therapeutic Drug Monitoring (TDM): TDM of asparaginase activity is available as a CLIA approved assay. Centers may elect to discontinue pegaspargase and switch to Erwinia asparaginase based upon CLIA-certified laboratory evidence of silent inactivation of asparaginase activity in the absence of clinical symptoms of hypersensitivity at their discretion.

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.[118, 119] 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.[120] Current COG trials have adopted pegaspargase as the preparation of choice, based on the results of CCG 1962.[121] 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 initially 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. In December 2014, the FDA expanded its approval to include intravenous as well as intramuscular administration.

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

Phase(s) of Treatment	Replacement Schedule for Erwinia asparaginase[#]
Standard Induction, Consolidation, Interim Maintenance, Delayed Intensification.	25,000 IU/m^2/dose IM or IV over 1 hour 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. No specific guidelines are 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 antithrombotic therapy, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing LMWH or antithrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate. For significant thrombosis, 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 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 (e.g., if the cyclophosphamide dose is 1000 mg/m^2, the total mesna dose is 600 mg/m^2 or 200 mg/m^2/dose). Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat 4 and 8 hours after the start of cyclophosphamide. This total daily dose of mesna can also be administered as IV continuous infusion. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion.

Renal Dysfunction: If creatinine clearance or radioisotope GFR is < 10 mL/min/1.73 m^2, reduce dose of cyclophosphamide by 50%. Prior to dose adjustment of cyclophosphamide, the creatinine clearance should be repeated with good hydration.

5.3 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. Once Consolidation (C) or Delayed Intensification (DI) has started do not interrupt for uncomplicated myelosuppression; do hold for proven or presumed serious infection. Do make up missed doses.

5.4 Intrathecal Cytarabine

Do not withhold dose given on Day 1 of Induction in front-line protocols.

5.5 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.

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:[122]

Direct Bilirubin	% Dose Reduction
< 1.2 mg/dL	Full dose
1.2 – 3.0 mg/dL	50%
3.1 – 5.0 mg/dL	75%
> 5.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

Extravasation:

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

5.6 Dasatinib

Dasatinib treatment shall continue without planned interruption until the completion of maintenance therapy and held only for toxicity. All therapy, including dasatinib, should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated.

Myelosuppression:
If neutropenia and/or thrombocytopenia result in delay in starting the next course of therapy > 14 days, interrupt dasatinib and resume at the same dose level once the next course of therapy begins.

Non-Hematological Toxicity (Not Including Liver and Cardiac Toxicities):
Grade 2:
If a patient experiences Grade 2 toxicity that is likely or definitely related to dasatinib that does not resolve despite symptomatic treatment, dasatinib should be withheld until the toxicity resolves to ≤ Grade 1. Upon recovery, dasatinib may be resumed at the same dose. If the toxicity recurs, dasatinib must be withheld until the toxicity resolves to ≤ Grade 1. Upon recovery, dasatinib may be resumed at 48 mg/m^2 daily, up to a maximum of 110 mg/day. If tolerated, without return of Grade 2 toxicity, dasatinib may be restarted at full dose with the next cycle of therapy.

Grade 3 or 4:
If a patient experiences Grade 3 or 4 toxicity that is likely or definitely related to dasatinib, hold dasatinib until toxicity resolves to ≤ Grade 1. Upon recovery, dasatinib may be resumed at 48 mg/m^2 daily, up to a maximum of 110 mg/day. If tolerated, without return of Grade 3 or 4 toxicity, dasatinib may be restarted at full dose with the next cycle of therapy.

Liver Toxicity:
Grade 3 or 4:
Hold dasatinib for ALT > 15x ULN or direct bilirubin > 5x ULN until ALT returns to < 2.5x ULN and direct bilirubin returns to < 1.5x ULN. Upon recovery, dasatinib may be resumed at 60 mg/m^2 daily. If toxicity recurs at ALT > 15x ULN or direct bilirubin > 5x ULN, hold dasatinib until ALT returns to < 2.5x ULN and direct bilirubin returns to < 1.5x ULN. Upon recovery, dasatinib may be resumed at 48 mg/m^2 daily, up to a maximum of 110 mg/day. If tolerated, without return of ALT > 15x ULN or direct bilirubin > 5x ULN, dasatinib may be restarted at full dose with the next cycle of therapy.

Cardiac Toxicity:
Dasatinib should not be administered to patients with prolonged QTc. If patient has ≥ Grade 1 QTc interval, hold dasatinib. Dasatinib may be resumed if prolongation of QTc resolves and was unrelated or unlikely to be related to dasatinib. If the patient experiences ≥ Grade 2 cardiac toxicity, discontinue dasatinib.

Edema/Effusions:
If the patient experiences ≥ Grade 2 pericardial, pleural effusions, or edema, hold dasatinib. Dasatinib may be resumed if edema/effusion resolves and was unrelated or unlikely to be related to dasatinib.

5.7 Intrathecal Methotrexate/Triple Intrathecal Therapy

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

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.[123-125] 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.[125-130] 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,[131] 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 Ara-C 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.[132] 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.[133-135] 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.[136] For patients who return to their "pre-event" status, without residual deficits o 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.[136] There have been questions about potential interference of leucovorin with the efficacy of the IT MTX, but there are little data to support or refute this position. Moreover, the administration 48 hours later would minimize any potential interference. If the event does not recur, resumption of standard therapy should be considered, following 1 modified or omitted IT dose. In the face of multiply recurrent events, or evidence of progressive encephalopathy, another evaluation is warranted and the treating physician may consider a more prolonged or definitive change in therapy. These decisions are extremely difficult and may hinge on an individual's view of the importance of quality of life versus an increase in the risk of relapse. Since the greatest impact of CNS prophylaxis occurs early in therapy, the timing of these events may also influence clinical decisions. Cranial radiation has been suggested as an alternative to continued IT therapy though much of the literature on long-term neurocognitive dysfunction supports a more deleterious effect from

CRT than IT therapy.[137-140] 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.[141-144] At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander et al [145] 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 IV Methotrexate

5.8.1 High/Intermediate Dose (HD/ID MTX) and Leucovorin Rescue

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.

HD/ID MTX Infusion Guidelines
See Appendix IV-A and IV-B for flowcharts of the HD MTX/LCV and ID MTX/LCV guidelines.

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

Hold trimethoprim/sulfamethoxazole (TMP-SMX), any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HD/ID MTX infusion and for at least 72 hours after the start of the HD/ID MTX infusion and until the MTX level is less than 0.4 µM for HD MTX and 0.2 µM for ID MTX. *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 acetate or bicarbonate bolus (0.5-1 mEq/kg over 15 min) may be given to raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HD/ID MTX infusion. Recommend hydration for a minimum of 54 hours after the MTX bolus is started for patients who meet expected clearance parameters. In patients with delayed MTX clearance, continue hydration and leucovorin as instructed (Appendix IV-A) until the plasma MTX concentration is below 0.1 µM.

5.8.1.1 Non Down syndrome Patients

Hour 0: MTX 500 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the 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 and Appendix IV-A)

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. 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 6hrs until MTX level < 0.1 µM (draw q12-24 hrs).
	10 to 19.9 µM	6 to 9.9 µM	Increase to 15 mg/m^2 q 3hrs until MTX level < 0.1 µM (draw q 6-24 hrs). Consider glucarpidase.
	20 to 200 µM	10 to 100 µM	Increase to 100 mg/m^2 q 6hrs until MTX level < 0.1 µM (draw q 6-24 hrs). Consider glucarpidase.
	> 200 µM	> 100 µM	Increase to 1000 mg/m^2 q 6hrs until MTX level < 0.1 µM (draw q 6-24 hrs). Consider glucarpidase.

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

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

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 HD MTX to a patient with this degree or renal impairment, assuming that prolonged excretion can be managed with glucarpidase.

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G_2, Voraxaze™).[146, 147] 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 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	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. Notify Study Chair.

* Please see COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp for TMP/SMX substitutions.

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

Mucositis: For Grade 3-4 mucositis, withhold IV MTX until resolved. Increase leucovorin rescue following the next course from 3 to 5 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3-4 mucositis, attempt to decrease the leucovorin. If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25%, increase hydration to 200 mL/m^2/hr and continue increased leucovorin as above. Should subsequent courses be well tolerated, use a stepwise approach to resuming a standard approach to drug delivery. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

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

5.8.1.2 Down syndrome Patients

Dose of 2000 mg/m^2:

Hour 0: MTX 200 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 1800 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the ID MTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Leucovorin rescue: 15 mg/m^2 PO/IV q 6h beginning **30 hrs** after the start of the infusion for a minimum of 5 doses if 48 hr plasma MTX is < 0.2 µM. If the first cycle of ID MTX is tolerated, defined as no delayed clearance, no treatment delay due to myelosuppression, no mucositis of Grade 2 or higher, and no nephrotoxicity (pre-treatment serum creatinine >1.5x baseline or GFR creatinine clearance < 65 mL/minute/1.73m^2), subsequent cycles of ID MTX should be followed by leucovorin 15 mg/m^2

PO/IV q 6hrs beginning **36 hrs** after the start of the infusion for a minimum of 4 doses if 48 hour plasma MTX is < 0.2 µM.

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

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).

If the 24 hour level is < 60 µM draw the next level at hour 42 and refer to table below.

If the 24 hour level is ≥ 60 µM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table below.

If the 42 and 48 hour levels are ≤ 1 and 0.2 µM, respectively, continue Leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose (see above for initial leucovorin guidelines). 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 ≥ 60 µM. See below for guidelines**	1.01 to 9.9 µM	0.21 to 5.9 µM	Continue 15 mg/m^2 q 6hrs until MTX level < 0.1 µM (draw q12-24 hrs).
	10 to 19.9 µM	6 to 9.9 µM	Increase to 15 mg/m^2 q 3hrs until MTX level < 0.1 µM (draw q 6-24 hrs). Consider glucarpidase.
	20 to 200 µM	10 to 100 µM	Increase to 100 mg/m^2 q 6hrs until MTX level < 0.1 µM (draw q 6-24 hrs). Consider glucarpidase.
	> 200 µM	> 100 µM	Increase to 1000 mg/m^2 q 6hrs until MTX level < 0.1 µM (draw q 6-24 hrs). Consider glucarpidase.

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

++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 and/or ≤ 0.2 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

Dose modifications in subsequent courses for DS patients with evidence of toxicity:

- For Grade 2 mucositis, continue MTX at 2000 mg/m^2 and leucovorin rescue starting at 30 hrs after the start of MTX.
- For Grade 3-4 mucositis, withhold IV MTX until resolved.
- For Grade 3-4 mucositis or delayed excretion (level >0.2 µM at 48 hours after start of MTX infusion), decrease MTX dose by 25%, begin leucovorin rescue at 30 hrs after the start of MTX, increase leucovorin rescue to 7 doses on a q6 hr schedule and increase hydration to 200 mL/m^2/hr until level <0.1 µM. If subsequent course is not associated with Grade 3-4 mucositis or delayed

clearance, continue this methotrexate and leucovorin schedule for remaining courses. If mucositis or delayed clearance recurs despite the extended leucovorin and increased hydration, decrease the dose of MTX by another 25% (total of 50% dose reduction), and continue increased hydration and leucovorin as above. Should subsequent courses be well tolerated, continue but do not attempt to resume standard approach to drug delivery. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Nephrotoxicity and liver dysfunction: as per non-Down syndrome patient guidelines.

Myelosuppression: All chemotherapy should be held for ANC < 750/µL and platelets < 75 000/µL. If prolonged neutropenia and thrombocytopenia (ANC< 750/µL and platelets < 75 000/µL) for greater than 7 days, decrease MTX dose by 25% and begin leucovorin rescue at 30 hrs after the start of MTX for a minimum of 5 doses. For subsequent doses of MTX, do not attempt to increase the dose.

5.8.2 Capizzi Methotrexate

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

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

* Please see COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp for TMP/SMX substitutions.

Nephrotoxicity: Postpone course if serum creatinine is >1.5 x baseline or GFR creatinine clearance < 65 mL/1.73m²/minute.

Hold IV MTX for direct hyperbilirubinemia 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 persist or 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. In 4 days, if ANC ≥ 500/µL and platelets ≥ 50 000/µL, give same dose of methotrexate as previous cycle.
    2. In 4 days, if ANC is still < 500/µL or platelets < 50 000/µL, give VCR (and IT MTX if Day 31) and pegaspargase (if due) (omitting IV MTX) and repeat counts in 7 days to begin next dose of VCR and IV MTX if counts are adequate.

a. If after 7 days, ANC ≥ 500/µL or platelets ≥ 50 000/µL, reduce dose of IV MTX by 20% (Do not make up missed dose of MTX). For subsequent doses, resume escalation as per A-C.
b. If after 7 days ANC is still < 500/µL or platelets < 50 000/µL, hold therapy until counts recover to ANC > 500/µL and platelets > 50 000/µL. When ANC ≥ 500/µL and platelets ≥ 50 000/µL, resume at 80% of last dose of MTX. For subsequent doses, resume escalation as per A-C.

B) If ANC ≥ 500 but < 750/µL and platelets ≥ 50 000 but < 75 000/µL, give same dose of MTX as previously (i.e. no escalation).
C) If ANC ≥ 750 and platelets ≥ 75 000 escalate MTX by 50 mg/m^2.
D) Do not escalate MTX dose and resume at 80% of last dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume escalation as per A-C.

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

During Interim Maintenance with HD/ID MTX:
If ANC is < 750/µL and/or platelets < 75 000/µL, hold mercaptopurine. Restart mercaptopurine at full dose with next cycle of HD/ID 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.

During Maintenance:
If neutrophil count falls below 500/µL or if platelet count falls below 50 000/µL during Maintenance, MP and MTX will be held until recovery above these levels. For the first drop in ANC or platelets, resume chemotherapy (both MP and MTX) at the same dose the patient was taking prior to the episode of myelosuppression. If neutrophil count falls below 500/µL or if platelet count falls below 50 000/µL for a second (or greater) time, discontinue doses of MP and MTX until ANC is ≥ 750/µL and platelets are ≥ 75 000/µL. Restart both MP and MTX at 50% of the dose prescribed at the time the medication was stopped. Then continue to increase to 75% and then 100% of the dose prescribed prior to stopping the medication at 2-4 week intervals provided ANC remains ≥ 750/µL and platelets remain ≥ 75 000/µL. May increase both MP and MTX simultaneously. Consider discontinuing TMP/SMX as per COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp. If the neutrophil count falls below 500/µL or if the 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.

- For ANC ≥ 1500/µL on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s) alternately increase doses of MTX or MP by 25%. As a general rule, do not increase doses more often than every 4 weeks.
- If both MTX and MP are increased once without a fall in ANC, consider noncompliance as a possibility. Noncompliance can be assessed by obtaining a sample for RBC thioguanine nucleotides (TGNs). Consider observing the administration of an oral dose of MTX and checking plasma MTX concentration 2-4 hours later. This will document whether or not poor absorption contributes to lack of response and may facilitate discussions about noncompliance.

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 MP, especially if red cell MP methylated derivatives are elevated. Also consider liver biopsy.

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

Pharmacology Testing (Thiopurine and NUDT15) and Dosage Adjustments:
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).[148-151] Patients with low TPMT form higher concentrations of the 6-thioguanine nucleotides (6-TGN) and are more susceptible to acute thiopurine toxicity (primarily myelosuppression, involving neutropenia, thrombocytopenia, and anemia). Patients with the complete deficiency of TPMT tolerate less than 10% of protocol doses of MP (10 to 30 mg/m^2/day 3 days per week). About 35% of heterozygotes require a lower dose of MP to avoid dose-limiting myelosuppression.[152]

Recently, germline variants in the gene encoding the nucleoside diphosphate-linked moiety X-type motif 15 (*NUDT15*) were reported in approximately 4% of Hispanic/Native American and nearly 10% of East Asian children with ALL; these polymorphisms are strongly associated with 6-MP intolerance. [153]

There are now CLIA certified tests for TPMT genotype and phenotype, for the measurement of thiopurine metabolites (6-methyl mercaptopurine [6-MMP] and 6-TGN measurements), and for *NUDT15* polymorphisms. Only 3 SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide. [148, 154-157] Thus, the genotyping test has a low false negative rate, and may be preferable to TPMT phenotype testing in cases where a history of red cell transfusions would potentially confound assessments of RBC TPMT activity. When the genotyping result is coupled with a phenotyping test for TPMT or with thiopurine metabolite concentrations in erythrocytes, the reliability of the tests will be even greater. Moreover, metabolite levels can provide an index of patient compliance with thiopurine therapy.

Recommendations for Thiopurine Monitoring and Dosage Adjustments:
When myelosuppression has led to significant delays in therapy (> 2 weeks) or is disproportionate to the therapy, thiopurine testing should be performed:

- For subjects who have received full dose thiopurine therapy during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict TPMT status and actual thiopurine exposure.

- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status
- TPMT genotyping will be informative in all subjects, if at least 1 mutant allele is identified. If not, and myelosuppression continues, send samples for TPMT activity and/or metabolites since TPMT genotyping will miss 5%-10% of mutants. NOTE: *Genotyping can be done despite recent transfusions.*

Suggested Dose Adjustments in Patients With Unacceptable Myelosuppression:

- If the subject is *homozygous deficient* for TPMT or NUDT15, the thiopurine dose should be *reduced to* 10-20 mg/m^2/day 3 days per week. If the subject is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30%-50%. It is not yet clear how the dose of thiopurine should be adjusted for patients who are heterozyogous for NUDT15 but such patients should be monitored carefully while on thiopurines. If a patient has two polymorphisms in NUDT15 (i.e. heterozygous for both the R139C and R139H), they should be treated as if they were homozygous deficient. Gradual dose escalations should be attempted as outlined below.

- Do not increase the dose in response to a high ANC for 4 weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are not often necessary.

- If the subject is homozygous wild-type (high activity) for TPMT or NUDT15, then discontinue TMP/SMX and use pentamidine or dapsone. For modifications of the oral MP and MTX see the beginning of this section (5.10).

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.

Osteonecrosis (ON): Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) during Induction or Delayed Intensification. Omit Maintenance steroid for osteonecrosis Grade 2 or greater. 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: Dexamethasone dose may be reduced by 50% for severe psychosis. If symptoms persist, switch to prednisone.

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

Liver dysfunction: For clinical jaundice, hepatomegaly or splenomegaly during or within 2 weeks of completing the 2 week course(s) of thioguanine, obtain an ALT/AST/total and direct bilirubin. Consider Doppler ultrasound with an assessment for ascites and portal blood flow to assess for possible sinusoidal obstruction syndrome (SOS; formerly veno-occlusive disease, VOD). Hold thioguanine for a direct bilirubin of > 2.0 mg/dL or for new onset hepatomegaly or splenomegaly until SOS is ruled out. SOS may also present with unexplained thrombocytopenia and splenomegaly. Consider Doppler ultrasound in the presence of these symptoms. No further thioguanine should be administered in a patient with SOS.

5.12 Vincristine

PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (See text box below)

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

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[158 159]

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),
> 6.0 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.

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.

6.0 DRUG INFORMATION

6.1 ASPARAGINASE ERWINIA CHRYSANTHEMI

(*Erwinia chrysanthemi*, Erwinase®, Erwinaze®, Crisantaspase) NSC #106977 (11/17/17)

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 using the IM route of administration. In a multicenter study characterizing the pharmacokinetic profile of 25,000 International Units/m^2 Erwinaze® given intravenously over one hour on the same dosing schedule of Monday, Wednesday, Friday for 2 consecutive weeks, 83% (20/24) and 43% (9/21) of evaluable patients achieved an asparaginase activity level of ≥ 0.1 International Units/mL at 48 post-dose 5 and 72 hours post-dose 6, respectively.[160] 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. 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.

Erwinia asparaginase can be administered by intramuscular injection or by intravenous infusion. Use appropriate precautions for preparation of a hazardous agent. Visually inspect the powder in vial for foreign particles or discoloration prior to reconstitution.

For intramuscular administration, 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. 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.

For intravenous use, slowly inject the appropriate volume of reconstituted solution into a Normal Saline 100 mL infusion bag; do not shake or squeeze the bag. Infuse *Erwinia* asparaginase over 1 hour. Do not infuse other intravenous drugs through the same intravenous line while infusing *Erwinia* asparaginase.

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.

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.

Drug Ordering:
In the United States, asparaginase *Erwinia chrysanthemi* (Erwinaze®) is distributed by McKesson Plasma and Biologics. Verify your institution has a contract with McKesson Plasma and Biologics before ordering. If not, contact McKesson at 877-625-2566 for assistance setting up an account:

Orders may be placed online or via phone, fax, or email.
Orders may be placed online via http://Connect.McKesson.com
Orders may be submitted via fax to 888-752-7626
Orders may be submitted via email or MPBOrders@McKesson.com
Email all other information requests to MPB@McKesson.com
Regular order hours: M-F 9:00 am – 7:30 pm EST;
Emergency order after hours services (24/7/365): 877-625-2566
Orders placed by 7:30 pm EST will ship the next day.

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** (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: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, 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 (07/13/15)

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 t½ of about 10 minutes, with a secondary elimination phase t½ 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 t½ of about 2 hours.

Toxicity: (Intravenous, SubQ)

	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, swelling, pain and redness at the site of the medication injection (SubQ or IM injection)
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia),	Diarrhea, hypokalemia, hypocalcemia, hyperuricemia	Hepatotoxicity, sinusoidal obstruction syndrome (SOS, formerly VOD), urinary retention, renal dysfunction, pain and erythema of the palms and

	stomatitis, alopecia		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:
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. 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 D5W or 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/IM administration.

Intrathecal:
For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free 0.9% sodium chloride injection, 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 $t_{½}$ is approximately 45 minutes followed by a terminal $t_{½}$ 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 vials at room temperature, 15°-30°C (59°-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 DASATINIB

(Sprycel®, BMS-354825, NSC 732517) 12/20/18

Source and Pharmacology:

Dasatinib (BMS-354825) (an aminothiazole analogue) is indicated for treatment of chronic, accelerated, myeloid or lymphoid blast phase chronic myeloid leukemia in adults who are resistant or intolerant to prior therapy including imatinib. It is also indicated for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia in adults who are resistant or intolerant to prior therapy. Dasatinib is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinase families: BCR-ABL, SRC family kinases, c-KIT, ephrin (EP) receptor kinases, and PDGFβ receptor. Each of these protein kinases has been strongly linked to multiple forms of human malignancies. Dasatinib targets most imatinib-resistant BCR-ABL mutations (except the T315I and F317V mutants) by distinctly binding to active and inactive ABL-kinase.

Pharmacokinetics:

Dasatinib exhibits linear pharmacokinetics with dose-proportionate increases in AUC. Dasatinib is rapidly absorbed following oral administration. At the adult therapeutic dose of 70 mg BID, neither disease status nor study day had a marked influence on the Tmax of dasatinib in subjects with leukemia. Maximum plasma concentrations are observed between 0.5 and 6 hours (Tmax) following oral administration. High fat meal may increase absorption of dasatinib, but not clinically significant. It has a large volume of distribution (2505 L), suggesting extensive distribution into extravascular space. Dasatinib is highly protein bound (96% parent drug, 93% active metabolite). The overall mean terminal elimination half-life of dasatinib is 3 to 5 hours. Dasatinib is likely to reach steady state conditions by the second day of treatment at 70 mg BID. Elimination is predominantly in the feces, mostly as metabolites. Following a single oral dose of [14C]-labeled dasatinib, approximately 85% of the dose was recovered in the feces within 10 days, and approximately 4% of the administered radioactivity was recovered in the urine. Unchanged dasatinib accounted for 19% and 0.1% of the administered dose in feces and urine, respectively, with the remainder of the dose being metabolites.

It undergoes extensive hepatic metabolism by CYP3A4 (primarily), flavin-containing mono-oxygenase-3 (FOM-3) and uridine diphosphate-glucuronosyltransferase (UGT) to an active metabolite and other inactive metabolites (the active metabolite plays only a minor role in the pharmacology of dasatinib). Dasatinib is also a significant inhibitor of CYP3A4. It may decrease the metabolic clearance of drugs that are significantly metabolized by the CYP3A4 enzyme. CYP3A4 substrates known to have a narrow therapeutic index should be administered with caution in patients receiving dasatinib (Appendix X). Concomitant use of dasatinib and drugs that inhibit CYP3A4 may increase exposure to dasatinib and should be avoided. Drugs that induce CYP3A4 activity may reduce exposure to dasatinib and concomitant use of potent CYP3A4 inducers with dasatinib should be avoided.

Due to the potential of dasatinib to prolong the QT/QTc, use caution when administering dasatinib with other potential QTc-prolonging medications. Due to the possibility of gastrointestinal, cardiac, and cutaneous hemorrhage, avoid using medications that inhibit platelet function or anticoagulants with dasatinib. Dasatinib is not a p-glycoprotein inhibitor.

Toxicity: Fetal toxicities and teratogenic effects of dasatinib have been noted in animals. It is unknown whether the drug is excreted in breast milk.

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Dasatinib (BMS-354825, Sprycel, NSC 732517)

The Comprehensive Adverse Events 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 (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 2937 patients.* Below is the CAEPR for Dasatinib (BMS-354825, Sprycel).

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.

Version 2.7, September 10, 2018[1]

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			**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		
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Pericardial effusion		
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
	Gastrointestinal hemorrhage[2]		
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (superficial edema)		***General disorders and administration site conditions - Other (superficial edema) (Gr 2)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
INFECTIONS AND INFESTATIONS			
	Infection[3]		***Infection[3] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Electrocardiogram QT corrected interval prolonged	
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight gain		
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Hypocalcemia		
	Hypokalemia		
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Growth suppression[4]	
		Musculoskeletal and connective tissue disorder - Other (epiphyses delayed fusion)[4]	
		Musculoskeletal and connective tissue disorder - Other (osteopenia)[4]	
Myalgia			***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Headache			***Headache (Gr 3)***
		Intracranial hemorrhage	
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Gynecomastia[4]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
Dyspnea			***Dyspnea (Gr 3)***
	Laryngeal mucositis		
	Pharyngeal mucositis		
Pleural effusion			***Pleural effusion (Gr 3)***
	Pneumonitis		
		Pulmonary hypertension	
	Tracheal mucositis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Erythema multiforme	
	Pruritus		
	Rash acneiform		
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	

Adverse Events with Possible Relationship to Dasatinib (BMS-354825, Sprycel) (CTCAE 5.0 Term) [n= 2937]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Flushing		

Adverse events reported on Dasatinib (BMS-354825, Sprycel) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Dasatinib (BMS-354825, Sprycel) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (cardiomegaly); Cardiac disorders - Other (heart rate increased); Chest pain - cardiac; Myocarditis; Palpitations; Pericarditis; Sinus tachycardia; Ventricular tachycardia
CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (Keratosis follicular)
EAR AND LABYRINTH DISORDERS - Ear pain; Middle ear inflammation; Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (optic nerve neuritis); Periorbital edema
GASTROINTESTINAL DISORDERS – Anal fissures; Ascites; Colitis; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (enteritis); Gastrointestinal disorders - Other (oral soft tissue disorder); Gastrointestinal disorders - Other (tongue eruption); Gastrointestinal ulcer[5]; Ileus; Oral pain; Pancreatitis; Periodontal disease; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (temperature intolerance); Localized edema; Malaise
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS - Anaphylaxis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; CD4 lymphocytes decreased; CPK increased; Creatinine increased; Electrocardiogram T wave abnormal; GGT increased; Investigations - Other (bone densitometry); Investigations - Other (thermometry abnormal); Lymphocyte count decreased; Lymphocyte count increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (muscle stiffness); Musculoskeletal and connective tissue disorder - Other (nuchal rigidity); Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis; Osteoporosis; Pain in extremity; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (hemangiomatosis)
NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Amnesia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysgeusia; Ischemia cerebrovascular; Lethargy; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Libido decreased; Suicidal ideation
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm; Epistaxis; Hypoxia; Oropharyngeal pain; Pulmonary edema; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Hair color changes; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (acute febrile neutrophilic dermatosis); Skin and subcutaneous tissue disorders - Other (panniculitis); Skin ulceration; Urticaria
VASCULAR DISORDERS - Hematoma; Hot flashes; Hypertension; Hypotension; Phlebitis; Superficial thrombophlebitis; Thromboembolic event; Vasculitis

Note: Dasatinib (BMS-354825, Sprycel) 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.

Formulation and Stability:
Dasatinib is available as 5 mg, 20 mg, and 50 mg film-coated tablets for oral administration. Store the intact bottles at controlled room temperature (15°C-25°C) and protect from light.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.
May be taken without regard to food. Swallow whole; do not break, crush, or chew. Proton Pump Inhibitors and H2-antagonists may decrease the serum concentration of dasatinib and should be avoided. Antacids (taken 2 hours before or after dasatinib administration) can be used in place of the proton pump inhibitor or H2-antagonists if some acid-reducing therapy is needed.
Special Handling: Dasatinib tablets consist of a core tablet (containing the active drug) surrounded by a film coating to prevent exposure to the active drug substance. If tablets are accidentally crushed or broken, caregivers should wear disposable chemotherapy gloves. Pregnant women should avoid exposure to crushed and/or broken tablets.

For Children unable to swallow tablets:
The intact dasatinib tablets can be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. PLEASE NOTE: THE DASATINIB TABLETS SHOULD NOT BE CRUSHED.

The following 7 steps describe the procedure for preparation of the lemonade dosing solution. (For preservative-free apple juice or preservative-free orange juice, steps 2 thru 7 should be followed.).

1. Mix the contents of one 12 ounce can of Minute Maid Premium Frozen Concentrate with 2 cans (i.e. the emptied lemonade container) of water. This will produce lemonade that is a little more than twice as concentrated as the instructions on the can with a sweeter taste. Refrigerate the lemonade solution when not in use.
2. Place 1 ounce (30 mL) of this lemonade (or preservative free apple or orange) solution into a drinking glass.
3. Place the proper dose of intact tablets into the lemonade (or preservative free apple or orange juice). Wear protective gloves when handling the medication. A mask is not required when handling the medication. Always use the 1 oz of lemonade (or preservative free apple or orange juice). Do not increase the solution volume.

4. Start timing for 20 minutes. At approximately the 5 minute mark, swirl the contents of the glass well for about 3 seconds.

5. At approximately the 15 minute mark, swirl the contents of the glass a second time. At the 20 minute mark, swirl the contents of the glass one last time. Immediately administer the entire contents of the glass.

6. In order to ensure administration of the entire medication dose, a rinsing step is necessary. Add 0.5 ounce (15 mL) of lemonade (or preservative free apple or orange juice) into the same glass that has just been emptied. Swirl the contents to remove any remaining signs of tablets from the sides or bottom of the glass.

7. Administer the washing lemonade (or preservative free apple or orange juice) to the patient.

Supplier: Dasatinib is supplied by Bristol-Myers Squibb and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. **Do not use commercial supply.**

Obtaining the Agent

Agent Ordering

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 for the Procedures for Drug Accountability and Storage and to obtain a copy of the NCI *Oral* Drug Accountability Record Form and Clinical Drug Request form.

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.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

6.6 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 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 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 lymphoblastic 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 concentrations. 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 (1 mL and 10 mL vial sizes). 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 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.

6.7 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 may be 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 0.9% NaCl 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.

6.8 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ (11/15/16)

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio ®)
NSC #614629

Source and Pharmacology:

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). Filgrastim exhibits nonlinear pharmacokinetics with clearance dependent on filgrastim concentration and neutrophil count. Filgrastim is cleared by the kidney. The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2-8 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		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subq):skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, rash or exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS
Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:

Neupogen® supplied as a clear solution of 300 mcg/mL in 1 mL or 1.6 mL vials. Neupogen ® vials are preservative free single use vials. Discard unused portions of open vials.

Neupogen®, Granix®, and Zarxio® are also available as single use prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim for subcutaneous administration.
Store refrigerated at 2º-8ºC (36º-46ºF). Protect from light. Do not shake. Prior to injection, filgrastim and filgrastim-sndz may be allowed to reach room temperature for a maximum of 24 hours (infusion must be completed within 24 hours of preparation). TBO-filgrastim may be removed from 2°C-8°C (36°F-46°F)

storage for a single period of up to 5 days between 23°C to 27°C (73°F to 81°F). Avoid freezing and temperatures > 30ºC.

For IV use, dilute filgrastim (Neupogen®) and tbo-filgrastim (Granix®) in D5W only to concentrations > 15 mcg/mL. Filgrastim-sndz (Zarxio®) may be diluted in D5W to concentrations between 5 mcg/mL and 15 mcg/mL At concentrations below 15 mcg/mL, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/mL) in order to minimize the adsorption of filgrastim to plastic infusion containers and equipment for all 3 products (communication on file from Teva Pharmaceuticals USA). Filgrastim or filgrastim-sndz dilutions of 5 mcg/mL or less are not recommended. Tbo-filgrastim dilutions below 2 mcg/mL are not recommended. Diluted filgrastim biosimilar products should be stored at 2º-8ºC (36º-46ºF) and used within 24 hours. Do not shake.

Do not dilute with saline-containing solutions at any time; precipitation will occur.

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

Filgrastim biosimilar products should not be administered within 24 hours of (before AND after) chemotherapy.

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

6.9 INTRATHECAL TRIPLES (Methotrexate/Hydrocortisone/Cytarabine, IT-3) (05/08/12)

Source and Pharmacology:
The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a $t_{½}$ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a $t_{½}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

Intrathecal Triple Therapy (Methotrexate/ Hydrocortisone/Cytarabine) 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, fever, headache	Arachnoditis: (headache, fever, vomiting, meningismus and pleocytosis)	Rash, anaphylaxis (L), paresis, bleeding into subarachnoid or subdural space (risk > with platelet counts <20,000), confusion, fatigue, disorientation, seizures
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, somnolence, ataxia, cranial nerve palsy, transient and rarely permanent paraplegia (L), speech disorders
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L), learning disabilities (L)	Demyelating leukoencephalopathy[1] (L), blindness[1]
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by systemic therapy such as high dose methotrexate or cytarabine and/or cranial irradiation. (L) Toxicity may also occur later.*

Formulation and Stability:
Methotrexate 25 mg/mL **preservative free** 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate100 mg vial sterile powder for injection.

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

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

Patient Age (years)	Doses (MTX/Hydrocortisone/ARAC)	Recommended volume	10% CSF volume	CSF Volume *
0 – 0.99	7.5 mg / 7.5 mg / 15 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
1 – 1.99	8 mg / 8 mg / 16 mg	5–10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	10 mg / 10 mg / 20 mg	5-10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	12 mg / 12 mg / 24 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg / 15 mg / 30 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.

Intrathecal triples are stable in NS for 24 hours at 25ºC but contain 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 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.		

Formulation and Stability:
Leucovorin calcium for injection is supplied as a sterile ready to use liquid and a sterile powder for injection. The 10 mg/mL preservative free liquid is available in 50 mL vials containing sodium chloride 400 mg/vial. Store preservative free liquid in the refrigerator at 2°-8°C (36°-46°F) protected from light. The powder for injection is available in 50 mg, 100 mg, 200 mg, and 350 mg vials. Store at room temperature 15°-25°C (59°-77°F) protected from light. Reconstitute the sterile powder with sterile water for injection or bacteriostatic water for injection to a concentration of 10 mg/mL leucovorin calcium. **Do not use diluents containing benzyl alcohol for doses > 10 mg/m² or in infants < 2 years of age or patients with allergy to benzyl alcohol.** When Bacteriostatic Water is used, the reconstituted solution is good for 7 days. If reconstituted with SWFI, use solution immediately as it contains no preservative. One milligram of leucovorin calcium contains 0.004 mEq of leucovorin and 0.004 mEq of calcium.

The oral form of leucovorin is available as 5 mg, 10 mg, 15 mg, and 25 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: corn starch, dibasic calcium phosphate, magnesium stearate, pregelatinized starch, lactose, microcrystalline cellulose, and sodium starch glycolate.

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

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.

6.11 MERCAPTOPURINE (MP, Purinethol®, 6-mercaptopurine) NSC #000755 (11/27/17)

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 6-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:

Incidence	Toxicities
Common (>20% of patients)	Neutrophil count decreased, white blood cell decreased, anorexia, fatigue
Occasional (4 - 20% of patients)	Diarrhea, nausea, vomiting, malaise, oligospermia, infection, fever, platelet count decreased, anemia, mucositis, stomach pain, ulcerative bowel lesion, skin rash, alanine aminotransferase increased, aspartate aminotransferase increased
Rare (≤3% of patients)	Urticaria, skin hyperpigmentation, alopecia, hyperuricemia, hepatic failure, hepatic necrosis, blood bilirubin increased, pulmonary fibrosis, secondary malignant neoplasm, renal toxicity, uricosuria, pancreatitis
Pregnancy and Lactation	**Pregnancy Category D** Mercaptopurine can cause fetal harm, including an increased incidence of abortion and stillbirth. Advise women to avoid becoming pregnant while receiving mercaptopurine. Mercaptopurine was embryo-lethal and teratogenic in several animal species (rat, mouse, rabbit, and hamster). It is not known whether mercaptopurine is excreted in human milk; breastfeeding should be avoided.

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. In the United States, mercaptopurine is also available as an oral suspension in a concentration of 20 mg/mL (2000 mg/100 mL per bottle). The oral suspension is a pink to brown viscous liquid supplied in amber glass multiple-dose bottles with a child resistant closure. It should be stored at 15°-25°C (59°-77°F) in a dry place.

NOTE: the concentration of the commercially available suspension (20 mg/mL) and the compounded suspension (50 mg/mL) are NOT the same; doses should be prescribed in the milligrams required, not mL.

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

Mercaptopurine should be taken consistently at the same time every day. 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 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. **PLEASE NOTE there is a difference in the concentration of the commercially available (20 mg/mL) and extemporaneously compounded (50 mg/mL) oral suspensions.**

6.12 METHOTREXATE (MTX, amethopterin, Trexall®, Xatmep ®) NSC #000740 (11/27/17)

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 Frequency and Timing:	Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted 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/µL),
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 tablets are 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 is also available as a clear yellow to orange oral solution (Xatmep®) that contains 2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL) in a 120 mL bottle. Inactive ingredients include purified water, sodium citrate, citric acid, methylparaben sodium, propylparaben sodium, and sucralose. It may also contain sodium hydroxide or hydrochloric acid for pH adjustment. It is packaged in a high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal. Store oral solution under refrigeration (2°C to 8°C/36°F to 46°F) prior to dispensing. Avoid freezing and excessive heat. After dispensing, patients may store methotrexate oral solution at room temperature (20°C to 25°C/68°F to 77°F) for up to 60 days; excursions permitted to 15°C to 30°C (59°F to 86°F).

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 (59º- 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, if an oral solution formulation is not readily available (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 IM/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 ≤ 25mg/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 sulfamethoxazole/trimethoprim 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, or 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 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.

6.13 PEGASPARGASE

(PEG-asparaginase, PEGLA, PEG-L-asparaginase, polyethylene glycol-L-asparaginase, Oncaspar®,)
NSC #624239 (06/05/17)

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 of 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: Commercially available. See package insert for further information.

6.14 PEGFILGRASTIM (02/10/16)

(pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®) NSC #725961

Source and Pharmacology:

Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period postchemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years-old, and 21.2 (+/- 16) hours in children 12 to 21 years-old.

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		Local irritation at the injection site (pain, induration, and local erythema), headache	Low grade fever, allergic reactions (anaphylaxis, angioedema, or urticaria), generalized erythema and flushing
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, sickle cell crises in patients with sickle cell disease (SCD), excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			ARDS
Unknown frequency and timing:	Fetal toxicities and teratogenic effects of pegfilgrastim in humans are unknown. Conflicting data exist in animal studies. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:

Supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex). Store refrigerated at 2º-8ºC (36º-46ºF) and in the carton to protect from light. Prior to injection, pegfilgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

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

Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy. Do not shake. The manufacturer does not recommend use of the 6-milligram (mg) fixed-dose formulation of pegfilgrastim in infants, children, or adolescents under 45 kilograms.

Supplier: Commercially available. See package insert for further information.

6.15 PREDNISO(LO)NE

(Deltasone ®, PredniSONE Intensol ®, Rayos ®, Meticorten ®, Liquid Pred ®, Pediapred®, Millipred ®, OraPred ODT ® NSC #010023 (prednisone), NSC# 9151 (prednisolone)

(11/16/17)

Source and Pharmacology:

Prednisone and prednisolone are a synthetic compounds 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 lymphoblasic leukemia. Leukemia 2003; 17: 541-6.
(L) Toxicity may also occur later.

Formulation and Stability:
Prednisone is available vailable 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.

Prednisolone is available as 5 mg scored tablets (base) and 10 mg, 15 mg, and 30 mg orally disintegrating tablets (ODT; sodium phosphate [strength expressed as base]). Liquid formulations of prednisolone are available as 15 mg/5 mL oral solution (base); 5 mg/5 mL, 10 mg/5 mL, 15 mg/5 mL, 20 mg/5 mL oral solution (sodium phosphate [strength expressed as base]; and 15 mg/5 mL oral syrup (base). Inactive ingredients vary depending on manufacturer. Tablet formulations may contain dyes and liquid formulations may contain edetate disodium, methylparaben, saccharin sodium.
Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol.

PredniSONE and prednisolone are equipotent corticosteroids.

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

6.16 THIOGUANINE
(6-thioguanine, tioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, WR-1141, Tabloid®, Lanvis®) NSC #752 (12/05/16)

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%).

6-TG 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.)

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.
Thioguanine should be taken consistently at the same time every day.

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.

6.17 VINCRISTINE SULFATE (Oncovin®, VCR, LCR) NSC #67574 (08/16/12)

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.”

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

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

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).

7.1a Required and Optional Clinical, Laboratory and Disease Evaluations – HR B-ALL

Studies	Induction	Consolidation	IM	DI	Maintenance
REQUIRED					
Hx/PE/Wt /Ht[1]	Weekly	Start of Phase	Start of Phase	Start of Phase	Every 4 weeks
CBC/diff/platelets	Weekly	Weekly	Prior to each IV MTX dose	Weekly	Every 4 weeks
Bone Marrow	Baseline, & Day 29[2]	Day 56[3]			
Peripheral Blood	Day 29[4]				
CSF cell count and cytospin	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, ALT, and Creatinine	Baseline, & Day 29	Start of Phase	Prior to each IV MTX dose	Days 1, 29	Day 1 of each 12 week cycle
Echocardiogram	Baseline			Prior to first doxorubicin dose [5]	
Pregnancy test, if applicable	Baseline				
OPTIONAL					
TPMT and NUDT15 genotype	During Induction				As clinically indicated[6]
Thiopurine metabolites[7]					As clinically indicated[6]
Risk Classifiers[8]	Baseline				
Osteonecrosis study (Pain Assessment/MRIs)		End of phase, within 4 weeks of starting IM			Day 1[9]
Osteonecrosis study (Drug levels)		Day 1 and 22 (See Appendix V)		Day 8 (See Appendix V)	
Neurocognitive study		Day 15 and onwards, but prior to start of IM			Day 84[10]

[1] The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle.

[2] Send Day 29 BM to both the ALL Molecular Reference Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).

NOTE: IF THE DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

[3] For patients with Induction Day 29 MRD ≥ 0.01% BMA for morphology is required (may be obtained on Day 1 of IM for convenience; carry out at institution).

[4] Send Day 29 PB sample to ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1 (*if available for ALL patients*)

[5] ONLY for patients from AALL0932 who are transferred onto AALL1131 post-Induction.

[6] For patients in whom TPMT or NUDT15 genotyping was not previously performed (see Section 5.9).

[7] Optional RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for HR B-ALL patients during any Maintenance cycle in which MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.10).

[8] Send diagnostic BM to both the ALL Molecular Reference Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).

[9] For patients enrolled on this study, evaluations are due at the beginning of Maintenance therapy (within 4 weeks of starting Maintenance) and at the end of study therapy (within 4 weeks of the completion of protocol therapy). See Section 15.0 for details of evaluation schedule. **Note: It is required that scans are submitted within 30 days of being done.**

[10] For patients enrolled on this study, evaluations are due at the end of Maintenance Cycles 2, 4, 6, 10 (boys only) and 12 months post-therapy. See Section 16.0 for details of evaluation schedule.

7.1b Required and Optional Clinical, Laboratory and Disease Evaluations – VHR B-ALL

Studies	Induction	Consolidation	IM I	DI	IM II	Maintenance
REQUIRED						
Hx/PE/Wt/Ht[1]	Weekly	Start of Phase	Start of Phase	Days 1, 29 & 36	Start of Phase	Every 4 weeks
CBC/diff/platelets	Weekly	Days 1, 29, 36 & 43	Prior to each IV MTX dose	Weekly	Prior to each IV MTX dose	Every 4 weeks
Bone marrow	Baseline & Day 29[2]	Day 29[3], 56[4,9]	Day 1[4,9]			
Peripheral blood	Day 29[5]					
CSF cell count and cytospin	With each IT	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, ALT, AST[6], Lipase[6] and Creatinine	Baseline, & Day 29	Days 1[6], 29, 36 & 43	Prior to each IV MTX dose	Days 1, 29	Prior to each IV MTX dose	Day 1 of each 12 week cycle
Echocardiogram	Baseline			Prior to first doxorubicin dose[7]		
Performance status[8]		Prior to Day 1 therapy				
Pregnancy test, if applicable	Baseline					
OPTIONAL						
TPMT and NUDT15 genotype	During Induction					As clinically indicated[10]
Thiopurine metabolites[11]						As clinically indicated[10]
Risk classifiers[12]	Baseline					
Osteonecrosis study (Pain Assessment/MRIs)		End of phase, within 4 weeks of starting IM I				Day 1[13]
Osteonecrosis study (Drug levels)		Day 1 and 22 (See Appendix V)		Day 8 (See Appendix V)	Day 22 (See Appendix V)	
Neurocognitive study		Day 15 and onwards, but prior to start of IM				Day 84[14]

[1] The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle

[2] Send Day 29 BM to both the ALL Molecular Reference Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).

NOTE: IF THE DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

[3] For patients with Induction Day 29 M2/M3 marrow.

[4] BMA for morphology is required.

[5] Send Day 29 PB sample to the ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements)

[6] Obtain AST and Lipase on Consolidation Day 1 ONLY

[7] ONLY for patients from AALL0932 who are transferred onto AALL1131 post-Induction.

[8] Perform prior to Day 1 therapy. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

[9] For patients enrolled after Amendment #6, send a 2 mL aliquot of the Consolidation Day 56 (or IM Day 1 for convenience) BM sample to the **Eastern or Western COG ALL Flow Cytometry Reference Lab** for MRD testing (see Section 7.4 for shipping requirements and addresses). DECENTRALIZED MRD TESTING **DOES NOT** APPLY TO THIS SPECIMEN.

[10] For patients in whom TPMT or NUDT15 genotyping was not previously performed (see Section 5.9).

[11] Optional. RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for VHR B-ALL patients during any Maintenance cycle in which 6MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.10).

[12] Send diagnostic BM to both the ALL Molecular Reference Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*)) for shipping requirements and addresses).

[13]For patients enrolled on this study, evaluations are due at the beginning of Maintenance therapy (within 4 weeks of starting Maintenance) and at the end of study therapy (within 4 weeks of the completion of protocol therapy). See Section 15.0 for details of evaluation schedule. **Note: It is required that scans are submitted within 30 days of being done.**

[14]For patients enrolled on this study, evaluations are due at the end of Maintenance Cycles 2, 4, 6, 10 (boys only) and 12 months post-therapy. See Section 16.0 for details of evaluation schedule.

7.1c Required and Optional Clinical, Laboratory and Disease Evaluations – DS HR B-ALL

Studies	Induction	Consolidation	IM	DI	Maintenance
REQUIRED					
Hx/PE/Wt/Ht.[1]	Weekly	Start of Phase	Start of Phase	Start of Phase	Every 4 weeks
CBC/diff/platelets	Weekly	Weekly	Prior to each IV MTX dose	Weekly	Every 4 weeks
Bone Marrow	Baseline, Day 15[2] & Day 29[3]	Day 56[4,10]			
Peripheral Blood	Day 29[5]				
CSF cell count and cytospin	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, ALT, and Creatinine	Baseline	Start of Phase	Prior to each IV MTX dose	Days 1, 29	Day 1 of each 12 week cycle
Echocardiogram	Baseline[6]				
IgG	Baseline	Days 1 & 29	Start of phase	Days 1 & 29	Day 1 & 57 of each 12 week cycle
Pregnancy test, if applicable	Baseline				
OPTIONAL					
Varicella titer	Baseline				
TPMT and NUDT15 genotype	During Induction				As clinically indicated[7]
Thiopurine metabolites[8]					As clinically indicated[7]
Risk Classifiers[9]	Baseline				

[1] The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle

[2] Send Day 15 BM for morphology. ***This sample is very important.***

[3] Send Day 29 BM to both the ALL Molecular Reference Lab and a COG-Approved ALL Flow Cytometry Lab (see AALL08B1 or APEC14B1(*if available for ALL patients*)) for shipping requirements and addresses).
NOTE: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-Approved ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

[4] For patients with Induction Day 29 MRD ≥ 0.01% BMA for morphology is required (may be obtained on Day 1 of IM for convenience).

[5] Send Day 29 PB sample to the ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1(*if available for ALL patients*) for shipping requirements)

[6] Must be done prior to Day 15, if unable to obtain at baseline.

[7] For DS SR B-ALL patients in whom TPMT and NUDT15 genotyping was not previously performed (see Section 5.9).

[8] Optional. RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for DS HR B-ALL patients during any Maintenance cycle in which 6MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.10).

[9] Send diagnostic BM to both the ALL Molecular Reference Lab and a COG-Approved ALL Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for t ALL patients*) for shipping requirements and addresses).

[10] For patients enrolled after Amendment #6, send a 2 mL aliquot of the Consolidation Day 56 (or IM Day 1 for convenience) BM sample to the **Eastern or Western COG ALL Flow Cytometry Reference Lab** for MRD testing (see Section 7.4 for shipping requirements and addresses). DECENTRALIZED MRD TESTING **DOES NOT** APPLY TO THIS SPECIMEN.

7.1d Required and Optional Clinical, Laboratory and Disease Evaluations – Dasatinib Arm

Studies	Induction	Consolidation	IM I	DI	IM II	Maintenance
REQUIRED						
Hx/PE/Wt /Ht[1]	Weekly	Start of Phase	Start of Phase	Start of Phase	Start of Phase	Every 4 weeks
CBC/diff/platelets	Weekly	Weekly	Prior to each IV MTX dose	Weekly	Prior to each IV MTX dose	Every 4 weeks
Bone Marrow	Baseline, & Day 29[2]	Day 56[3]				
Peripheral Blood	Days 29[4]					
CSF cell count and cytospin	With each IT	With each IT	With each IT	With each IT	With each IT	With each IT
Bilirubin, ALT, and Creatinine	Baseline, & Day 29	Start of Phase	Prior to each IV MTX dose	Days 1, 29	Prior to each IV MTX dose	Day 1 of each 12 week cycle
EKG		Start of Phase				
Echocardiogram	Baseline					
Pregnancy test, if applicable	Baseline					
OPTIONAL						
TPMT and NUDT15 genotype	During Induction					As clinically indicated[5]
Thiopurine metabolites[6]						As clinically indicated[5]
Risk Classifiers[7]	Baseline					

[1] The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle.

[2] Send Day 29 BM to both the ALL Molecular Lab and a COG-Approved ALL Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).

NOTE: IF THE DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.

[3] For patients with Induction Day 29 MRD ≥ 0.01% BMA for morphology is required (may be obtained on Day 1 of IM for convenience; carry out at institution).

[4] Send Day 29 PB sample to the ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements)

[5] For patients in whom TPMT and NUDT15 genotyping was not previously performed (see Section 5.9).

[6] Optional RBC TGN (or 6-TGN level) & RBC Methyl MP (or 6-MMPN level). Recommended only for HR B-ALL patients during any Maintenance cycle in which MP/MTX has been held and restarted or in case of persistent ANC elevation and concern for non-compliance (see Section 5.10).

[7] Send diagnostic BM to both the ALL Molecular Reference Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).

7.2 **Studies Suggested to be Obtained After Stopping Therapy**

Note: Refer to COG's Long-term Follow-Up Guidelines for monitoring of long-term complications of therapy, available at: http://www.survivorshipguidelines.org/

1st year	PE, CBC/diff/platelets q 4-8 weeks, ALT q 2 months until normal BMA, CSF, as clinically indicated*
	Note: for patients enrolled on the ancillary studies, see Sections 15.0 (Osteonecrosis study) and 16.0 (Neurocognitive study) for details of end-therapy evaluation schedule.
2nd year	PE, CBC/diff/ platelets q 2 months
3rd year	PE, CBC/diff/ platelets q 3 months
4th year	PE, CBC/diff/ platelets q 6 months
5th year	PE, CBC/diff/ platelets q 6-12 months

* Obtain at any point after the end of therapy when it is clinically indicated.

7.3 **At Relapse**

Patients who relapse and have consented to cell banking when they consented to AALL08B1 or APEC14B1 (*if open for ALL patients*), should have samples of bone marrow sent to the Molecular Reference Laboratory for cell banking as described in AALL08B1 or APEC14B1.

ALL Molecular Reference Laboratory

Julie Gastier-Foster, PhD
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215

Phone: (614) 722-2866
Fax: (614) 722-2887
Email: MGLab@nationwidechildrens.org

7.4 **Sample and Shipping Information for MRD at End Consolidation [1] or Day 1 of Interim Maintenance I for VHR and EOI MRD Positive DS B-ALL Patients**.

DECENTRALIZED MRD TESTING **DOES NOT** APPLY TO THIS SPECIMEN.

For EOC MRD testing only, specimens may be submitted to either the Western or Eastern Flow Cytometry Reference laboratories. When submitting specimens for MRD testing, a specimen transmittal form **MUST** accompany each submission (please refer to the CRFs). Failure to include the AALL1131 specimen transmittal form with the shipment will result in costs billed to the institution.

Specimen	Studies	Laboratory
Bone marrow 2 mL	• MRD	John Hopkins University or the University of Washington, Seattle Flow Cytometry Reference Laboratory*

[1] Samples to be obtained at the end of Consolidation (or Day 1 of IM for convenience) upon count recovery in VHR B-ALL patients after completing Consolidation therapy.

Eastern Flow Cytometry Laboratory	**Western Flow Cytometry Laboratory**
Michael Borowitz, MD, PhD Johns Hopkins Medical Institution Flow Cytometry Lab Weinberg Building - Room 2300 401 N Broadway Baltimore, MD 21231-2410 Phone: (410) 614-2968 Fax: (410) 502-1493 Email: mborowit@jhmi.edu	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 Email: woodbl@u.washington.edu

8.0 SUPPORTIVE CARE GUIDELINES

8.1 General Guidelines

Aggressive supportive care improves outcome. The following guidelines are intended to give general direction for optimal patient care and to encourage uniformity in the treatment of this study population. Notify Study Chair of any unexpected or unusually severe complications. Please also see the COG Supportive Care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp

See Section 8.3 for DS patients.

8.1.1 Blood Components

Blood products should be irradiated and leukodepleted following current FDA guidelines found at: http://www.fda.gov/OHRMS/DOCKETS/98fr/981218g2.pdf

Investigators in Canadian institutions need to follow the CSA standards for Blood and Blood Components CAN/CSA-Z902-10 issued in February 2010 and available at: http://www.shopcsa.ca

Red Blood Cells (RBC)

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

Platelets

Transfusion with platelets is indicated to correct bleeding manifestations and may be indicated for severe thrombocytopenia without bleeding particularly prior to an invasive procedure.

8.1.2 Infection Prophylaxis

Pneumocystis jiroveci

All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 5 mg/kg/dose divided BID 2-3 sequential days per week. For patients allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone, aerosolized, atovaquone or IV pentamidine may be considered.

Antifungals

Azole antifungal agents (i.e. fluconazole, itraconazole, posaconazole, voriconazole, or isavuconazole [isavuconazonium sulfate])) given concurrently with vincristine may increase the risk of neurotoxicity. Caution is advised if azole antifungals are used.

8.1.3 Treatment of Established or Presumed Infections

Post Amendment #2

Infectious Complications During Consolidation Part 2, in Patients on the VHR Arms Enrolled Prior to Study Suspension, 14 Sept 2012:

Sterile site infections during Consolidation Part 2, in each of the three arms of the VHR strata prior to temporary suspension, 14 September 2012, are shown in Table 1.

Table 1.

Organism Name	Control Arm (N=26)	Experimental Arm A (N=49)	Experimental Arm B (N=50)
Gram Positive	**1**	**1**	**8**
Streptococcus mitis	1		3
Coag negative			1

Staphylococcus			
Staphylococcus aureus			1
Streptococcus viridans		1	1
Staphylococcus epidermidis			1
Staphylococcus saprophyticus			1
Gram Negative	**0**	**1**	**7**
Klebsiella pneumoniae			3
Pseudomonas aeruginosa			2
Escherichia coli		1	2
Anaerobic	**0**	**0**	**1**
Clostridium difficile			1
Fungus	**1**	**0**	**9**
Candida tropicalis			1
Blastoschzomyces capitatus			1
Aspergillus			
Aspergillus nos	1		3
Aspergillus terreus			1
Aspergillus versicolor			1
Aspergillus fumigatus			1
Geotrichum (yeast)			1
Total	**2**	**2**	**25**

Fever with Neutropenia

For patients with ANC < 500/µL or expected to fall to this level within the next 48 hours and an oral-equivalent temperature ≥ 38.3°C once or between 38.0°C and 38.3°C twice within 12 hours, empiric broad spectrum antibiotics should be instituted after obtaining appropriate cultures. Patients who present with severe sepsis should have empiric antibiotic coverage widened to include resistant Gram-negative, Gram-positive, and anaerobic bacteria.

The risk of bacteremia and infectious mortality is higher during Induction and during profound neutropenia. The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on each institution's experience regarding the type of infecting organisms, and their antibiotic sensitivity patterns.

For prolonged fever and neutropenia (≥ 96 hours), empiric antifungal therapy with either caspofungin or liposomal amphotericin B should be given during periods of anticipated prolonged neutropenia including induction.

Also, please see the COG Fever and Neutropenia Guidelines at:
https://childrensoncologygroup.org/downloads/COG_SC_FN_Guideline_Document.pdf

Primary Varicella Infection (Chickenpox)

Patients should be treated promptly with IV acyclovir, 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 patient's clinical and laboratory profile as well as institutional infection patterns. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a fungal infection, consider using broad spectrum antibiotics. If the patient develops progressively worsening clinical or laboratory features, or if, the pulmonary lesions on the CT scan are suggestive of a fungal infection (Aspergillus, Mucor), then more aggressive diagnostic measures should be undertaken. Pulmonary infiltrates may be evaluated with bronchoscopy and biopsy, lavage or open lung biopsy. If a procedure cannot be tolerated, and/or if there is high clinical suspicion consider beginning empiric fungal treatment. It is advisable to seek an infectious disease consult under these circumstances. If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis and brain and ocular exams 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, posaconazole, itraconazole, voriconazole, isavuconazole) given concurrently with vincristine may INCREASE the risk of neurotoxicity. 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 or cefepime + aminoglycoside + metronidazole; or piperacillin-tazobactam + aminoglycoside), Sitz baths, a strong barrier technique and effective analgesia.

8.1.4 Prevention and Management of Chemotherapy-induced Nausea and Vomiting (CINV)

Please refer to the COG Endorsed guidelines on prevention and management of CINV at: https://childrensoncologygroup.org/downloads/COG_SC_CINV_Guidelines_Document_Feb_2018.pdf

The routine use of steroids including dexamethasone, is discouraged but may be appropriate in select patients with demonstrated intolerance to higher-dose chemotherapeutic agents.

8.1.5 Use of myeloid growth factors

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

8.1.6 Osteonecrosis (ON)

Osteonecrosis (also referred to as avascular necrosis) may develop during or following therapy and often involves multiple joints over time. Osteonecrosis is not limited to weight bearing joints; common sites include hip, knee, ankle, heel, shoulder and elbow. Symptoms and exam findings may include joint pain, joint stiffness, limited range of motion (e.g. pain with internal rotation of the hip), limited mobility or ambulation, and/or gait abnormalities. Diagnostic imaging is indicated in any patient with suggestive findings. MRI is superior in sensitivity and specificity to other modalities, especially with early bone changes. Patients with negative studies, but who have persisting, progressive, or recurrent symptoms, should be re-imaged. For modifications of B-ALL therapy, see Section 5.10.

8.1.7 Gastrointestinal (GI) Protection

While patients are on steroid therapy, consider using an H2 blocker or proton pump inhibitor.

8.2 Guidelines for Induction

8.2.1 Acute Tumor Lysis Syndrome

Patients with ALL at high risk of tumor lysis should be assessed rapidly for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Suggested initial studies, obtained prior to initiating antileukemia therapy, may include a complete blood count (CBC), prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes, including creatinine, BUN, uric acid, phosphorus, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

The risk for serious acute tumor lysis syndrome (TLS) is usually restricted to the first 72 hours 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 initiated:

1. Begin allopurinol at a dose of 300 mg/m²/day or 10 mg/kg/day (maximum 800 mg/day) in 2-3 divided doses and continue until peripheral blasts and extramedullary disease are reduced. In some patients, such as those with oliguria or severe renal dysfunction, or in those with marked hyperuricemia, it may be also be appropriate to use rasburicase. Note that rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
2. Hydrate at 2,400-3,000 mL/m²/day to maintain urine output > 100 mL/m²/hour until peripheral blasts and extramedullary disease are reduced. Potassium should not be added to the hydration fluids.
3. Urine alkalinization is NOT necessary for TLS prophylaxis. There is paucity of evidence demonstrating benefit of urine alkalinization and it can potentially lead to calcium phosphate precipitation and/or metabolic acidosis.

8.2.2 Diagnostic Lumbar Puncture

As there are data suggesting that traumatic diagnostic lumbar punctures may have an adverse effect on prognosis, consider interventions to minimize the chances of a traumatic diagnostic lumbar puncture (LP).[161] These interventions may include:

a) Correcting any coagulopathy or thrombocytopenia present prior to the diagnostic LP
b) Performing the diagnostic LP while the patient is in a controlled environment such as under moderate or deep sedation.[161]
c) Administering intrathecal cytarabine at the time of the diagnostic lumbar puncture.
d) Having the diagnostic lumbar puncture performed by an experienced provider.

8.2.3 Induction – Infectious Complications

Since the induction phase is associated with a higher rate 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 steroids may mask fever, as well as other components of the systemic inflammatory response 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 serious toxic events can have an intestinal etiology. Patients with subtle GI symptoms should be monitored very closely.

8.3 Patients with Down syndrome (DS)

Patients with DS B-ALL and DS B-LLy have a significantly increased risk of morbidity and treatment-related mortality in most published series.[37] Therefore, they require a diligent and conservative approach to supportive care. Infectious complications during times of neutropenia are of greatest concern. The pattern of treatment-related mortality among HR-DS patients enrolled on AALL1131 as of May 2015

suggests there may be an increased risk associated with age greater than or equal to 15 years and/or obesity during the following treatment phases: Induction, Consolidation, and Delayed Intensification. Infections in children with Down syndrome may be very sudden in onset and progress rapidly mandating close surveillance and aggressive management intervention or treatment.

Due to their unique risks, the following are recommended for patients with Down syndrome:

1. **Hospitalization**: It is strongly recommended that children with Down syndrome be *monitored in the hospital* during Induction, Consolidation, and Delayed Intensification until they show signs of bone marrow recovery and are afebrile and clinically stable. If a patient experiences profound myelosuppression at any other time, there should also be a very low threshold for hospitalization and inpatient management until there is evidence of bone marrow recovery.
2. **Antibacterial prophylaxis** against Gram-positive and Gram-negative organisms (e.g. Levofloxacin [162, 163]) may be considered during peroids of myelosuppression until patients meet criteria for discharge or get switched to broad-spectrum intravenous antibiotics per institutional guidelines if a patient develops febrile neutropenia while receiving prophylactic antibiotics.
3. **Antifungal prophylaxis** may also be considered during periods of myelosuppression. Options include an echinocandin such as caspofungin or micafungin, or an azole. Investigators should be cautious however as **azole antifungal agents (i.e., fluconazole, posaconazole, itraconazole, voriconazole, isavuconazole) given concurrently with vincristine may increase the risk of neurotoxicity.**
4. **IgG replacement:** IgG levels should be monitored monthly and strong consideration given to IVIG therapy for levels less than 400 mg/dL. IgG levels and route of IVIG administration should be recorded on study CRF.

Children with DS B-ALL and DS B-LLy may not develop fever in response to infection, even with sepsis, particularly when they are receiving steroids. Therefore extra vigilance is needed, with a lower threshold for drawing cultures and starting antibiotics, even for subtle changes in clinical status. Aggressively manage episodes of fever (≥ 100.5ºF/ 38°C) during Induction, Consolidation (if HR), and Delayed Intensification or when the patient is neutropenic with an ANC ≤ 1,000/μL. The risk of life threatening infection is high so these patients should be hospitalized with immediate institution of broad spectrum IV antibiotics adjusted appropriately for local patterns of antibiotic resistance. Adequate coverage for gram-negative and gram-positive organisms including viridans streptococci. Broad spectrum antibiotics, once started, should continue until evidence of bone marrow recovery. In the absence of response after 3-5 days, antifungal therapy should be strongly considered. *Stress-dose steroids and/or filgrastim or biosimilar* should be considered in DS B-ALL and DS-BLLypatients with fever and neutropenia who are very ill or not responding appropriately to antibiotic therapy.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

a) Recurrent leukemia following complete remission.
b) Refusal of further protocol therapy by patient/parent/guardian.
c) Identified as Philadelphia chromosome-positive (BCR-ABL1)
d) Completion of planned therapy.
e) Down syndrome patient identified as Induction failure (M3 at Day 29)
f) Physician determines it is in patient's best interest.
g) Development of a second malignancy.
h) Adverse Event/Side Effects/Complications
i) Incomplete Induction data for risk stratification
j) Induction failure (patient not M1 by Day 1 of Interim Maintenance of VHR study or Dasatinib Arm)
k) Inevaluable
l) Identified as VHR at the end of Induction (EXCEPT for **Ph-like with a predicted TKI-sensitive mutation eligible for the Dasatinib arm for Consolidation therapy; OR EOI MRD positive patients eligible to receive Consolidation therapy on the VHR Control Arm**.
m) Other*

*Includes –
Completion of Consolidation therapy on VHR Control Arm (patients who were EOI MRD positive);
Patients classified as HR at the end of Induction (AFTER the HR randomization is closed to accrual);
Patients identified as Ph-like with a predicted TKI-sensitive mutation without access to dasatinib at the treating institution.

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) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence) with the exception of COG AALL1421, a Phase 2 study of IV pegcristantaspase, a pegylated Erwinia asparaginase, as a replacement for pegaspargase in patients with pegaspargase hypersensitivity.
d) Withdrawal of consent for any further data submiss ion.
e) Tenth anniversary of study entry.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Design (Amendment #3B and Amendment #5A)

Primary Endpoints

- To determine if the administration of post-Induction age adjusted ITT on an MBFM-IMHDM backbone will improve 5-year disease free survival (DFS) of children with HR B-ALL compared to age adjusted IT MTX. (**Completed effective March 19, 2018**)

- To determine, in a randomized fashion, if the cyclophosphamide + etoposide containing regimen (Experimental Arm 1) will improve the 4-year DFS of children, adolescents, and young adults with VHR B-ALL compared to a modified MBFM-IMHDM + CMTX regimen that contains a second IM (Control Arm). (**Closed effective February 15, 2017)**

Secondary Endpoints

- To determine the toxicity and tolerability of post-Induction age adjusted ITT compared to age adjusted IT MTX in children with HR B-ALL. (**Completed effective March 19, 2018**)

- To determine the toxicity and tolerability of Experimental Arm 1 compared to the Control Arm in children, adolescents, and young adults with VHR B-ALL. (**Closed effective February 15, 2017)**

- To determine whether a single-arm, modified Induction and post-Induction therapy regimen with MBFM-IMIDM and enhanced supportive care in children with DS and HR B-ALL will result in a ≥ 65% 5-year DFS and < 10% Induction mortality.

- To describe outcomes for children and young adults with Ph-like B-ALL and a predicted TKI-sensitive mutation treated with dasatinib plus MBFM-IMHDM.

- To determine the toxicity and tolerability of MBFM-IMIDM in children with Down's syndrome.

- To estimate overall survival (OS) rates both overall and by regimen for a) HR B-ALL and b) VHR B-ALL.

- For ancillary studies, see Sections 15.0 and 16.0.

Exploratory Aim

- To determine if the reduction of MRD from end-Induction to end-Consolidation is greater for children, adolescents, and young adults with VHR B-ALL receiving Experimental Arms 1 and/or 2 compared to the Control Arm. (**Closed effective Amendment #6)**

10.2 Patient Accrual and Expected Duration of Trial

Patients will be stratified into the following groups at enrollment -
Stratum 1: Down syndrome B-ALL
Stratum 2: Non-Down syndrome B-ALL
Stratum 3: Post Induction patients from AALL0932

All patients will be stratified as follows at the end of Induction (including those enrolled after Induction therapy on the NCI SR trial AALL0932:

Stratum 4	HR (AALL0932 patients; no favorable genetics)
Stratum 5	HR (AALL0932 patients; favorable genetics)
Stratum 6	HR (AALL1131 patients)
Stratum 7	HR Down Syndrome
Stratum 8	VHR (AALL0932 D29 MRD Positive ≥ 0.01, < 1.0 %; no unfavorable features)
Stratum 9	VHR (AALL0932 D29 MRD Positive ≥ 1.0 %; no unfavorable features)
Stratum 10	VHR (AALL1131 D29 MRD Positive ≥ 0.01, < 1.0 %; no unfavorable features)
Stratum 11	VHR (AALL1131 D29 MRD Positive ≥ 1.0 %; no unfavorable features)
Stratum 12	VHR (AALL1131; age 13+ years, D29 MRD Negative, no unfavorable features)
Stratum 13	VHR (All others: CNS3, MLL-R, Induction Failure, Hypodiploidy, iAMP21 regardless of MRD)

The randomizations will be balanced respectively for the HR and VHR studies within the various strata given above.

The study will accrue annually around 600 newly diagnosed NCI High Risk (HR) patients (including around 12 patients with CNS or testicular disease at diagnosis), and about 14 NCI Standard Risk (SR) patients with CNS or testicular disease at diagnosis. At the end of Induction therapy on the COG NCI SR trial AALL0932 the following patients will also be eligible to enroll on this study for post-Induction therapy: 89 NCI SR patients without favorable cytogenetic features (*ETV6-RUNX1* or trisomy of chromosomes 4 and 10) that have Day 8 PB MRD ≥1% and Day 29 BM MRD < 0.01%, 70 NCI SR patients with favorable cytogenetic features (*ETV6-RUNX1* or trisomy of chromosomes 4 and 10) that have Day 29 BM MRD ≥0.01% (with any Day 8 PB MRD), 79 NCI SR patients without favorable cytogenetics who have Day 29 MRD ≥0.01%, and 38 NCI SR patients with other very high risk features (Induction Failure – M3 marrow, hypodiploidy, *MLL* rearranged, or iAMP21).

Of the 614 NCI HR patients and NCI SR CNS3/testicular disease patients enrolled at diagnosis on this study, about 21 will have Down syndrome and will be assigned to a separate stratum/treatment arm. About 33 Ph+ B-ALL patients will not be eligible for post-Induction therapy on this study, but will be eligible to transfer to AALL0622 or successor trial for Ph+ ALL. Of the remaining 560 patients who will receive Induction therapy on this study, about 296 patients will have VHR B-ALL features (154 age≥13yrs with Day 29 MRD<0.01%; 64 Day 29 MRD ≥0.01%; 22 CNS3 at diagnosis, 56 patients with other very high risk features including Induction Failures – M3 marrow, hypodiploidy, or *MLL* rearranged, or iAMP21) and will be eligible to participate in the post-Induction VHR B-ALL randomization on this trial. The remaining 264 patients (4 testicular disease at diagnosis; 260 NCI HR age 1-12 years with Day 29 MRD < 0.01%) will be eligible for the post-Induction HR B-ALL randomization on this study. The 159 NCI SR pts (89 without favorable cytogenetic features that have Day 8 PB MRD ≥ 1% and Day 29 BM MRD < 0.01%, 70 with favorable cytogenetic features with Day 29 BM MRD ≥ 0.01%) will not be eligible to continue on AALL0932 and will be eligible to participate in the post-Induction HR B-ALL randomization. The 79 NCI SR patients without favorable cytogenetics who have Day 29 MRD ≥ 0.01%; and 38 NCI SR patients with other very high risk features (Induction Failure – M3 marrow, hypodiploidy, *MLL* rearranged, or iAMP21 will be eligible for the VHR randomization. About 5 SR patients with Down syndrome who have Day 29 BM MRD ≥ 0.01%, will also be eligible for the same post-Induction therapy as the NCI High risk Down syndrome patients on this study. A total of about 4450 patients will be accrued over 5 years.

Hence, a total of 423 patients will be eligible annually at the end of Induction for the *HR B-ALL randomization* to IT MTX vs. ITT. Adjusting for loss due to refusals/loss to follow up etc., the number of eligible/evaluable patients to be randomized to this question is estimated to be about 360 per year. A total

of 1800 eligible/evaluable patients will be accrued over 5 years with minimum follow up of 2 years.

A total of 413 patients/year will be eligible at the end of Induction for the *VHR B-ALL randomization*. Although all these patients are eligible for the chemotherapy randomization, subjects with Induction Failure or hypodiploidy will have the option of going off therapy at the end of Consolidation for allogeneic SCT, and hence only the rest (age ≥ 13yrs with Day 29 MRD < 0.01%, CNS3 at diagnosis, *MLL* rearranged, iAMP21, or MRD positive at end of Induction) will contribute to the primary chemotherapy efficacy question (~373 patients/year). Accounting for refusals and other losses, an estimated 300 eligible/evaluable patients/year will be randomized and contribute to the primary efficacy question. A total of 1500 eligible/evaluable patients will be accrued over 5 years with minimum follow up of 2 years.

Amendment #2
With this amendment, due to excessive toxicities, accrual to the VHR randomization will be restarted at the lower dose of clofarabine. As of March 1, 2013, this randomization has accrued 136 patients. In order to accrue 136 VHR patients to the randomization, overall an additional 445 patients would be accrued on the study either at diagnosis or end of Induction. Hence the total projected accrual to this study will be increased from 4450 to 4895 to account for these patients.

Amendment #3B
With this amendment and the permanent closure of Experimental Arm 2 of the study, the VHR substudy will become a 2-way randomization (weighted 1:2) between the Control Arm and Experimental Arm 1. This change in study design will require a total of 850 evaluable patients to be accrued to the VHR substudy. As of 05/07/2014, 145 evaluable VHR patients (47 in the control arm and 98 in Arm 1) have been enrolled. Uniform accrual rates are assumed for enrollments prior to this amendment and also for those post this amendment. Based on current accrual rates of approximate 293/year, the additional 705 VHR evaluable patients will be randomized 1:2 to the 2 arms over 2.4 years with approximately 3 years of follow up.

With the shortened accrual duration for the VHR substudy, the total accrual to the HR substudy will also be lower. Based on current accrual rates of 311/year, a total of 1727 eligible/evaluable patients will be randomized to the two HR arms by the time the accrual target for the VHR study is met. All patients will be followed for approximately 3 years.

Based on current accrual rates, a total of 4808 patients will be accrued on study in order to get the required number of eligible, evaluable patients randomized to the HR and VHR substudies.

Amendment #5A

Patients will be stratified into the following groups at enrollment -
Stratum 1: Down syndrome B-ALL
Stratum 2: Non-Down syndrome B-ALL
Stratum 3: Post Induction patients from AALL0932

All patients will be stratified as follows at the end of Induction (including those enrolled after Induction therapy on the NCI SR trial AALL0932:

Stratum 4	HR (AALL0932 patients; no favorable genetics)
Stratum 5	HR (AALL0932 patients; favorable genetics)
Stratum 6	HR (AALL1131 patients)

Stratum 7	HR Down Syndrome
Stratum 8	VHR (AALL0932 D29 MRD Positive ≥ 0.01, < 1.0 %; no unfavorable features)
Stratum 9	VHR (AALL0932 D29 MRD Positive ≥ 1.0 %; no unfavorable features)
Stratum 10	VHR (AALL1131 D29 MRD Positive ≥ 0.01, < 1.0 %; no unfavorable features)
Stratum 11	VHR (AALL1131 D29 MRD Positive ≥ 1.0 %; no unfavorable features)
Stratum 12	VHR (AALL1131; age 13+ years, D29 MRD Negative, no unfavorable features)
Stratum 13	VHR (All others: CNS3, MLL-R, Induction Failure, Hypodiploidy, iAMP21 regardless of MRD)
Stratum 14	Ph like – Dasatinib arm

With this amendment, patients who receive Induction therapy on the AALL1131 and are identified to have Ph-like expression with a predicted dasatinib-sensitive mutation will be eligible to continue on non-randomized post-Induction treatment with dasatinib on the MBFM-IMHDM backbone (Dasatinib Arm), and will not be eligible to be randomized to the HR or VHR arms of this study. Patients who receive Induction therapy on AALL1131 and are identified as having a Ph-like expression with a CRLF2r or JAK/STAT pathway kinase mutation will have the option of enrolling onto the AALL1521 ruxolitinib study or continuing on AALL1131 in the randomization that would have been otherwise defined by their risk group (HR or VHR). Patients who received Induction therapy on AALL0932 with either of these mutations will not be eligible for the Dasatinib Arm, or the AALL1521 ruxolitinib study but may continue on study in the randomization that would have been otherwise defined by their risk group (HR or VHR) on AALL1131.

According to the past data on AALL1131, it is projected that about 4.9% of VHR and 3.1% of HR patients will be identified to be Ph-like and harbor a predicted dasatinib sensitive mutation. Approximately 12.4% of VHR and 13.7% of HR patients will be identified as having a Ph-like expression with a CRLF2r or JAK/STAT pathway kinase mutation, and 60% of them are expected to enroll onto the AALL1521 ruxolitinib study. So in total, approximately 12.3% of VHR and 11.3% of HR patients who receive Induction therapy on the AALL1131 will not continue in the corresponding randomization on AALL1131.

As of 11/13/2015, a total of 269 VHR patients were randomized between the control arm and experimental arm A. The projected accrual rate for eligible and evaluable randomized VHR patients is 270 per year, including 74 per year from AALL0932 and 196 per year from AALL1131. Assuming this amendment will be activated in April 2016, and accounting for the 12.3% of VHR patients who will either continue on the Dasatinib arm or go off study to enroll on AALL1521, a total of 850 eligible and evaluable randomized VHR patients are expected to be accued by April 2018.

The total number of HR patients will be adjusted accordingly. As of 11/13/2015, 1132 HR patients were randomized. Based on the accrual rate of 314 per year, including 126 per year from AALL0932 and 188 per year from AALL1131, after accounting for the 11.3% of HR patients who will either continue on the Dasatinib arm or go off study to enroll on AALL1521, approximately 1825 eligible and evaluable randomized HR patients are expected to be accued by the time the accrual target for the VHR substudy is met.

Based on current accrual rates, a total of 5437 patients will be accrued on study using an estimated accrual rate of 954 per year, in order to get the required number of eligible, evaluable patients randomized to the HR and VHR substudies. The number of patients who will be eligible to continue onto the Dasatinib arm is projected to be 32 (20 VHR and 12 HR) and the number of patients who may go off study to the AALL1521 study is estimated to be 63 (31 VHR and 32 HR).

Amendment #6
Patients will be stratified into the following groups at enrollment -
Stratum 1: Down syndrome B-ALL
Stratum 2: Non-Down syndrome B-ALL
Stratum 3: Post Induction patients from AALL0932

All patients will be stratified as follows at the end of Induction (including those enrolled after Induction therapy on the NCI SR trial AALL0932:

Stratum 4	HR (AALL0932 patients; no favorable genetics)
Stratum 5	HR (AALL0932 patients; favorable genetics)
Stratum 6	HR (AALL1131 patients)
Stratum 7	HR Down Syndrome
Stratum 8	VHR (AALL0932 D29 MRD Positive ≥ 0.01, < 1.0 %; no unfavorable features)
Stratum 9	VHR (AALL0932 D29 MRD Positive ≥ 1.0 %; no unfavorable features)
Stratum 10	VHR (AALL1131 D29 MRD Positive ≥ 0.01, < 1.0 %; no unfavorable features)
Stratum 11	VHR (AALL1131 D29 MRD Positive ≥ 1.0 %; no unfavorable features)
Stratum 12	VHR (AALL1131; age 13+ years, D29 MRD Negative, no unfavorable features) Closed 02/2017
Stratum 13	VHR (All others: CNS3, MLL-R, Induction Failure, Hypodiploidy, iAMP21 regardless of MRD) Closed 2/2017
Stratum 14	Ph like CRLF2 or JAK pathway alteration (HR)
Stratum 15	Ph like CRLF2 or JAK pathway alteration (VHR) Closed 2/2017
Stratum 16	Ph-like ABL class alteration
Stratum 17	VHR (AALL1131 D29 MRD Positive ≥0.01% WITH CNS3, OR *KMT2A* (*MLL*)-R, OR iAMP21)

As of the temporary closure to accrual on 09/08/2017, a total of 1719 HR patients were randomized between Arms A and B. The estimated accrual rate for post-Induction randomization for HR patients is approximately 30/month (from AALL0932 and AALL1131). The remaining 106 patients required to meet HR accrual targets, are expected to be accrued in approximately 4 months after activation of Amendment #6. As of the temporary closure, AALL1131 has accrued a total of 5031 patients (including NCI SR and NCI HR), and is expected to accrue an additional 305 patients (5336 total) by the time the HR randomization is meets accrual goals. AALL0932 will be closed to accrual at this point. AALL1131 will then remain active as a screening protocol and accrue NCI High Risk patients until the next high risk protocol AALL1732 is activated. Assuming it is open as a screening study for about 10 months, an additional 620 NCI HR patients will be accrued, giving an overall expected accrual of 5956 for the study. As of the temporary closure, a total of 5 eligible patients were accrued to the dasatinib arm (with predicted TKI-sensitive mutation), and it is projected that an additional 25 patients (30 total) will be accrued by the end of the study. About 50 patients who are EOI MRD positive are expected to continue on consolidation on AALL1131 post amendment #6.

10.3 Statistical Analysis Methods

Sample size with power justification

Primary endpoint for both HR B-ALL and VHR B-ALL groups is the comparison of disease-free survival (DFS), where DFS is defined as the time from start of consolidation therapy to first event (relapse,

secondary malignancy, remission death) or date of last contact for patients who do not experience an event.

HR B-ALL randomization: The baseline 5-year DFS for patients on the previous high risk trial AALL0232 who fall into this risk category is around 90%. With a total of 1800 patients accrued over 5 years with minimum follow up of 2 years, randomized 1:1 to the 2 arms, we will be able to detect an improvement in 5-year DFS from 90% to 94% (HR=0.5873) between IT MTX and ITT based regimens (2-sided log rank test, alpha=5%), with 84.2% power. If the baseline 5-year DFS for these patients is lower than projected (say 88%), then there is 76.5% power to detect an improvement to 92% DFS; and 92.9% power to detect an improvement to 93% DFS. Similarly if the projected baseline DFS rate is higher (say 92%), then there is 68.7% power to detect an improvement to 95% DFS, and there is 92.3% power to detect an improvement to 96% 5-year DFS. The ITT therapy is expected to improve outcomes by reducing the incidence of CNS relapses. Hence the 5-year cumulative incidence of CNS relapses (+/- marrow) will be compared between the 2 regimens. Baseline CNS and marrow relapse rates in this population were obtained from AALL0232. With 1800 patients there is over 95% power to detect a reduction in the cumulative incidence rates (4% vs. 2%) at 5-years on the two randomized regimens (1-sided test, alpha=5%). There is 87.2% power to detect a reduction from 4% to 2.5% in the 5-year cumulative incidence rate for CNS relapses. At the same time, the cumulative incidence rate of marrow relapses will also be monitored, to ensure there is no significant increase in marrow relapses on the ITT therapy arm. A sample size of 1800 patients gives 96% power to detect an increase in the cumulative incidence rates at 5-years from 4% to 8% on the 2 arms (1-sided test, alpha=5%). Toxicities on the 2 randomized regimens will be closely monitored and compared at the time of biannual reporting to the COG DSMC. Excessive incidence of any toxicity on either arm will cause the study to be flagged for review.

Amendment #3B

The changes to study design for the VHR substudy due to this amendment, shortened the overall accrual duration for the study and hence resulted in a lower total accrual for the HR randomization. As of 12/31/2014, we have accrued 851 evaluable HR patients to the study and the corresponding accrual rate is approximately 311 per year. Assuming this amendment will be activated in late May, it is projected that a total of 1727 eligible/evaluable patients will be randomized to the two HR arms by the time the study closes. Assuming a cure-rate model for DFS with exponential distribution during the first 5 years followed by a flat curve and approximate 3 years of follow-up, a total of 128 events are expected to be observed, which gives 81.4% power to detect an improvement in 5-year DFS from 90% to 94% (HR=0.587) between the IT MTX and ITT based regimens (2-sided log rank test, alpha=5%). If the baseline 5-year DFS for these patients is lower than projected (say 88%), then there is 73.2% power to detect an improvement to 92% DFS; and 91.1% power to detect an improvement to 93% DFS. Similarly if the projected baseline DFS rate is higher (say 92%), then there is 65.2% power to detect an improvement to 95% DFS, and there is 90.4% power to detect an improvement to 96% 5-year DFS. These power calculations have taken into account the 5 interim monitoring looks for efficacy at approximately 20%, 40%, 60%, 80% and 100% of information (see details in Section 10.4).

The ITT therapy is expected to improve outcomes by reducing the incidence of CNS relapses. Hence the 5-year cumulative incidence of CNS relapses (+/- marrow) will be compared between the 2 regimens. Baseline CNS and marrow relapse rates in this population were obtained from AALL0232. With 1727 patients and 3 years of follow-up, there is 78.6% power (~ 48 CNS relapses) to detect a reduction in the 5-year cumulative incidence rates (4% vs. 2%) on the two randomized regimens based on a one-sided logrank test at alpha level of 0.05. There will also be 53.1% power (~ 52 CNS relapses) to detect a reduction in the 5-year cumulative incidence from 4% to 2.5% for CNS relapses. At the same time, the cumulative incidence rate of marrow relapses will also be monitored, to ensure there is no significant increase in marrow relapses on the ITT therapy arm. A sample size of 1727 patients gives 96.8% power (96 marrow relapses) to detect an increase in the cumulative incidence rates at 5-years from 4% to 8% on the 2 arms (1-sided test, alpha=5%). Toxicities

on the 2 randomized regimens will be closely monitored and compared at the time of biannual reporting to the COG DSMC. Excessive incidence of any toxicity on either arm will cause the study to be flagged for review.

Amendment #5A

It is projected that a total of 1825 eligible and evaluable patients will be randomized to the two HR arms by the time the accrual target for VHR substudy is met. Considering that a small portion of HR patients (i.e. ~11.3% of those who receive Induction therapy on the AALL1131 study) will either continue onto the Dasatinib arm or go off to the AALL1521 study after activation of this amendment, it is appropriate to assume that the accrual of HR patients is roughly uniformly distributed. Assuming a cure-rate model for DFS with exponential distribution during the first 5 years followed by a flat curve and approximate 3 years of follow-up, a total of 136 events are expected to be observed, which gives 83.7% power to detect an improvement in 5-year DFS from 90% to 94% (HR=0.587) between the IT MTX and ITT based regimens (2-sided log rank test, alpha=5%). The following table provides additional power calcuations to look for an improvement of 2-4% in 5-year DFS from the baseline 5-year DFS ranging from 88%-92%. These power calculations have taken into account the 5 interim monitoring looks for efficacy at approximately 20%, 40%, 60%, 80% and 100% of information (see details in Section 10.4).

5-year DFS		Hazard Ratio	Power	# of Events
IT MTX	ITT			
88%	92%	0.652	0.758	170
88%	93%	0.568	0.927	162
89%	93%	0.623	0.796	153
89%	94%	0.531	0.949	145
90%	93%	0.689	0.572	145
90%	94%	0.587	0.837	136
91%	94%	0.656	0.618	127
91%	95%	0.544	0.879	119
92%	95%	0.615	0.676	110
92%	96%	0.490	0.920	102

The ITT therapy is expected to improve outcomes by reducing the incidence of CNS relapses. Hence the 5-year cumulative incidence of CNS relapses (+/- marrow) will be compared between the 2 regimens. Baseline CNS and marrow relapse rates in this population were obtained from AALL0232. With 1825 patients and 3 years of follow-up, there is 80.7% power (~ 51 CNS relapses) to detect a reduction in the 5-year cumulative incidence rates (4% vs. 2%) on the two randomized regimens based on a one-sided logrank test at alpha level of 0.05. There will also be 55.0% power (~ 55 CNS relapses) to detect a reduction in the 5-year cumulative incidence from 4% to 2.5% for CNS relapses. At the same time, the cumulative incidence rate of marrow relapses will also be monitored, to ensure there is no significant increase in marrow relapses on the ITT therapy arm. A sample size of 1825 patients gives 97.5% power (~102 marrow relapses) to detect an increase in the cumulative incidence rates at 5-years from 4% to 8% on the 2 arms (1-sided test, alpha=5%). Toxicities on the 2 randomized regimens will be closely monitored and compared at the time of biannual reporting to the COG DSMC. Excessive incidence of any toxicity on either arm will cause the study to be flagged for review.

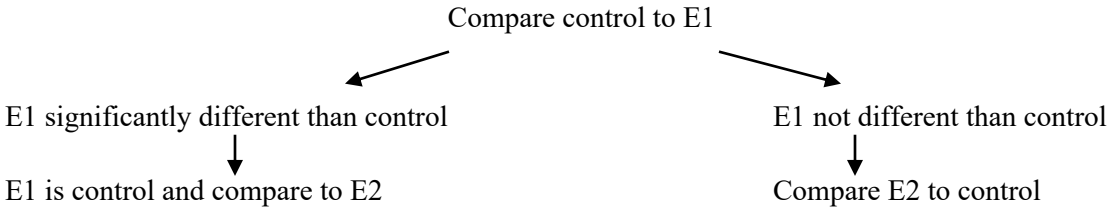
VHR B-ALL randomization:

Amendment #2

With this amendment and restarting of accrual to the VHR B-ALL randomization at the lower dose of clofarabine, there will be no changes to the power calculations and testing strategy stated below. The

136 patients who are already accrued to this randomization, will be analyzed separately for efficacy and adverse events. Due to the small sample sizes, all analyses will be descriptive.

A total of 1500 patients accrued over 5 years will be randomized 1:2:2 to the 3 arms (300 on the Control Arm; 600 on Experimental Arms 1 and 2 each). The 4-year DFS for patients in this risk category on the previous standard risk and high risk trials AALL0331/AALL0232 is around 70%. A hierarchical testing strategy as given below will be utilized.



The 4-year DFS will be compared between arms as shown above. If E1 is significantly better than control, then there will be no interest to compare E2 to control; E2 will be compared to the 'new control' E1. If E1 is not different from control, then E2 will be compared to control. If E2 is better than control, then as secondary analyses E1 and E2 can be compared computing confidence intervals around the estimated DFS rates. All comparisons will be made at the 0.025 significance level.

This design will have 86.8% power (1-sided log rank test, adjusted alpha=0.025 for multiple comparisons) to detect an improvement in 4-year DFS from 70% to 79% (HR=0.661) between the control arm and either one of the 2 experimental arms. A 1-sided comparison is justified because both experimental regimens are expected to have more toxicity than the control and hence will be selected only if they improve DFS. If the baseline 4-year DFS rate for the control arm is lower than projected (say 68%), then there is 85.2% power to detect an improvement to 77%. Similarly, if the 4-year baseline DFS rate is higher than projected (say 72%), then there is 80% power to detect an improvement to 80% 4-year DFS.

If the 2 experimental arms E1 and E2 are compared for differences in DFS rates, with 600 patients on each experimental arm, there is sufficient power to detect differences from 6%-9% in 4-year DFS rates using a 1-sided log rank test, and alpha=0.025 (see Table 1 below).

Table 1. Power calculations for comparison of DFS rates between regimens E1 and E2

4-year DFS comparisons of E1 vs E2	**Hazard Ratio**	**Power**
70% vs 77%	0.733	82.3%
72% vs 79%	0.718	84.2%
75% vs 82%	0.690	87.5%
77% vs 84%	0.667	89.9%
78% vs 85%	0.654	91.1%
79% vs 85%	0.689	81.5%
80% vs 86%	0.676	83.2%
82% vs 88%	0.644	86.9%

Amendment #3B

With the redesign of the VHR substudy, the 1:2 randomization to Control vs. Experimental Arm 1 will accrue a total of 850 evaluale patients. As of 05/07/2014, 145 evaluable VHR patients (47 in the control arm and 98 in Arm 1) have been enrolled to the study. Based on current accrual rates of approximate 293/year, the additional 705 VHR evaluable patients will be randomized 1:2 to the 2 arms over 2.4 years.

Assuming a cure-rate model for DFS with exponential distribution during the first 4 years followed by a flat curve and with approximately 3 years follow-up (to observe the required events), total sample size of 850 randomized subjects, a total of 196 events (35 events are projected to be observed among the 145 evaluable VHR patients enrolled prior to 05/07/2014 based on a survival rate of 0.70 and 0.79 for the two randomized arms; and 161 events are projected to be observed among the 705 additional VHR patients to be enrolled after activation of this amendment) are expected to be observed at the time of final analysis. This will give 80% power (2-sided, alpha = 0.05) to detect an improvement in 4-year DFS from 70% to 79% (HR=0.661) between the control arm and experimental arm 1. This power calculation takes into account the 5 interim monitoring looks for efficacy at 20%, 40%, 60%, 80% and 100% of information (see details in Section 10.4). Table below gives power calculations for scenarios if the baseline 4-year DFS rate for the control arm is different from that projected.

4-year DFS comparisons Std vs Expt arm	**Hazard Ratio**	**Power**
68% vs 77%	0.678	78.0%
70% vs 79%	0.661	80.1%
72% vs 81%	0.642	82.2%
74% vs 83%	0.619	84.8%

Down syndrome:
A total of 130 eligible/evaluable NCI HR and SR DS patients will be accrued over the duration of this study. This will allow estimation of DFS for the DS patients with a maximum standard error of 4.2%. In addition, the DFS for these patients will be monitored to ensure it does not fall below 65% (with 130 patients there is 83.7% power, alpha of 5%, one-sided test to detect a reduction in DFS to 53%). A DFS no lower than 65% was chosen as a stopping rule based on the 5-year DFS of 66.5 ± 13.6%. in DS HR B-ALL patients enrolled on AALL0232. Induction mortality rate for the DS HR B-ALL patients will be closely monitored to ensure it is not significantly more than 10%. A total of 105 DS HR B-ALL patients are expected to get Induction therapy on this study. If 4 Induction deaths occur among the first 50 DS enrollments, the study will be temporarily closed to DS patients and the data on deaths reviewed closely by the study committee, with a decision made on possible modifications to Induction therapy for these patients. With this rule, the probabilities of stopping are 23.9%, 57.5%, 74.9%, and 86.6%, when the true Induction death rates are 5%, 8%, 10%, and 12%, respectively. Again, if 9 deaths occur among the 105 patients, the Induction therapy will be deemed too toxic. The probabilities of deeming the therapy too toxic are 8%, 46.5%, 73.4%, and 89.6%, when the true Induction death rates are 5%, 8%, 10%, and 12%, respectively. Adjusting for loss due to Induction failures/deaths and inclusion of NCI standard risk DS patients to the post-Induction therapy, the above rule will also be applied to remission deaths post-Induction. All Grade 3/4 toxicities (including stomatitis, hyperglycemia, and infections) will be closely monitored in this cohort. Delays of >2 weeks in beginning the next phase of therapy will also be monitored. Data on these toxicities will be summarized and presented in each bi-annual report to the COG Data safety monitoring committee (DSMC); the rates will be compared descriptively with those seen on CCG 1961 and AALL0232.

The toxicity and tolerability of MBFM-IMIDM in children with Down's syndrome will also be assessed. The cumulative dose of ID MTX received by patients during the IM phase, will be collected. Occurrence of Grade 4 GI and renal toxicities, and delays in treatment delivery (>2 weeks) will also be monitored. Deaths occurring during this phase will be closely monitored. A second death would prompt review of data and possible modifications to therapy.

Amendment #3B
Based on current accral rates, a total of 168 eligible/evaluable NCI HR and SR DS patients will be accrued over the duration of this study. This will allow estimation of DFS for the DS patients with a maximum standard error of 3.9%. In addition, the DFS for these patients will be monitored to ensure it does not fall

below 65% (with 168 patients there is 82.8% power, alpha of 5%, one-sided exact test to detect a reduction in DFS to 55%). A DFS no lower than 65% was chosen as a stopping rule based on the 5-year DFS of 66.5 ± 13.6% in DS HR B-ALL patients enrolled on AALL0232. Induction mortality rate for the DS HR B-ALL patients will be closely monitored to ensure it is not significantly more than 10%. A total of about 135 DS HR B-ALL patients are expected to get Induction therapy on this study. If 4 or more Induction deaths occur among the first 50 DS enrollments, the study will be temporarily closed to DS patients and the data on deaths reviewed closely by the study committee, with a decision made on possible modifications to Induction therapy for these patients. With this rule, the probabilities of stopping are 23.9%, 57.5%, 74.9%, and 86.6%, when the true Induction death rates are 5%, 8%, 10%, and 12%, respectively. Again, if 9 deaths occur among the 135 patients, the Induction therapy will be deemed too toxic. The probabilities of deeming the therapy too toxic are 23.5%, 76.1%, 93.1%, and 98.5%, when the true Induction death rates are 5%, 8%, 10%, and 12%, respectively. Adjusting for loss due to Induction failures/deaths and inclusion of NCI standard risk DS patients to the post-Induction therapy, the above rule will also be applied to remission deaths post-Induction. All Grade 3/4 toxicities (including stomatitis, hyperglycemia, and infections) will be closely monitored in this cohort. Delays of >2 weeks in beginning the next phase of therapy will also be monitored. Data on these toxicities will be summarized and presented in each bi-annual report to the COG Data safety monitoring committee (DSMC); the rates will be compared descriptively with those seen on CCG 1961 and AALL0232.

The toxicity and tolerability of MBFM-IMIDM in children with Down's syndrome will also be assessed. The cumulative dose of ID MTX received by patients during the IM phase, will be collected. Occurrence of Grade 4 GI and renal toxicities, and delays in treatment delivery (>2 weeks) will also be monitored. Deaths occurring during this phase will be closely monitored. A second death would prompt review of data and possible modifications to therapy.

Amendment #5A

Based on current accrual rates, a total of 200 eligible/evaluable NCI HR and SR DS patients will be accrued over the duration of this study. This will allow estimation of DFS for the DS patients with a maximum standard error of 3.5%. In addition, the DFS for these patients will be monitored to ensure it does not fall below 65% (with 200 patients there is 88.7% power, alpha of 5%, one-sided exact test to detect a reduction in DFS to 55%). A DFS no lower than 65% was chosen as a stopping rule based on the 5-year DFS of 66.5 ± 13.6% in DS HR B-ALL patients enrolled on AALL0232. Induction mortality rate for the DS HR B-ALL patients will be closely monitored to ensure it is not significantly more than 10%. A total of about 153 DS HR B-ALL patients are expected to get Induction therapy on this study. If 7 or more Induction deaths occur among the first 50 DS enrollments, the study will be temporarily closed to DS patients and the data on deaths reviewed closely by the study committee, with a decision made on possible modifications to Induction therapy for these patients. With this rule, the probabilities of stopping are 23.0%, 47.9%, 63.9%, and 82.0%, when the true Induction death rates are 10%, 13%, 15%, and 18%, respectively. Again, if 19 deaths occur among the 153 patients, the Induction therapy will be deemed too toxic. The probabilities of deeming the therapy too toxic are 19.1%, 62.1%, 84.4%, and 97.6%, when the true Induction death rates are 10%, 13%, 15%, and 18%, respectively. Adjusting for loss due to Induction failures/deaths and inclusion of NCI standard risk DS patients to the post-Induction therapy, the above rule will also be applied to remission deaths post-Induction. All Grade 3/4 toxicities (including stomatitis, hyperglycemia, and infections) will be closely monitored in this cohort. Delays of >2 weeks in beginning the next phase of therapy will also be monitored. Data on these toxicities will be summarized and presented in each bi-annual report to the COG Data safety monitoring committee (DSMC); the rates will be compared descriptively with those seen on CCG 1961 and AALL0232.

The toxicity and tolerability of MBFM-IMIDM in children with Down's syndrome will also be assessed. The cumulative dose of ID MTX received by patients during the IM phase, will be collected. Occurrence of Grade 4 GI and renal toxicities, and delays in treatment delivery (>2 weeks) will also be monitored. Deaths

occurring during this phase will be closely monitored. A second death would prompt review of data and possible modifications to therapy.

Amendment #6
Based on current accrual rates, a total of 276 eligible/evaluable NCI HR and SR DS patients will be accrued over the duration of this study. This will allow estimation of DFS for the DS patients with a maximum standard error of 3.0%. In addition, the DFS for these patients will be monitored to ensure it does not fall below 65% (with 276 patients there is 95.2% power, alpha of 5%, one-sided exact test to detect a reduction in DFS to 55%). A DFS no lower than 65% was chosen as a stopping rule based on the 5-year DFS of 66.5 ± 13.6% in DS HR B-ALL patients enrolled on AALL0232. Induction mortality rate for the DS HR B-ALL patients will be closely monitored to ensure it is not significantly more than 10%. A total of about 212 DS HR B-ALL patients are expected to get Induction therapy on this study. If 26 deaths occur among the 212 patients, the Induction therapy will be deemed too toxic. The probabilities of deeming the therapy too toxic are 16.2%, 65.5%, 89.0%, and 99.1%, when the true Induction death rates are 10%, 13%, 15%, and 18%, respectively. Adjusting for loss due to Induction failures/deaths and inclusion of NCI standard risk DS patients to the post-Induction therapy, the above rule will also be applied to remission deaths post-Induction. All Grade 3/4 toxicities (including stomatitis, hyperglycemia, and infections) will be closely monitored in this cohort. Delays of >2 weeks in beginning the next phase of therapy will also be monitored. Data on these toxicities will be summarized and presented in each bi-annual report to the COG Data safety monitoring committee (DSMC); the rates will be compared descriptively with those seen on CCG 1961 and AALL0232.

The toxicity and tolerability of MBFM-IMIDM in children with Down's syndrome will also be assessed. The cumulative dose of ID MTX received by patients during the IM phase, will be collected. Occurrence of Grade 4 GI and renal toxicities, and delays in treatment delivery (>2 weeks) will also be monitored. Deaths occurring during this phase will be closely monitored. A second death would prompt review of data and possible modifications to therapy.

Other secondary analyses:

Overall Survival (OS)
A secondary endpoint for both HR B-ALL and VHR B-ALL groups is the estimation and comparison of overall survival (OS) rates, where OS is defined as the time from date of diagnosis to death or date of last contact for patients who are still alive.

HR B-ALL
The 5-year OS rates both overall and on each treatment regimen, will be estimated for this group. With 1800 patients (900 on each arm) this can estimated with a maximum standard error of 0.07% and 1%, respectively. Due to low event rates, there will be insufficient power for a formal statistical comparison of OS rates between the 2 arms, but they will be compared informally.

Amendment #3B
With the updated total sample size of 1727 HR patients (863 on each arm), the 5-year OS rates both overall and by treatment regimen will be estimated with a maximum standard error of 1.2% and 1.7%, respectively. Due to low event rates, there will be insufficient power for a formal comparison of OS rates between the two arms, but informal comparisons will be conducted.

Amendment #5A
With the updated total sample size of 1825 HR patients (912 on each arm), the 5-year OS rates both overall and by treatment regimen will be estimated with a maximum standard error of 1.2% and 1.7%,respectively. Due to low event rates, there will be insufficient power for a formal comparison of OS rates between the two arms, but informal comparisons will be conducted.

VHR B-ALL

The 4-year OS rates both overall and on each of the 3 treatment regimen, will be estimated for this group. With 1500 patients (300 on control and 600 each on the 2 experimental arms) this can estimated with a maximum standard error of 0.09% (overall), 2.1% (control) and 1.5%(each experimental arm), respectively. Due to low event rates, there will be insufficient power for a formal statistical comparison of OS rates between the 2 arms, but they will be compared informally.

Amendment #3B
The 4-year OS rates both overall and on each of the two randomized treatment arms (control vs. experimental arm 1), will be estimated for the VHR patients. With a total accrual of 850 randomized VHR patients (283 on the control arm and 567 on Arm 1), the OS rates can be estimated with a maximum standard error of 1.7% (overall), 3.0% (control arm) and 2.1% (Arm 1), respectively. There will be insufficient power for a formal comparison of OS rates between treatment regimens, but they will be compared informally.

Adverse Event Monitoring
The incidence rates of the following key adverse events (in addition to any Grade 4 non-hematologic toxicities) will be estimated across all patient subgroups on this trial in order to provide data for linked correlative biology studies that seek to develop biomarkers predictive of patients at risk for such events:

1. CNS hemorrhage requiring medical intervention (Grade 2 or 3)
2. GI bleed requiring operative or interventional radiology intervention (Grade 3)
3. Pancreatitis requiring medical intervention (Grade 2 or 3)
4. Osteonecrosis interfering with function (Grade 2 or 3)
5. Transient ischemic attacks (All grades)
6. Stroke (All grades)
7. Encephalopathy (Grade 3)
8. Neuropathy; motor or sensory, interfering with ADL (Grade 3)
9. Seizure (Grade 2 or 3)
10. Allergic reaction (Grade 3)
11 Ileus (Grade 3)
12. Mucositis/stomatitis; functional (Grade 3)
13. Bilirubin (Grade 3)
14. Thrombosis (Grade 3)

Dasatinib Arm
Amendment #5A
The 4-year DFS and OS rates will be estimated for patients enrolled onto the the Dasatinib arm. With an estimate of 32 patients to be accrued, the DFS/OS rates can be estimated with a maximum standard error of 8.8%. There will be insufficient power for a formal comparison of EFS/OS rates of this arm to a historical control.

Amendment #6
The 4-year DFS and OS rates will be estimated for patients enrolled onto the the Dasatinib arm. With an estimate of 30 patients to be accrued, the DFS/OS rates can be estimated with a maximum standard error of 9.1%. There will be insufficient power for a formal comparison of EFS/OS rates of this arm to a historical control.

10.4 **Interim Analysis Methods** *(Amendment #2, 3B):*

Induction Deaths:
As of January 22, 2013, there have been 11 Induction deaths among 410 (2.68%) non-Down syndrome subjects that have completed Induction therapy. In order to closely monitor Induction mortality, this

amendment will include monitoring rules for overall Induction deaths and also Induction deaths associated with fungal infections.

The Induction mortality death rate seen on the prior COG study for the treatment of high risk ALL (AALL0232) was 1.98% on the AALL0232 Dexamethasone Arm (10 mg/m^2/day; Days 1-14) and 1.8% on the AALL0232 Prednisone Arm (60 mg/m^2/day; Days 1-28). Assuming a "null' Induction mortality rate of 2%, a Pocock monitoring boundary (truncated at 3 standard deviations) was constructed with 10 interim looks (after every 200 patients to a sample size of 2000) with the following property: the likelihood of crossing the boundary at any time when the true Induction mortality rate is 2% is 0.10 (10%).

The boundary is as follows: Concern regarding the Induction mortality rate would be triggered if the mortality rate is equal to or exceeds:

Sample size	Number of Induction deaths to trigger concern (Pocock boundary, alpha = 10%)	Percent of Induction deaths that trigger concern (Pocock boundary, alpha = 10%)
200	10	5.00%
400	15	3.75%
600	20	3.33%
800	25	3.13%
1000	30	3.00%
1200	35	2.92%
1400	39	2.79%
1600	44	2.75%
1800	48	2.67%
2000	53	2.65%

The Induction mortality rate will be calculated every 6 months for the first 2 years and annually after that if there are no concerns about the Induction mortality rate at that time and the boundary calculated as stated above using an alpha-spending function approach to spending the type-1 error as specified in the table (10%).

Because it is possible that Induction deaths will be reported immediately and successful completion on Induction therapy will await the completion of Induction therapy and the reporting period case report form, these analyses will be performed including only those patients with at least 60 days of potential follow-up at the scheduled data freeze for analysis.

In addition, a monitoring rule for Induction deaths due to fungal infections, is also detailed below. It will be concerning if more than 50% of Induction deaths are found to be related to fungal infections. Based on this, a monitoring rule has been developed using 1% as the rate of concern. The rule will use a Pocock monitoring boundary (truncated at 3 standard deviations) with 10 interim looks (after every 200 patients who have completed Induction therapy), with the following property: the likelihood of crossing the boundary at any time when the true fungal infection death rate is 1% is 0.10 (10%).

The boundary is as follows: Concern regarding the Induction mortality rate would be triggered if the mortality rate is equal to or exceeds:

Sample size	Number of Induction deaths to trigger concern (Pocock boundary, alpha = 10%)	Percent of Induction deaths that trigger concern (Pocock boundary, alpha = 10%)
200	7	3.50%
400	10	2.50%
600	12	2.0%
800	15	1.88%

1000	17	1.70%
1200	20	1.67%
1400	22	1.57%
1600	25	1.56%
1800	27	1.50%
2000	29	1.45%

The Induction mortality rate will be calculated every 6 months for the first 2 years and annually after that if there are no concerns about the induction mortality rate at that time and the boundary will be calculated as stated above and using an alpha-spending function approach to "spending" the type-1 error as specified in the table (10%).

HR B-ALL randomization: Interim monitoring rules for early indications of efficacy for the IT MTX vs. ITT question will use an αt^2 spending function. Futility monitoring will be based on the method of Freidlin and Korn.[164] We will do repeated testing of the alternative hypothesis at a p-value of 0.05 (1-sided), which will allow the randomization to be suspended if there is early evidence not consistent with a true relative risk reduction of 0.5873 as planned. The first interim analysis comparing regimen outcomes will be conducted at 20% of the information (140 events: projected combined DFS event horizon for the randomized groups being compared). Subsequent efficacy and futility analyses will be done at the time of study reporting to the COG DSMC every 6 months. The distribution of relapse events will be reviewed at the time of each interim monitoring and the cumulative incidence rates of CNS and marrow relapses will be estimated and monitored.

Amendment 3B
Interim monitoring rules for early indications of efficacy for the IT MTX vs. ITT regimens will use an $\alpha \times t^2$ spending function. Futility monitoring will be based on the method of Anderson and High.[165] We will do repeated testing of the alternative hypothesis at a p-value of 0.024 (1-sided), which will allow the randomization to be suspended if there is early evidence not consistent with a true relative risk reduction of 0.587 as planned. The first interim analysis comparing regimen outcomes will be conducted after 20% of the information (26 events: projected combined DFS event horizon for the randomized groups being compared). Subsequent efficacy and futility analyses will be done at approximately 40%, 60% and 80% information, at the time of biannual reporting to the COG Data Safety Monitoring Committee.

<u>Amendment #5A</u>
Interim monitoring rules for early indications of efficacy for the IT MTX vs. ITT regimens will use an $\alpha \times t^2$ spending function. Futility monitoring will be based on the method of Anderson and High.[165] We will do repeated testing of the alternative hypothesis at a p-value of 0.024 (1-sided), which will allow the randomization to be suspended if there is early evidence not consistent with a true relative risk reduction of 0.587 as planned. The first interim analysis comparing regimen outcomes was conducted in Fall 2015 when 29 events were observed, which is equivalent to 22.7% information based on the previous design and 21.0% information based on current design. Under either situation, the boundary was not crossed. Subsequent efficacy and futility analyses will be done at approximately 40%, 60% and 80% information, at the time of biannual reporting to the COG Data Safety Monitoring Committee.

VHR B-ALL randomization: Interim monitoring rules for early indications of efficacy for the Experimental Arms will be applied using a hierarchical testing strategy. Initial monitoring for efficacy will compare control to E1, using an αt^2 spending function. Full information for this comparison will be 270 events. Formal interim monitoring will be scheduled at 100, 150 and 200 events, corresponding to 37%, 55% and 74% of the expected total information. If at any interim analysis, there is early evidence that E1 is superior to C, then the control arm C will be closed to accrual and E1 vs E2 will be compared starting at the time of the interim analysis leading to the closure of the control arm. Full information for the E1 vs. E2 comparison if the control arm is closed, is expected to be near 250 events. Thus for instance, should interim monitoring of E1 vs. E2 be initiated, at 55% of the expected control plus E1

events, E1 versus E2 would be compared at that time and again at about 185 events (corresponding to 74% of the expected E1+E2 information should the control arm be closed. If there is insufficient evidence based on the interim comparisons that E1 is better than control, then accrual will continue to completion on all 3 randomized arms as planned.

Futility monitoring will be based on Fleming-Harrington-O'Brien repeated testing of the alternative hypothesis at a p-value of 0.005 (1-sided) and conducted at the same time as efficacy monitoring. E1 and E2 will each be compared against control for futility. If there is early evidence that E1 is better than control, and the accrual to the control arm is closed, then futility monitoring in subsequent looks will be for the E1 vs. E2 comparison. Should either of the experimental regimens be abandoned for futility, futility monitoring will continue comparing the remaining regimen to control.

Amendment #3B, 5A
Interim monitoring rules for efficacy for the VHR substudy will use an αt^2 spending function. Futility monitoring will be based on the method of Anderson and High.[165] We will do repeated testing of the alternative hypothesis at a p-value of 0.024 (1-sided), which will allow the randomization to be suspended if there is early evidence not consistent with a true relative risk reduction of 0.661 as planned. The first interim analysis comparing regimen outcomes will be conducted after 20% of the information (39 events: projected combined DFS event horizon for the randomized groups being compared). Subsequent efficacy and futility analyses will be done at approximately 40%, 60% and 80% information, at the time of biannual reporting to the COG Data Safety Monitoring Committee.

Interim monitoring for the VHR substudy will not change with amendment 5A, as all design parameters remain the same.

Safety Monitoring Rules for VHR B-ALL Randomization

Amendment #2
With the restart of accrual to this randomization (at the reduced dose of clofarabine) with Amendment #2, the safety monitoring detailed below will be repeated after the first 100 patients are randomized to the 3 arms (20:40:40). Enrollment to the VHR strata will be suspended temporarily after 100 patients are enrolled (20 to Control and 40 each to Experimental Arms 1 and 2). After all patients have completed Consolidation and entered Interim Maintenance, the data will be reviewed. If the protocol defined safety criteria are met, then the VHR strata will reopen to accrual. If these criteria are not met, then Experimental Arm 2 will be closed permanently.

The study will be monitored to ensure that the addition of clofarabine in Experimental Arm 2 is feasible and does not result in excessive toxicities during the second half of Consolidation and the second half of Delayed Intensification as compared to the Control arm and Experimental Arm 1. Safety will be assessed by monitoring the toxicities listed below among the first 40 patients randomized to Experimental Arm 2 and compared to the incidence rates seen among the corresponding 20 patients randomized to the control arm and the 40 patients randomized to Experimental Arm 1. These toxicities will again be monitored in these 100 patients once they complete Delayed Intensification.

Baseline rates on the control arm for the toxicities listed below cannot be assessed accurately from the recent high risk study (AALL0232), as that trial did not require as detailed adverse event reporting as will be required on AALL1131. Pilot studies AALL07P4 and AALL08P1 for high risk ALL do require more detailed reporting but have relatively small patient numbers. Hence, the toxicities on the clofarabine arm (Experimental Arm 2) will be compared with the concurrent randomized controls and Experimental Arm 1 on this study. Toxicities will be closely monitored and specifically after the first 20 patients are accrued on each of the experimental arms. There are a set of toxicities for which rates significantly exceeding 1%

will raise concerns about the feasibility of the experimental regimens, and for this study they are treatment related mortality (TRM) and SOS. Occurrence of treatment related mortality or SOS in 2 out of the first 40 patients on one of the experimental arms will cause the related data to be reviewed in conjunction with the Cancer Therapy Evaluation Program (CTEP) for any possible action. If the true rate of these toxicities is 1% in the study population, then the probabilities of observing 2 or more events in the first 20 and 40 patients are 0.017 and 0.06, respectively.

Other toxicities that will be monitored (listed below) are viewed as less serious, although if their rates significantly exceeded 5% then this would raise concerns about a regimen's feasibility.

1) Incidence of Grade 4 infections
2) AEs resulting in greater than 14 day delay in starting Interim Maintenance I or Interim Maintenance II
3) Incidence of Grade 3/4 ALT, AST, Grade 4 amylase and lipase or Grade 3/4 bilirubin elevations that do not return to Grade 2 or less by the time Day 43 vincristine and asparaginase are scheduled to be administered during Consolidation or Delayed Intensification
4) Incidence of other non-hematologic Grade 3/4 toxicities that do not return to Grade 2 or less by the time Day 43 vincristine and asparaginase are scheduled to be administered during Consolidation or Delayed Intensification
5) Incidence of Grade 3/4 pancreatitis
6) Incidence of Grade 3/4 capillary leak syndrome
7) Incidence of Grade 3/4 acute kidney injury
8) Other Grade 3 or 4 AEs attributable to clofarabine

For these toxicities, observation of 3 events among the first 20 patients or 5 events among the first 40 patients will lead to review of the data and consideration of possible action. If the true rate of one of these adverse events in the study population is 5%, then the probabilities of observing 3 or more events in the first 20 and 5 or more events in the first 40 patients are 0.075 and 0.05, respectively.

Duration of Treatment Phase

The mean duration of the entire Consolidation phase on the PH arm on AALL0232 is 74 days (standard deviation of 12 days), or 17 days longer than the scheduled 57 days. Data on duration of Days 29-57 of Consolidation on the AALL0232 are not available. Hence the duration of Days 29-57 of Consolidation therapy with the clofarabine dose of 30 mg/m^2/day x 5 days will be compared with that on the control and Experimental Arm 1. If the mean duration is found to be significantly longer (> than 2 standard deviations above the mean duration observed on the control arm) then the study will be flagged for review. As noted above, we will also compare the number of patients on each arm who are unable to meet count parameters (ANC, platelets) for starting Interim Maintenance I (and II) on time and are more than 14 days late, with a 2-fold difference in numbers between arms to cause concern.

Other Grade 3 or 4 toxicities observed at a clofarabine dose of 30 mg/m^2/day x 5 days will also be monitored as outlined above. If the 30 mg/m^2/day dose of clofarabine in Experimental Arm 2 is determined not to be feasible, a reduction in the clofarabine dose to 20 mg/m^2/day x 5 days during both Consolidation and Delayed Intensification will be considered with the same period of monitoring among the first 40 patients randomized to each of the Experimental Arms at the lower dose. If 20 mg/m^2/day x 5 days of clofarabine in Experimental Arm 2 proves feasible, the study will be completed at this dose. If a dose of 20 mg/m^2/day x 5 days is not feasible to administer, Experimental Arm 2 of the study will be closed.

Additional Data to meet FDA Requirements

Additional data will be collected (specified below and at the times specified in Section 7.1b), for the first 200 patients randomized to Experimental Arm 1 (100 patients) and Experimental Arm 2 (100 patients)

post-Amendment #2: Total and direct bilirubin, AST, ALT, Na^+, K^+, Cl^-, HCO_3^-, BUN, Creatinine, Ca^{2+}, PO_4, Mg^{2+}, Lipase, Amylase, Alkaline Phosphatase. These data are required to meet an FDA request to provide additional data on the two experimental arms, and will be collected on a separate CRF in eRDE. These data will be summarized descriptively at the time of generation of the COG biannual study reports and when data are collected for all 200 patients. Summary tables together with the data listings from the eRDE system will be provided for submission to the FDA, after the completion of data collection at all specified time points for these 200 patients.

Amendment #3B
The randomization to the Clofarabine containing regimen has been closed permanently. Hence the Safety analyses detailed above will be limited to the patients enrolled prior to Amendment #3B.

10.5 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	487	722	1209
Not Hispanic or Latino	1915	2832	4747
Ethnic Category: Total of all subjects	2402	3554	5956*
Racial Category			
American Indian or Alaskan Native	17	25	42
Asian	55	83	138
Black or African American	157	233	390
Native Hawaiian or other Pacific Islander	1	1	2
White	2172	3212	5384
Racial Category: Total of all subjects	2401	3554	5956*

* These totals must agree

This distribution was derived from AALL0331 and AALL0232.

11.0 EVALUATION CRITERIA

11.1 Common Terminology Criteria for Adverse Events (CTCAE)
This study will utilize the Version 4.0 CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the active version of the CTCAE can be downloaded from the NCI website at: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf). Additionally, toxicities are to be reported on the appropriate case report forms.

11.2 Response Criteria for Patients with Leukemia
See Section 3.3.

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.

12.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.4 Specific Examples for Expedited Reporting

12.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

12.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI, COG, or industry sponsor IND/IDE since these are considered to be serious AEs.

12.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

12.4.4 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 CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome

- Treatment related secondary malignancy

12.4.5 Second Malignancy

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the inititial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

12.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

12.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions"*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

12.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero".* Any Pregnancy loss should be reported expeditiously, as **Grade 4 "*Pregnancy loss" under the "Pregnancy puerperium and perinatal conditions"* SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

12.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as "*Newborn death occurring during the first 28 days after birth*", should be reported expeditiously as **Grade 4, "*Death neonatal*" under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

12.5 Reporting Requirements for Specialized AEs

12.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as the existence of the pre-existing condition as part of the research chart (i.e. chart notes, HPI, etc) using CTCAE terminology and grade (these baseline abnormalities are not required to be reported in eRDE). An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (eg, elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.

c. No modification in grading is to be made to account for abnormalities existing at baseline.

12.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.
ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

12.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

12.6 Exceptions to Expedited Reporting

12.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

12.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

12.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

12.8 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

An expedited AE report must be submitted electronically via CTEP-AERS at:
https://eapps-ctep.nci.nih.gov/ctepaers

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**
- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention requires expedited reporting **within 24 hours** via e-mail to the COG CTEP-AERS Coordinator and Study Chair.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Fax supporting documentation to CTEP as the IND sponsor for this study at 301-230-0159 or email supporting documentation **for AEs related to investigational agents** to COG:
Fax # 310-640-9193; email: COGAERS@childrensoncologygroup.org;
Attention: COG AERS Coordinator.

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site".

12.9 **Reporting Table for Late Phase 2 and Phase 3 Studies – Table A**

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to CTEP **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	**7 Calendar Days**			**24-Hour Notification 5 Calendar Days**
Not resulting in Hospitalization ≥ 24 hrs	**Not Required**		**7 Calendar Days**	

NOTE: Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:

"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.

"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

12.10 **Protocol Specific Additional Instructions and Reporting Exceptions**

- **Grades 1- 4 myelosuppression do not require expedited reporting unless unexpected.**
- **Grades 1-2 AST/ALT elevations do not require expedited reporting unless unexpected.**

12.11 **Reporting of Adverse Events for commercial agents – CTEP-AERS 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 CTEP-AERS report to be submitted **within 7 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.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

12.12 **Routine Adverse Event Reporting**
Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and Grade 4 non-hematologic Adverse Events as well as the following specific toxicities identified by the ALL Toxicity Reporting Task Force to be collected on all future COG ALL trials:

1. CNS hemorrhage requiring medical intervention (Grade 2 or 3)
2. GI bleed requiring operative or interventional radiology intervention (Grade 3)
3. Pancreatitis requiring medical intervention (Grade 2 or 3)
4. Osteonecrosis interfering with function (Grade 2 or 3)
5. Transient ischemic attacks (All grades)
6. Stroke (All grades)
7. Encephalopathy (Grade 3)
8. Neuropathy; motor or sensory, interfering with ADL (Grade 3)
9. Seizure (Grade 2 or 3)
10. Allergic reaction (Grade 3)
11 Ileus (Grade 3)
12. Mucositis/stomatitis; functional (Grade 3)
13. Bilirubin (Grade 3)
14. Thrombosis (Grade 3)

12.12.1 Additional adverse event reporting for VHR B-ALL. (Required only for patients randomized prior to Amendment #3B)
In addition to the routine AE reporting given above, the specific adverse events detailed below are required to be reported via the eRDE system:

1) Incidence of Grade 2 or more infections during periods of neutropenia (ANC < 500/µL) and Grade 3 to 5 infections irrespective of ANC count after Day 29 of Consolidation and DI. Does not apply to a Grade 2 infection during Maintenance.
2) AEs resulting in greater than 14 days delay in starting IM I or IM II
3) Incidence of Grade 3/4 ALT, AST, Grade 4 amylase and lipase or Grade 3/4 bilirubin elevations that do not return to Grade 2 or less by the time Day 43 vincristine and asparaginase are scheduled to be administered during Consolidation or DI.
4) Incidence of other non-hematologic Grade 3/4 toxicities that do not return to Grade 2 or less by the time Day 43 vincristine and asparaginase are scheduled to be administered during Consolidation or DI
5) Incidence of Grade 3/4 pancreatitis
6) Incidence of Grade 3/4 capillary leak syndrome
7) Incidence of Grade 3/4 acute kidney injury
8) Other Grade 3 or 4 AEs attributable to clofarabine
9) Sinusoidal obstruction syndrome (see Section 5.2 for details of criteria defining SOS)

12.12.2 Additional adverse event reporting for DS HR B-ALL

In addition to the routine AE required for all patients on this trial, the following additional AEs are required to be reported for the patients with Down syndrome:

1) All Grade 3 or higher infectious toxicities.
2) Grade 3-4 febrile neutropenia

Note: for EACH infection and febrile neutropenia event reported, the CTCAE event "neutrophil count decreased" should also be reported separately using a new AE form, should it occur. "Neutrophil count decreased" can be found under "Investigations". DO NOT report low platelets or any other low hematologic AE for this study.

3) Immunologic Serum IgG levels at the start of each reporting period and whether intravenous infusion of immunoglobulins (IVIG) was administered during that reporting period.

IgG levels and whether IVIG was administered will be collected in order to assess the effectiveness of the supportive care changes implemented on this study. These data will be used to evaluate whether DS patients on this study who suffer severe or fatal infectious complications were hypogammaglobulinemic at the time, and whether they received IVIG replacement. These patients, as well as patients that experience toxic events, will be very few and, hence, these data will be evaluated individually and summarized descriptively.

13.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

13.1 CDUS

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

14.0 RADIATION THERAPY GUIDELINES

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

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

14.1 Cranial Irradiation

Cranial irradiation will be given to patients with CNS3 leukemia at diagnosis who do not proceed to HSCT after Consolidation therapy. Cranial radiotherapy is to begin during the first 4 weeks of Maintenance therapy and should be completed by Day 29 of Maintenance.

14.1.1 Equipment and Calibration

14.1.1.1 Modality

X-ray beams with a nominal energy of 4 or 6 MV. IMRT is not allowed.

14.1.1.2 Calibration

The calibrations of therapy units used in this protocol shall be verified by the Radiological Physics Center (RPC).

14.1.2 Target Volume

14.1.2.1 Cranial Irradiation

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

14.1.3 Target Dose

14.1.3.1 Prescription Points

The prescription point in each target volume is at or near the center. For multi-convergent beams, the prescription point is usually at the intersection of the beam axes.

14.1.3.2 Dose Definition

The absorbed dose is specified in centigray (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 Daily Dose

The daily dose to the prescription points for the cranial volume will be 180 cGy for patients with CNS3 leukemia at diagnosis.

14.1.3.4.2 Total Dose
Cranium: The total dose to the prescription point shall be 1800 cGy in 10 treatments for patients with CNS3 leukemia at diagnosis.

14.1.3.4.3 Fractionation
All radiation fields shall be treated once each day; the treatment shall be given 5 days a week.

14.1.3.4.4 Treatment Interruptions
No corrections will be made for treatment interruptions less than 7 days. For any interruptions greater than 7 days, contact the study coordinator.

14.1.3.4.5 Dose Uniformity
The dose variations in each target volume shall be within +7%, -5% of the prescription-point dose.

14.1.4 Treatment Technique

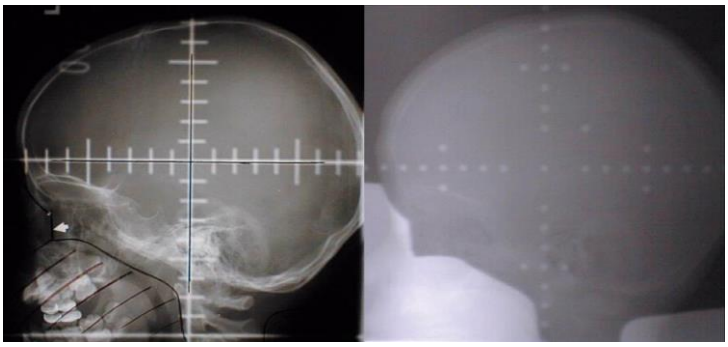
14.1.4.1 Patient Position
The patient can be treated prone or supine.

14.1.4.2 Beam Configuration
The cranial volume is treated with 2 lateral, equally weighted photon beams. The fields shall extend at least 1 cm beyond the periphery of the scalp.

14.1.4.3 Shielding

14.1.4.3.1 Blocks
Field-shaping shall be done with blocks which are at least 5 HVL thick. Multi-leaf collimators are also acceptable provided coverage is adequate.

Figure 14.1.4.3
Example of radiation simulation radiograph with cerrobend block design (left) and megavoltage portal film (right) for cranial irradiation volume.



14.1.4.3.2 Eye protection
A simple method to minimize lens irradiation, while irradiating the posterior halves of the eyes, is to let the central axes of the horizontal cranial beams go through both orbits. The anterior edges of the beams are defined by an external block or by an independently controlled collimator and meet at a point 1 cm anterior to the frontal lobe meninges. Shielding blocks cover the anterior halves of the eyes and protect the nose and mouth. Essentially the same geometry can be achieved with the central axes through the center of the head by angling the lateral fields so that the rays through the eyes lie in the same horizontal

plane. It is also acceptable to use a parallel-opposed beam-pair, without such angling, with shielding blocks that cover the anterior half of the proximal eye. The dose to the contralateral lens will be higher.

14.2 Testicular Irradiation

Testicular irradiation will be given to patients with testicular leukemia at diagnosis that does not resolve completely by the end of Induction. Testicular radiotherapy is to start during Consolidation and must be completed before the end of this phase of therapy.

14.2.1 Equipment and Calibration

14.2.1.1 Modality

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

14.2.1.2 Calibration

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

14.2.2 Planning Target Volume

Planning target volume consists of testes in scrotal sac. The field may be reduced if a palpable mass decreases in size during treatment.

14.2.3 Target Dose

14.2.3.1 Prescription Point

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 once a day with 200 cGy, administered Monday through Friday.

14.2.3.4 Dose Uniformity

Variations of dose within planning target volume will be within +7%, -5% of dose to prescription point. The Uniformity requirement can be met with electron beam of appropriate energy provided bolus is used, which is simplest technique. Bolus may also be needed for photon beams to fulfill dose uniformity requirement.

14.2.3.5 Treatment Interruptions

No corrections will be made for treatment interruptions less than 7 days. For interruptions greater than 7 days, contact the study coordinator.

14.2.4 Treatment Technique

14.2.4.1 Patient Position

Patient will be treated in supine position.

14.2.4.2 Field-shaping
Field shaping can be done with blocks of at least 5 HVL thick. Multi-leaf collimators are acceptable.

14.2.5 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 the field by fixing it to skin over symphysis pubis.

14.3 Quality Assurance Documentation

14.3.1 IROC RI (formerly 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 1 week of the completion of radiotherapy, the following data will be submitted:

- "RT-2 Radiotherapy Total Dose Record" form.
- Copy of patient's radiotherapy record, including prescription, and daily and cumulative doses.

14.3.2 Data must be sent to:

IROC Rhode Island (formerly QARC)
Building B, Suite 201
640 George Washington Highway, Suite 201
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
IROC Rhode Island (formerly QARC)
Building A, Suite 201
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: 401-753-7600
Fax: 401-753-7601

14.3.4 Questions regarding radiation therapy should be directed to:

Arthur K. Liu, MD PhD
The Children's Hospital
University of Colorado Denver
1665 Aurora Ct, MS F706
Aurora, CO 80045
Phone: (720) 848-0156
Fax: (720) 848-0234
E-mail: Arthur.Liu@ucdenver.edu

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 prescription point differs from that in protocol by more than 10%.

15.0 INCIDENCE AND NATURAL HISTORY OF OSTEONECROSIS (ON) (Closed to Accrual July 2016)

15.1 Specific Hypotheses and Aims

15.1.1 Specific Hypotheses:

- The incidence of radiologic ON without clinical symptoms (silent ON) is higher than clinical (symptomatic) ON.
- Progression of silent and clinical ON (with symptoms) is unpredictable.
- An objective radiologic definition of ON will provide the most definitive endpoint for a future intervention trial.
- Drugs in addition to corticosteroids contribute to the risk for ON.

15.1.2 Specific Aims:

- To determine the incidence of asymptomatic ON.
- To determine how often ON presents with asymptomatic vs. symptomatic disease.
- To determine how often asymptomatic disease progresses to subchondral collapse.
- To determine independent prognostic factors for subchondral collapse.
- To determine how often asymptomatic disease spontaneously resolves.
- To determine if exposure to ASNase and MTX affect the risk for development of ON.

15.2 Background/Rationale for Study

Sequential COG clinical trials for HR ALL have yielded significant improvements in EFS, [1, 3, 41, 43, 166] however, further progress is jeopardized by therapy-related osteonecrosis (ON). ON is one of the most common side effects of contemporary therapy and it causes significant short and long-term impairment in quality of life,[167] as it can lead to joint articular surface collapse with debilitating arthritis and the potential need for surgical interventions, including arthroplasty.[168] Adolescents are particularly prone to ON because with epiphyseal closure, corticosteroid-induced marrow fat cell hypertrophy results in elevated intraosseous pressure followed by reduced intramedullary blood flow, marrow ischemia and ultimately necrosis.

Osteonecrosis occurs in up to one third of adolescents and young adults with ALL; however, incidence reports have varied,[169-176] perhaps given differences in whether reporting is based on clinical symptoms or radiological findings. While ON is most closely associated with corticosteroid exposure, the role of other agents such as PEG-asparaginase (ASNase) and methotrexate (MTX)[177, 178] is also being assessed. To date, the overall 36 month cumulative incidence of ON in the COG AALL0232 HR B-ALL trial is 13.5 ± 1.1% and age is the strongest clinical predictor for this toxicity with an incidence of 3.1 ± 0.9% vs. 19.6 ± 1.6% for 1 to 9 and 10+ year olds, respectively ($p < 0.0001$). Three-year ON incidence rates on CCG-1882 were 0.9 ± 0.4% vs. 14.2 ± 1.3% for 1 to 9 and 10+ year olds, respectively ($p < 0.0001$).[171] Among patients 10 years of age or older on CCG-1961, the 5-year ON incidence rates were 9.9 ± 1.5% and 20.0 ± 4.3% for the 10 to 15 and 16 to 21 year age groups, respectively (unpublished data, CCG-1961). Notably, the incidence rates of ON in AALL0232 are early estimates and may change with longer follow-up. In addition, screening imaging studies have not been routinely performed in COG studies, so cases have been diagnosed largely based on clinical symptoms. At St. Jude Children's Research Hospital (SJCRH), prospective magnetic resonance imaging (MRI) screening of the hips and knees for ON was performed at 3 time points on all patients enrolled on the Total XV ALL trial (n=365), regardless of symptoms. In this

trial, the cumulative incidence for symptomatic ON (Grade 2-4) was 14.6% ± 1.6% one year from the start of therapy. At the completion of treatment, the cumulative incidence for symptomatic ON (Grade 2-4) was 17.6% ± 1.8% and therefore most symptomatic cases were diagnosed within 1 year. In contrast, the incidence of Grade 1 (asymptomatic disease with radiologic findings only) ON rose from 35.4% ± 2.2% to 53.9% ± 3.9% from 1 year into therapy to the end of treatment.[179]

Corticosteroid exposure and formulation have been shown to affect the risk for ON with a significantly higher incidence of bone toxicity among those randomized to 14 days of dexamethasone (DEX) vs. 28 days of prednisone (PRED) during Induction on AALL0232, [173] when the study first opened. In May 2008, the cumulative incidence of ON at 24 months in patients 10+ years of age who were randomized to receive DEX in induction was 17.2% vs. 12.6% for PRED (p =0.006; RHR is 1.79 for DEX vs. PRED). This prompted an amendment to the study that eliminated the induction steroid randomization in patients 10+ years of age and changed DEX administration to a discontinuous schedule (Days 1-7, 15-21) during Delayed Intensification and the steroid formulation to PRED for all patients during Maintenance, regardless of age.

A relationship to drugs in addition to glucocorticoids (e.g., ASNase and MTX) has also been hypothesized given the fact that some treatment regimens have a much higher frequency of ON than others, even with relatively similar steroid exposure. In studies of the influence of clinical variables and other drugs used in ALL therapy on DEX pharmacokinetics, Relling and colleagues observed that DEX clearance was closely linked to serum albumin concentration and patient age. Clearance was higher in individuals with a greater serum albumin concentration ($p < 0.001$) and DEX clearance was negatively related to age.[180] DEX clearance in a patient 19 years of age was 102.5% less than in patients 5 years of age, which is consistent with the greater toxicity associated with glucocorticoids among older children and young adults.[180] Hypoalbuminemia has been shown to result from ASNase exposure and it has been proposed that decreased serum albumin may be a biomarker for impaired hepatic synthesis of proteins involved in DEX clearance. Allergy has been shown to inactivate ASNase, resulting in less ASNase-mediated inhibition of protein synthesis and thus a greater serum albumin in patients who develop ASNase allergies.[180] On SJCRH protocol Total XV, after adjustment for age and treatment arm, severe Grade 3 to Grade 4 ON was linked to lower albumin levels, reflecting ASNase treatment, ($p=0.03$) and poor DEX clearance/higher DEX area under the curve (AUC) ($p=0.0005$).[179] These prior studies highlight the potential importance of the interactions between ASNase and DEX in assessing risk for development of ON and suggest that ASNase might potentiate the osteonecrotic effect of DEX.

There has also been evidence to suggest that MTX exposure may play a role in the risk for ON. Among the polymorphisms that have been previously found to be predictive of ON, several involved folate homeostasis.[181] Differences in the incidence of ON have also been observed when comparing children randomized to receive Capizzi escalating MTX and ASNase (PC arm) compared to HD MTX with leucovorin rescue (PH arm) on the COG AALL0232 study. For patients 10+ years of age enrolled after the amendment which closed the steroid randomization in Induction for patients 10+ years of age, there was a significant difference in cumulative incidence of ON rates by MTX arm (PC 17.2% vs. PH 10.3%; $p=0.01$). Incorporating biomarkers for ASNase and MTX exposure into the AALL1131 study will allow us to evaluate the possible contribution of these 2 agents to glucocorticoid induced ON in a major front line ALL study.

In looking more closely at the incidence of ON by age on AALL0232, among the 10+ year olds, the overall cumulative incidence of ON at 36 months was as follows after the most recent data update: 10 to 12 years 17.2 ± 2.53%, 13 to 15 years 21.9 ± 2.7% and 16+ years 21.2 ± 3.3%, although these data are early as patients are still accruing to this study. While DEX was administered continuously (Days 1-21) during Delayed Intensification in children 10 to 12 years of age when the study first opened, protocol therapy was modified in 2006 to adopt a discontinuous dosing schedule (Days 1-7, 15-21) in an effort to

reduce the risk of ON. After this change to discontinuous steroid dosing, the incidence of ON in patients 10-12 years of age decreased: continuous DEX during DI (28.9 ± 3.8% at 36 months, 46 ON cases) vs. discontinuous DEX (10.3 ± 3.1%, 30 ON cases) ($p< 0.0001$). The 10 to 12 year old age group will continue to be monitored very closely going forward.

Gender appears to be another important risk factor for ON with a higher incidence of ON in females.[171] Most cases of ON develop during the Maintenance phase of therapy (83% of all cases of ON have occurred during Maintenance on AALL0232) and within the first 3 years of therapy. On CCG-1882, 110 of 111 cases of ON were diagnosed within the first three years of treatment. Osteonecrosis causes considerable morbidity with the vast majority of patients having symptomatic disease (Grade 2 or higher) and many requiring surgical intervention. On AALL0232, using CTCAE v3.0 criteria, maximum clinical ON severity among 210 patients with available data showed: 6.7% Grade 1, 63.3% Grade 2, 29% Grade 3, and 1% Grade 4. The most common sites of involvement were the knees, followed by hips and ankles. Importantly, on CCG-1882 and 1961, skeletal morbidity was also considerable: approximately 85% of affected patients had multi-focal ON, 95% had involvement of at least one weight-bearing joint, and 25% required surgical intervention[171] (unpublished data, CCG-1961).

MRI has been proven to be a highly sensitive diagnostic tool for ON, allowing the earliest and most accurate diagnosis [182-187]. In addition, several studies utilizing MRI have demonstrated that large epiphyseal lesions (>25%) and involvement of the articular surface predict joint collapse. [188, 189] In a retrospective study conducted at SJCRH, epiphyseal involvement of >30% in the hip was the strongest predictor of joint outcome, with 80% of individuals with this extent of involvement progressing to articular surface collapse. [190] Similarly, in the original studies by Sugano and colleagues in adult patients with lupus, type C (> 2/3 of epiphyseal surface) MRI lesions portended a high incidence of joint collapse (75%), whereas progression to collapse was not observed for this with type A or B lesions. [191] The extent of epiphyseal involvement has also been shown to be prognostic of subchondral collapse in the knee. [188, 190] In contrast, some less extensive lesions detected by MRI have been shown to regress over time. [192]

Given the significant morbidity ON presents, therapeutic interventions are being pursued that will lessen its incidence and severity, while allowing optimal use of chemotherapy. Further, as the vast majority of patients who have entered AALL0232 study have had DNA collected for determination of host polymorphisms, analyses to define biomarkers that predict ON are underway. Essential to the success of future therapeutic interventions and defining predictive biomarkers is a better understanding of the true incidence and natural history of ON with contemporary treatment regimens. Objective measures such as MRI may be a more suitable endpoint in future studies because clinically-based diagnoses of ON can be biased by known results from imaging studies. Further, the pain associated with ON can be difficult to distinguish from neuropathic pain from vincristine and other musculoskeletal pain from corticosteroids, such that cases of ON can possibly be missed if symptoms are attributed to these other etiologies without imaging assessment. Finally, symptoms often lag behind imaging findings of ON [187] and there may be a subset of asymptomatic patients where early radiologic detection could be beneficial.

While MRI is the best imaging tool for ON, CT has been suggested as being more sensitive for diagnosing subchondral fractures. With current high-resolution technology, MRI has been proven to be a highly sensitive diagnostic tool for ON, allowing the earliest and most accurate diagnosis.[182-187] Moreover, CT is associated with risks of ionizing radiation. While MRI is sensitive, the significance of some abnormalities remains uncertain. For example, the natural history of radiologic abnormalities in the absence of any symptoms is not known. Essential to the success of a future intervention study will be the definition of true incidence rates based on objective measures and an understanding of the natural history of radiologic disease without interventions (i.e. how many individuals with abnormalities detected on MRI will progress and/or develop symptoms and what factors are predictive of adverse joint outcomes, as individuals with these features may be best suited for an intervention). Based on the experience from

SJCRH where MRI screening has been done prospectively[175], we hypothesize that the incidence of radiologically defined ON will be higher than that defined by clinical symptoms. The SJCRH study is very helpful in providing data on the feasibility of performing screening MRIs during ALL therapy at a single institution and the incidence of symptomatic vs. asymptomatic disease. However, SJCRH and COG ALL therapy differ with regard to exposures to dexamethasone, prednisone, methotrexate and asparaginase. Our goal is to develop a randomized trial incorporating an intervention to reduce the incidence of ON in the future and therefore knowledge about the true incidence and natural history of ON is essential to be able to interpret the potential impact of a given intervention and to define the population that may be best to consider for an intervention strategy. In addition, this study will also establish the feasibility of performing screening MRIs and utilizing uniform ON staging criteria in the cooperative group setting. Since the natural history of clinically silent radiologic disease is not known, therapy on the present trial will not be altered in cases of asymptomatic ON. Patients with symptomatic disease will have therapy modified following uniform guidelines (Section 5.10).

As noted above, while ON is most closely associated with corticosteroid exposure, the role of other agents such as ASNase and MTX is also being assessed. To determine the possible contribution of agents in addition to corticosteroids to the development of ON, MTX and ASNase levels, serum albumin (surrogate for ASNase effects) and anti-ASNase antibodies will be measured at 3 or 4 time points (HR B-ALL or VHR B-ALL respectively) during therapy.

15.3 Eligibility Criteria

- Patients must be 10 years of age or greater at the time of B-ALL diagnosis, enrolled on AALL1131.
- Patients with Down syndrome or Ph-like with dasatinib predicted TKI-sensitive kinase mutation are not eligible

15.4 Imaging Evaluation Schedule/Methods

Magnetic resonance images (MRIs) and pain assessment questionnaires will be obtained at the following time points during therapy in eligible subjects at the time of enrollment onto AALL1131:

- End of Consolidation
- Beginning of Maintenance
- End of therapy

These time points were chosen to determine the impact of different phases of therapy where drugs known and suspected to be associated with ON (i.e. corticosteroids, methotrexate and asparaginase) are administered. The first time point, end of Consolidation, will assess the impact of corticosteroid administration during Induction as well as other agents during Consolidation. The second time point (beginning of Maintenance) will assess corticosteroid exposure during Delayed Intensification (DI) as well as other agents during Interim Maintenance and DI. The final time point (end of therapy) will assess corticosteroid exposure during Maintenance pulses.

Clinical symptom severity (pain assessment) will be assessed via a questionnaire (available on the protocol webpage) completed by the patient/guardian. The data will be collected via the Osteonecrosis Pre-MRI Pain Assessment CRF (available under the AALL1131 Case Report Forms) and reported in the eRDES system prior to each imaging study to attempt to avoid reporting bias based on known imaging study results. Therapy will be continued without modification for all patients who are asymptomatic, regardless of radiologic stage. Corticosteroid therapy will be modified in patients with symptomatic disease (Section 5.10).

15.5 MR imaging Technique

The MR examination is the basis for determining the present, extent and progression of ON at end of consolidation, beginning of maintenance and end of therapy. The determination of ON will be based on abnormal anatomy. ON alters the signal pattern of marrow and best seen on non-enhanced, T1 –weighted images

15.5.1 MR Hips and Knees without Contrast

To document the presence, extent and progression of ON, MR imaging of the hips and knees without contrast must be performed. A standard research protocol can be used for these studies and they do not require review by a clinical radiologist. Study reports also do not need to be generated at local centers for these research imaging studies.

Hips

A. Position: supine. Slightly internally rotate hips (may tape toes together if needed and patient can tolerate).
B. Coil: Phase array or body coil, whatever is best fit for patient. Femoral heads should be in or as close to center of field as possible. One coil can be used for the entire examination to expedite study time.
C. Standard sequences
    1. Coronal spin echo T1. Time to repetition (TR) 450 – 800, Time to echo (TE) 12-15, flip angle 90^0, FOV 320 – 500 (must include fat lateral to greater trochanters), 3-4 mm slices with 1 mm intersection gap, 256 x 256 or 320 x 320 mm matrix, 2 acquisitions (ACQ), phase left to right. The final choice of final parameters should be machine (vendor) determined, but should match protocol as much as possible. Coverage: Sacrum to symphysis pubis.
    2. Sagittal spin echo T1: TR 450 – 800, TE 12-15, flip angle 90^0, FOV 240-280, 3-4 mm slices with 1 mm gap, 256 x 256 or 320 x 320 mm matrix, 2-3 ACQ, phase anterior to posterior. The final choice of final parameters should be machine (vendor) determined, but should match protocol as much as possible. Coverage: femoral head + femoral neck

Knee

A. Position: supine. Slightly internally rotate knees (may tape toes together if needed and patient can tolerate).
B. Phase array or body coil, whatever is best fit for patient. Need enough coverage to see distal 6-7 cm above and below joint line. One coil can be used for the entire examination to expedite study time.
C. Standard sequences:
    1. Coronal spin-echo T1. TR 450 – 800, TE 12-15, FOV 150-500, 3-4 mm slices with 1 mm gap, 256 x 192 matrix, 2 ACQ, phase left to right. The final choice of final parameters should be machine (vendor) determined, but should match protocol as much as possible. Coverage: minimum 4 slices behind tibia and 2 slices through back of patella.
    2. Sagittal spin-echo T1. TR 450 – 800, TE 12-15, flip angle 90^0, FOV 150-280, 3-4 mm slices. The final choice of final parameters should be machine (vendor) determined, but should match protocol as much as possible.

15.6 MR Evaluation of ON

Three magnetic resonance images (MRIs) will be completed in each of 300 evaluable patients. These studies will be focused MRIs of the hips and knees in the coronal plane and sagittal planes.

15.6.1 Subjective Diagnosis of ON

The presence or absence of ON will be determined in the proximal and distal femurs with T1-weighted imaging. ON will be confirmed as a geographic area of decreased signal on T1-weighted images. Typically the abnormal signal on T1-weighted images is surrounded by a low-signal line which has well-defined and distinct borders, allowing identification of the lesion.

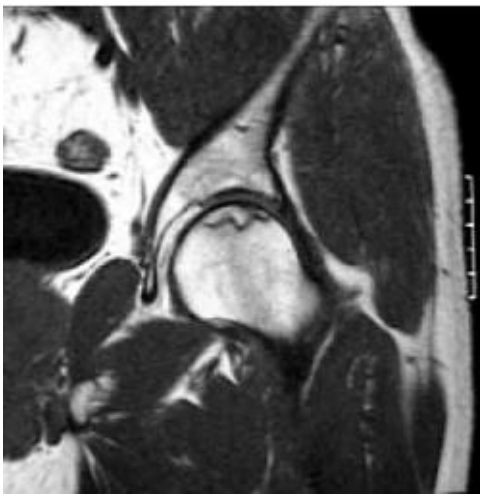


Fig 1. Coronal T1-weighted unenhanced image of the femur shows osteonecrosis as geographic areas of decreased peripheral signal.

The epiphysis, metaphysis and diaphysis will be evaluated. Presence or absence of disease in the epiphysis, metaphysis and diaphysis of each lower extremity will be noted and captured on forms. Disease will be coded as present or absent. However, only epiphyseal disease will be measured.

15.6.2 ON Objective Measurements

The index of necrotic extent, as modified by Cheng will be used to quantify the extent of ON. The modified index of necrosis is determined by measuring the angle created by the extent of subchondral involvement. The reader first determines which images demonstrate the maximal lesion size in the sagittal and coronal slices and then assesses the abnormal T1 signal within the femoral head on these slices. The lesion size will be estimated by measuring the angle of the arc of the necrotic segment in the femoral head, which can be defined as the necrotic arc angle. The necrotic arc angle on the coronal and sagittal images are designated A and B, respectively (Fig. 2).[193] The index of necrotic extent is calculated as (A/180) × (B/ 180) × 100.

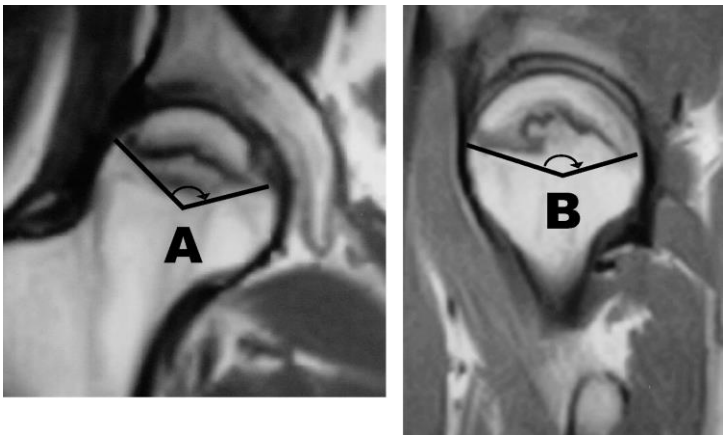


Fig 2 Objective Measurements of Osteonecrosis from Cherian et al[193]
A- Coronal View B Sagittal View

This system had been used in a study of 25 patients who had Stage-I or II osteonecrosis of the femoral head. Images were independently examined on 2 separate occasions by 3 observers of different specialty backgrounds and experience. The correlation coefficients demonstrated nearly perfect agreement when they measured the modified index of necrotic extent. Survivorship analysis revealed that the percent involvement ($p < 0.05$), index of necrotic extent ($p < 0.007$), and modified index of necrotic extent ($p < 0.04$) were prognostically significant predictors of subchondral fracture. This system is statistically reliable and valid and is clinically feasible and easy to perform, which will minimize interobserver variability.

The method of Koo evaluated ON in the midsagittal and midcoronal planes, but the Koo method may not be adequate because of inconsistencies among observers with regard to estimating which are the midsagittal and midcoronal images. Moreover, this method tends to underestimate the true extent of ON of the femoral head because the lesions are usually not centered in the superior, central part of the head. Instead they are concentrated in the anterior-superior segment of the head. The modified index takes this into account. There are methods for calculating the true volume or surface area of necrosis with use of image analysis software, but although they may accurately measure necrotic volume they are too complicated for everyday clinical application. The modified necrotic index is statistically reliable and valid and is clinically feasible and easy to perform, which will minimize interobserver variability.

The index of necrotic extent will be classified into 3 categories:

- Stage A: small necrosis, ≤33;
- Stage B: medium necrosis, 34 to 66; and
- Stage C: large necrosis, 67 to 100.
- Presence or absence of subchondral fracture will also be noted.

Lesion size of the distal femur/proximal tibia will be determined by drawing a line parallel to the articular cartilage of the proximal femur and parallel to the physis of the distal femur and then a perpendicular through the center of the distal femur and proximal tibia as shown below (Fig 3).[191, 194]

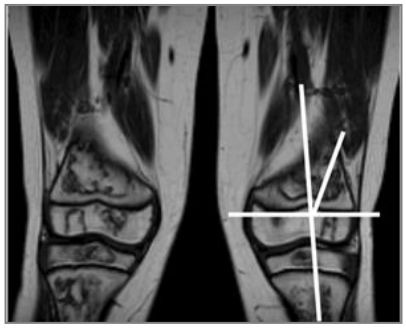


Figure 3. Adapted from Sugano et al[191] & Karimova et al[194]

Four stages of lesions will be determined for each epiphyseal surface of the joint (2 surfaces per knee (distal femur, proximal tibia):

- Stage 0: no MRI abnormalities of the joint in question
- Stage 1: 1%-25% epiphyseal involvement
- Stage 2: >25%-50% epiphyseal involvement
- Stage 3: >50%-75% epiphyseal involvement
- Stage 4A: total epiphyseal involvement without collapse
- Stage 4B: total epiphyseal involvement with articular surface collapse
- Stage N: joint was not assessed at the specified time point

This staging system does not involve precise 3D volume measurement of the lesions or image-processing software; therefore, it can be applied easily during clinical image review.

15.7 Central Review Image Analysis

A central review will be performed after each of the 3 time points to determine presence or absence of ON, sites of involvement and extent of disease. Central review will be batched and read on a regular basis, but will not be returned to sites. **It is required that scans are submitted within 30 days of being done.**

The following scans should be submitted for central review for all patients: hip and knee MR, including T1-weighted coronal and sagittal scans. MRI studies must be submitted for rapid Central Review in Dicom format on a CD or electronically. Film copies will not be accepted.

For each MR examination, the index of necrotic extent will be measured and classified into 3 categories for the femoral head: Stage A, Stage B and Stage C. Presence or absence of subchondral fracture will also be noted. The knee will be classified into Stage 0, 1, 2, 3, 4A, or 4B. These data will allow for an analysis of incidence of ON and how often ON presents with asymptomatic or symptomatic disease.

For each MR examination, we will define disease progression as: 1) progression in stage, from A to B or B to C, etc. or 2) change from no fracture to development of subchondral fracture. These data will allow analysis of how often asymptomatic disease progresses and/or resolves.

Additional imaging is strongly encouraged whenever a patient becomes symptomatic regardless of the phase of therapy. These studies may be sent for central review and the data will be incorporated into the study database. The images will be subjectively reviewed for the diagnosis of ON, but the extent of ON will not be quantified.

15.8 Address Information

Copies of films of the required studies for central review should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: 401-753-7600
Fax: 401-753-7601

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in Dicom format. These files can be burned to a CD and mailed to IROC Rhode Island (formerly QARC). Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Electronic submission of the scans is acceptable via Dicommunicator. Contact IROC Rhode Island at www.IROCRI.QARC.org for further information.

15.9 Measurements of dexamethasone (DEX), methotrexate (MTX) and asparaginase (ASNase) levels

These studies are optional for those HR and VHR patients 10+ years of age participating in the MRI screening study.

Collection of blood (10 mL) for drug levels will occur at the following 4 time points, which coincide with scheduled visits for chemotherapy administration (**Blood draws should occur only at these time points relative to scheduled drug administration so they accurately reflect relevant drug exposures**):

- Day 1 of Consolidation: ASNase level, anti-ASNase antibodies and serum albumin

- Day 22 of Consolidation: ASNase level, anti-ASNase antibodies and serum albumin
- Day 8 of Delayed Intensification: Dexamethasone level, ASNase level, anti-ASNase antibodies and serum albumin
- Day 22 of Interim Maintenance II: Plasma MTX level, ASNase level, anti-ASNase antibodies and serum albumin prior to the administration of Day 22 PEG-ASP in VHR B-ALL patients only

See Appendix V for details regarding sample collection and shipment. Note that Appendix V requires dosing information (date, time, and dose normalized per BSA) for the following agents:

Day 1 of Consolidation: Date, time, dose and formulation of "Day 4" of Induction asparaginase.

The Day 1 PEG-ASP ASNase level will be entered into an asparaginase pharmacokinetic model[195] so that the ASNase level can be normalized to a standardized time post-dose in all patients. This will account for differences in dose and in differences in time-post-dose among patients. In order to perform this modeling, the date, time, formulation, and dose administered (IU/m^2) must be collected.

Day 22 of Consolidation: Date, time, dose and formulation for "Day 15" of Consolidation asparaginase.

The Day 22 PEG-ASP ASNase level will be entered into an asparaginase pharmacokinetic model[195] so that the ASNase level can be normalized to a standardized time post-dose in all patients. This will account for differences in dose and in differences in time-post-dose among patients. In order to perform this modeling, the date, time, formulation, and dose administered (IU/m^2) must be collected.

Day 8 of Delayed Intensification: Date, time, dose and formulation for "Day 4" of Delayed Intensification asparaginase and the date, time, and dose of the most recent prior dexamethasone dose (generally Day 7 of DI phase).

The Day 8 PEG-ASP ASNase level will be entered into an asparaginase pharmacokinetic model[195] so that the ASNase level can be normalized to a standardized time post-dose in all patients. This will account for differences in dose and in differences in time-post-dose among patients. In order to perform this modeling, the date, time, formulation, and dose administered (IU/m^2) must be collected. Likewise, the Day 8 dexamethasone plasma level will be entered into a dexamethasone pharmacokinetic model[178] so that the dexamethasone level can be normalized to a standardized time post-dose in all patients. This will account for differences in dexamethasone dose and in differences in time-post-dose among patients. In order to perform this modeling, the date, time, and dose administered (mg/m^2) must be collected.

Day 22 of Interim Maintenance II (VHR patients only): Date, time, dose and formulation for "Day 2" of IM II asparaginase and the date, time, and dose of the most recent prior methotrexate dose (generally Day 21 of IM II phase).

The Day 22 PEG-ASP ASNase level will be entered into an asparaginase pharmacokinetic model[195] so that the ASNase level can be normalized to a standardized time post-dose in all patients. This will account for differences in dose and in differences in time-post-dose among patients. In order to perform this modeling, the date, time, formulation, and dose administered (IU/m^2) must be collected. Likewise, the Day 21 methotrexate plasma level will be entered into a methotrexate pharmacokinetic model[196] so that the methotrexate level can be normalized to a standardized time post-dose in all patients. This will account for differences in methotrexate dose and in differences in time-post-dose among patients. In order to perform this modeling, the date, time, and dose administered (mg/m^2) must be collected.

15.10 Statistical Design

15.10.1 Definitions

- Imaging progression: 1) progression in stage, from A to B or B to C or 2) change from no fracture to development of subchondral fracture.
- Clinical progression: Development of pain or a decline in function in an affected joint (CTC Grade 2 or higher), which is not attributed to another cause (e.g. neuropathy from vincristine). This will be assessed by questionnaires administered prior to each MR scan and end of course reports. Clinical progression will also be defined as appearance of ON in another joint.

15.10.2 Statistical Considerations

A total of 300 evaluable patients will be accrued over a period of 2 years from all institutions that elect to participate in this study. Based on age distribution on past ALL trials, it is projected that 105 patients will be 10 to 12 years of age, 110 will be 13 to 15 years old, and 85 will be 16+ years old at diagnosis. Assuming that about 15% of patients will not complete studies at all required time points for various reasons, a total of 345 patients will be accrued in order to ensure that we have the required 300 evaluable patients with complete data at all time points.

A primary objective is to determine the overall incidence and pattern of joint involvement of ON according to stage and age as defined above. We will estimate the proportion of patients in each age group that develop ON by MRI, and also determine the distribution of stage (0, 1, 2, 3, and 4) within each age group. Given the estimated sample sizes in each age group, the incidence of ON can be estimated in each age group with a maximum standard error of 5.5% in the smallest group (16 years old and older).

The serial MRIs, done at 3 time points during and at the end of therapy, will be used to determine the phase in therapy/time point when ON is first detected by MRI. Changes in MRI over time will be assessed to determine the percentage of patients that have radiologic progression from baseline. Another objective is to determine the percentage of patients with clinically silent ON who develop symptomatic disease (CTC v. 4.0, Grade 2 or higher ON) according to stage on initial screening. MRI findings will be correlated with clinical symptom severity as graded by CTC v. 4.0 codes. Logistic regression analysis will be used to correlate clinical and radiologic progression with baseline clinical and radiologic features including radiologic stage at on initial screening, age, gender, race, treatment regimen. Data on number and type of surgical procedures done will be collected and summarized for the patients who develop ON.

Multiple logistic regression will be used to determine the association of ASNase and MTX plasma levels, anti-ASNase antibodies, and serum albumin with the risk of ON (CTCAE Grades 2-4) as described previously.[179]

Using pharmacokinetic modeling,[195, 196] the drug levels will be normalized for differences in time post dose, adjusting for differences in normalized doses, as described above in Section 15.9. The multiple regression analysis will include information on most recent dose formulation (for asparaginase), most recent dose per BSA (for asparaginase, methotrexate, and dexamethasone), and on cumulative number of doses of asparaginase, methotrexate, and dexamethasone.

16.0 LONGITUDINAL, COMPUTERIZED ASSESSMENT OF NEUROCOGNITIVE FUNCTIONING IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH HIGH-RISK ACUTE LYMPHOBLASTIC LEUKEMIA (HR B-ALL)

16.1 Specific Objectives and Aims

AIM 1: To determine if the prevalence of cognitive deficits measured by CogState, in children (ages 6 to < 13 years at diagnosis of ALL) with HR- and VHR B-ALL at 1 year off therapy, is significantly higher than the normative population (> 14%) in the following domains: working memory, executive function, visual motor, processing speed, and visual attention.

HYPOTHESIS 1: The prevalence of a significant cognitive deficit (defined as > 1 standard deviation below the normative mean), in children with HR- and VHR B-ALL at 1 year off therapy will be at least 20%. Each of the 5 domains will be analyzed separately.

AIM 2: To determine if there are significant declines in neurocognitive functioning as measured by CogState, in children (ages 6 to < 13 years at diagnosis of B-ALL) with HR- and VHR B-ALL over time, with clinically meaningful decrease in mean scores apparent at 1 year off therapy in the following domains: working memory, executive function, visual motor, processing speed, and visual attention.

HYPOTHESIS 2: There will be significant declines in neurocognitive functioning in children with HR- and VHR B-ALL over time, with clinically meaningful decreases (defined as a drop of 0.5 SD) in mean scores being apparent at 1 year off therapy. Each of the 5 domains will be analyzed separately.

EXPLORATORY AIM 3: To determine demographic (e.g., SES, gender), disease (e.g., risk status), treatment (e.g. chemotherapy and anesthetic exposures), and behavioral predictors of neurocognitive deficits and neurocognitive decline as measured by CogState in children (ages 6 to < 13 years at diagnosis of B-ALL) with HR- and VHR B-ALL in the following domains: working memory, executive function, visual motor, processing speed, and visual attention.

HYPOTHESIS 3: As this aim is exploratory, we have not developed specific hypotheses for all variables expected to enter the models. However, based on extant literature, it is predicted that females[197] and children of low SES will experience a significantly greater incidence of neurocognitive deficit and decline, as will children who are younger at diagnosis, in the following domains: working memory, executive function, visual motor, processing speed, and visual attention. Further, children with elevated behavioral ratings of executive function difficulties will also exhibit significantly greater deficit and decline compared with children who have executive function rated in the average range. Lastly, children with specific treatment exposures, including higher cumulative exposure to anesthesia, will have greater deficits in neurocognitive functioning.

16.2 Background/Rationale

Survivors of childhood ALL are at risk for neurocognitive deficits of varying severity. Unfortunately, relatively little is known about the number of children who have detectable abnormalities while on therapy, at what point these deficits become manifest, the factors associated with increased risk of neurocognitive deficits, or how these deficits evolve during and after completion of therapy. The limited numbers of studies that have prospectively evaluated neurocognitive function in this population are hampered by small sample size, few assessments during treatment, and significant attrition.[198] In addition these studies often have limited ability to control for host and treatment variables such as age, sex, socioeconomic status and the use of cranial radiation.[199] All of these factors have been affected by the historical reliance on traditional, lengthy, and expensive neurocognitive batteries which require highly trained professionals to administer, score, and interpret.

Although the incidence of observed neurocognitive late effects has decreased with protocols that minimize the use of cranial irradiation, it still ranges from 20%–40% among survivors of ALL.[200] However, descriptions of the breadth and severity of neurocognitive sequelae among survivors treated without radiation are relatively inconsistent, in part due to methodological variations and small subject numbers in published studies (e.g., more than half of studies included in a recent meta-analysis used samples of 30 or fewer participants).[198] In addition, cross-sectional and retrospective samples are frequently reported in the literature, limiting our ability to accurately describe change over time in samples free of participation bias. Finally, findings also vary with changes in modern treatment protocols. These factors prompted authors of one recent study to characterize *"the spectrum of neurocognitive changes…[as] a moving target (p.585)".*[201] It is clear that despite over 3 decades of work by investigators in this area, critical information is still lacking. Prospective, longitudinal studies with large, diverse samples of participants are needed to elucidate the incidence and severity of neurocognitive deficits and decline in this population.

16.2.1 Type and Severity of Neurocognitive Difficulties

In studies using traditional neuropsychological measures as outcomes, the extant literature suggests increased risk for deficits in processing speed, visual motor function, attention, working memory and executive function, with increased incidence and severity of deficits occurring for children treated with cranial radiation therapy.[197, 198, 202-205] Two recent meta-analytic reviews of the literature supported the presence of deficits in these areas even with contemporary, chemotherapy-only protocols. Specifically, Campbell and colleagues[198] reported standardized effect sizes (Hedges *g*) for 13 studies ranging from -0.34 to -0.71, indicating that, as a group, survivors of ALL performed roughly one-third to three-quarters of a standard deviation below normative samples or comparison groups on a variety of neurocognitive tasks. However, the authors state that most of the studies used small, cross-sectional samples of convenience.

Several recent studies also have confirmed the presence of difficulties in the areas of executive function, attention, memory, and processing speed, supporting the findings with correlative studies in structural and functional neuroimaging.[201, 203, 206, 207] These domains are considered "higher order" functions, largely of the prefrontal cortex, typically recruited for complex information processing. Because the areas of the brain responsible for higher-order processes continue to develop throughout childhood and adolescence, they are thought to be particularly vulnerable to therapeutic agents used to treat ALL.[201]

Of importance, whereas many survivors experience measurable declines in these areas over time, global intellectual functioning is typically still within normal limits for most children treated with chemotherapy evaluated within the first 10 years of survivorship.[205] However, this finding may mask the significance of specific deficits in attention, processing speed, and working memory, which collectively can make it harder for children to process, store, and integrate new information. Indeed, it is believed that difficulties in these areas may contribute to subtle declines in intellectual and academic performance over time.[159, 197, 208]

16.2.2 Onset and Course of Neurocognitive Difficulties

The onset and development of neurocognitive sequelae is less reliably described by previous investigations than the nature of the deficits. Whereas intellectual functioning typically remains within normal limits, specific deficits have been observed as early as the first year of therapy,[209-212] Preliminary evidence from one recent study of 123 ALL survivors indicated that nearly 40% show impairments on a measure of sustained attention by the end of treatment. [213] In another recent trial, nearly 70% of patients treated with chemotherapy only showed deficits in working memory.[202] There have been a number of reports from the Childhood Cancer Survivor Study characterizing the functioning of adult survivors of childhood ALL treated with and without cranial radiation therapy (CRT), and most of these indicate that ALL survivors treated with chemotherapy only protocols attain developmental milestones of adulthood at

rates typical of their healthy peers.[214-216] It is difficult to generalize these results to younger survivors, however, as the CCSS papers describing long-term outcomes in childhood ALL survivors all characterize a cohort of patients who were not treated using modern treatment protocols. Survivors who were treated from the late 1970s through the mid-1980s with chemotherapy only protocols were likely to have been lower risk patients, since they survived following less aggressive therapy then patients currently receive. Studies of patients receiving modern chemotherapy only regimens demonstrate a similar pattern of neurocognitive deficits as those seen in patients treated with CRT, though less severe. Because we have yet to acquire long term follow-up data on childhood ALL survivors treated with modern chemotherapy only protocols, we do not yet have good information about their long-term functioning. However, from the CCSS cohort, we know that cognitive deficits of the kind seen in children treated for ALL with chemotherapy only protocols are associated with long term psychosocial problems, even when controlling for radiation exposure.[217] Indeed, after controlling for radiation treatment, survivors in the CCSS total cohort experiencing problems with task efficiency, memory, and emotional regulation had a reduced likelihood of being employed as a professional (but not of being employed in a blue-collar position). This suggests that even when survivors (albeit not specific to ALL) are meeting basic developmental milestones of adulthood, they may experience functional impairments related to their neurocognitive sequelae, such as underemployment. As such, it is important to better understand the nature and course of specific areas of neurocognitive deficits and/or decline associated with HR B-ALL treatment.

Lastly, in addition to understanding the type, severity and course of neurocognitive impairments further data is needed to understand predictors of neurocognitive impairments in children receiving contemporary ALL therapy. The design of this study will allow for the analysis of impact of neurocognitive outcomes of demographic and treatment factors including age at diagnosis, biological sex, insurance status, chemotherapy exposures, as well as cumulative anesthesia exposures. Anesthesia exposure has been demonstrated to be associated with impairment of attention and processing speed in survivors of ALL in a single center study.[218]

Exposure to anesthesia may represent an important modifiable risk factor. Animal data has demonstrated that exposure to anesthetic agents, at developmentally sensitive times, is associated with neurotoxicity.[219,220,221]In children without cancer, evidence linking anesthesia exposure at young ages and subsequent neurocognitive impairments has been mixed. The data however were sufficient for the FDA to issue a warning in 2016 that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of childrens' brains."[222] Anesthesia exposure may be even more detrimental in children who have also received neurotoxic chemotherapies for ALL.

Children with ALL undergo multiple painful procedures (central venous catheter placement, bone marrow aspirates, lumbar punctures) commonly supported with anesthetics to minimize discomfort and distress. The type of anesthesia varies by procedure, patient, and institution. However, a recent survey of anesthetic practices for children undergoing lumbar punctures at Children's Oncology Group (COG) institutions described near universal use of anesthesia, with propofol being the most common agent but with wide variation in doses and medications used.[223] Children treated on AALL1131 protocols undergo 24-31 lumbar punctures for the administration of intrathecal therapy, requiring sequential anesthetics. Further data in a large cohort of uniformly treated children across multiple institutions is required.

16.2.3 Research Strategy

One strategy to maximize cognitive functioning may be early identification of processing deficits so that early interventions can be implemented to preclude functional deficits. However, the design of a trial aimed at early intervention requires an accurate description of when cognitive deficits begin to emerge, along with a comprehensive description of the magnitude, variability, and evolution of problems.[199] Preliminary data from research on traumatic brain injuries[224] and 22q11 deletion syndrome[225] suggests

that there may be a therapeutic window of opportunity following primary brain injury. Specifically, early identification and intervention within a critical timeframe may attenuate problems. If the onset of neurocognitive deterioration could be identified, it may be possible to intervene and prevent functional manifestations. In addition, identification of potentially modifiable risk factors for cognitive impairments, such as anesthesia exposure, would inform practice change.

This study evaluates neurocognitive functioning in children receiving treatment for HR B-ALL using a brief battery consisting of computerized tasks (patient-completed) and behavioral ratings (parent- and/or patient-completed). Before describing the approach more fully, it is first important to distinguish the aims of this study from that of other COG investigations seeking to characterize neurocognitive functioning in this patient population. Specifically, the COG AALL06N1 trial, which is currently accruing patients, was designed to elucidate and compare neurocognitive functioning following the completion of therapy among non-irradiated patients randomized to receive high dose methotrexate with leucovorin rescue or lower dose escalating IV methotrexate without leucovorin rescue. The results of that trial will be critical to understanding methotrexate-related neurotoxicity. However, the neurocognitive components of this correlative study and AALL06N1 are complimentary not duplicative

For this study, we have chosen to maximize our ability to study a large, diverse number of individuals with minimal institutional and participant burden. Towards this aim, we use a brief computerized assessment system (CogState; see below) that targets the neurocognitive processes known to be most affected in ALL survivors (i.e., attention, processing speed, and memory), and a widely-used rating scale (the BRIEF,[226] see below) to evaluate real-world behaviors related to these processes. We plan to examine neurocognitive functioning in children aged 6-11 years at time of B-ALL diagnosis, as most studies documenting neurocognitive impairments in survivors have described samples of children diagnosed in this age range or younger.

The technology for computer-based assessment of a range of neurocognitive functions has only recently become widely available, and offers several advantages over traditional evaluation methods. These benefits are of particular relevance to multi-site, longitudinal trials. First, computer-based assessments may be administered by bachelor's-level clinical or research staff that have completed brief training, often available online. Batteries are typically briefer and less expensive than traditional measures, yet have solid psychometric properties. In particular, most computerized measures of attention and memory functioning (including CogState) are able to eliminate or minimize practice effects. Thus, more assessments are possible at shorter time intervals than are recommended for traditional measures.

For the assessment of the impact of anesthesia on neurocognitive outcomes we will retrospectively collect anesthesia exposure data on the group of patients enrolled on AALL1131 and who co-enrolled on the embedded neurocognitive function ancillary study.

Summary

In summary, despite a large body of literature addressing the neurocognitive functioning of survivors of ALL, data is lacking or inconsistent in 3 primary areas:

1) The proportion of survivors who experience neurocognitive **deficit** relative to the population of typically-developing peers (i.e., how many are impaired?)
2) The timing and trajectory of neurocognitive **decline** relative to survivors' baseline functioning (i.e., how many have experienced a change in cognition?)
3) The disease, treatment, and sociodemographic **predictors** of neurocognitive deficit and decline

To both address these gaps in our knowledge and to maximize participation and compliance, we have selected a brief, focused battery which taps only those domains of neurocognitive functioning identified

by previous investigators as being most consistently problematic for ALL survivors. Our innovative application of this emergent technological advance allows the first, large-scale cooperative study to prospectively evaluating neurocognitive functioning in children, adolescents, and young adults with HR B-ALL treated with contemporary therapies. The computerized assessment tool, CogState, is a robust, inexpensive, and easily applied measure which allows longitudinal assessment of specific neurocognitive processes in children, adolescents, and young adults with HR B-ALL. Data provided by this study have the potential to provide essential data that will permit implementation of effective prevention/amelioration strategies that can be administered before the onset of functional cognitive impairments.

16.2.4 Rationale for the modification to Eligibility Age Criteria

The closure of the VHR arm of AALL1131 will impact our ability to reach our original accrual goal of 515 participants. As of 2/28/2017, study enrollment has reached 433 participants, of which 25% were assigned to the VHR arm. With the loss of 25% of the patients who were enrolling, we will likely fall short of our target accrual for the neurocognitive aim prior to study closure. Therefore, we have increased the eligibility criteria to the upper age limit for participants to 13 years of age. There is no evidence to indicate that 12 year olds are at significantly different risk of neurocognitive toxicity than the currently eligible 11 year old patients. Thus, increasing the age eligibility to 13 may allow us to meet our accrual goals without affecting study integrity and without impacting statistical power for our primary aims.

16.3 **Study Design**

16.3.1 Eligibility Criteria:

1) Enrolled on the High Risk B-ALL trial (AALL1131)
2) Aged 6 to < 13 years at time of B-ALL diagnosis
3) English-, French- or Spanish-speaking (languages in which the assessment is available)
4) No known history of neurodevelopmental disorder prior to diagnosis of B-ALL (e.g., Down syndrome, Fragile X, William's Syndrome, mental retardation)
5) No significant visual impairment that would prevent computer use and recognition of the visual test stimuli

16.3.2 Consent:

This correlative study is embedded within the larger therapeutic study. Consent for this study is incorporated into the consent for enrollment of HR B-ALL patients into their respective arms of the parent study. Patients who enroll in AALL1131 and meet the eligibility requirements listed above may elect to enroll on this ancillary study as an **option**, not a requirement.

Enrollment onto the neuropsychological function study ALTE07C1 is strongly encouraged, if available.If the family agrees to participate in ALTE07C1, a separate informed consent for ALTE07C1 must be signed. AALL1131 patients who are not on the ancillary neurocognitive study are not eligible to enroll on ALTE07C1. ALTE07C1 is a neurocognitive study that has been a companion to a number of COG brain tumor studies. Participation in ALTE07C1 involves brief (60-90 minutes) neurocognitive testing, conducted by a psychologist. The ALTE07C1 battery provides information about cognitive and psychosocial functioning that complements the information from the CogState and BRIEF portion of the neurocognitive ancillary study on AALL1131. This evaluation also may be helpful in determining if there is a need for further assessment, intervention or help with school.

16.3.3 Required Observations:

The required observations for participants in the neurocognitive study is included in the AALL1131 therapy delivery maps. Serial assessments (5 for girls, 6 for boys) is to be conducted according to the schedule described below. To reduce participant burden, all study assessments coincide with regularly

scheduled clinic visits when possible. For each assessment, participants will complete a 25-30 minute computerized cognitive evaluation, administered by a clinical research assistant, nurse, psychologist, or any other professional available in the pediatric oncology clinic who completes our online training in administration of CogState. The CogState program was selected in part because of its ease of use and its availability to be administered by individuals with no specialized training in traditional neurocognitive evaluations. Data are automatically stored by the computer program and can be uploaded to COG for centralized data management. While patients are completing the computerized assessment, their parent/guardian will be asked to complete a questionnaire measure of executive functioning (the BRIEF, see below). Completion of the BRIEF takes approximately 10-15 minutes.

The following table depicts the evaluation schedule for the 6 assessments, presented separately for girls and boys. Note that, in order to obtain data at the 1-year off-therapy point for *all* participants, girls will receive 5 evaluations and boys will receive 6 evaluations.

Observation Number	**Treatment Phase: Boys**	**Treatment Phase: Girls**	**Months from Start of Maintenance**	**Months Post-Diagnosis**
1	During Consolidation	During Consolidation	--	≈ 3
2	End of Maintenance Course 2	End of Maintenance Course 2	6	≈ 13
3	End of Maintenance Course 4	End of Maintenance Course 4	12	≈ 19
4	End of Maintenance Course 6	End of Maintenance Course 6	18	≈ 25
5	End of Maintenance Course 10	One Year Off-Therapy	30	≈ 37
6	One Year Off- Therapy	--	42	≈ 49

Although there is no true "baseline" available for neurocognitive evaluation of HR B-ALL patients, it is generally considered optimal to obtain an initial assessment as soon after diagnosis as is feasible for participants. We believe that the end of Consolidation is the earliest reasonable time to obtain the initial evaluation, for several reasons. First, risk status for HR B-ALL patients will be not be determined until the end of Induction, so approximately 25% of the sample population will not be consented and randomized until at least that time. Moreover, participants are likely to feel unwell (e.g., experience nausea and fatigue) more consistently during Induction and Consolidation phases of treatment. Jansen and colleagues[227] reported that nearly 26% of their sample was unable to complete neurocognitive testing within 2 weeks of diagnosis due to feeling unwell; thus, we timed the initial assessment with the hope of maximizing the number of participants who will be able to complete the evaluation. Consolidation treatment does not include the use of steroids, so by timing the initial evaluation at the end of Consolidation, the last dose of steroids should have occurred 8 weeks prior for most children. Finally, by waiting to begin assessments until approximately 3 months after diagnosis, our intent is to not burden families who may be overwhelmed at diagnosis. By waiting until the end of Consolidation, families may have some time to adjust before they make decisions about participation in ancillary studies. To reduce the effect of confounding relative to pulses of steroids, vincristine and intrathecal therapies, assessments during Maintenance will ideally be conducted at least 4 weeks after the delivery of intrathecal therapy. As noted above, every effort will be made to schedule neurocognitive evaluations during a regular clinic day for the child. If the evaluation day also includes planned administration of intrathecal chemotherapy (though with the timing of assessments occurring at the end of Maintenance courses, that should be rare), the neurocognitive assessment will be completed prior to the procedure. It should also be noted that, for all time points, there will be a 1-month grace period around the scheduled time point during which the data for that time point may still be collected. Participants who relapse during the study will be excluded

from further assessment, though any data they provided up to that point will be included in the exploratory analyses. For each subject, data on demographics and treatment will be collected as part of the parent trial. Collection of data on cumulative anesthesia exposure will include the number of anesthetic events, the total cumulative exposure to each anesthetic agent, adjusted for weight, and the total cumulative duration of anesthesia.

16.4 **Study Measures**

16.4.1 Cogstate Computerized Assessment

CogState[228] is a computerized testing software package that offers a range of semi-automated assessment modules for individuals aged 6-90 years. The software can be installed on most computer systems and can be proctored by a research assistant after completing minimal training. Touch-screen technology is employed to facilitate use by children and to allow for motor function and processing speed to be more reliably assessed. Data are automatically scored and stored. There are 14 tasks in the battery, from which individual tasks may be selected to form a study-specific battery. All tasks were developed as computerized adaptations of traditional neuropsychological measures. For this study, we use 5 tasks, described in the table below, in the following domains: (1) visual motor; (2) processing speed; (3) visual attention; (4) executive function, and (5) working memory. These tasks were selected because they measure the neurocognitive functions identified in previous research as being most susceptible to decline in the pediatric ALL population. The entire battery is estimated to take approximately 13 to 20 minutes.

Unlike many traditional neurocognitive measures, CogState utilizes culture-neutral test stimuli to minimize bias when evaluating individuals from different racial, ethnic, geographic, or sociocultural backgrounds. This measure is thus consistent with recent recommendations for the use of culturally fair tasks by authors of a meta-analytic review of neurocognitive sequelae in children with ALL treated with chemotherapy only.[205] Another advantage of this technology, particularly for the measurement of attention, motor, and memory functioning, is the availability of an increased number of trials compared with traditional measures. When tasks have a small number of trials, they become susceptible to skewed distributions as well as floor and ceiling effects.[229] These scores usually do not span a large range and the data are thus ordinal in nature, rather than interval; as Betts and colleagues[230] noted, *"...the difference between an individual with two errors compared to four errors suggests that, while the individual with fewer errors is better, he/she is not necessarily twice as good (p. 208)"*. With CogState, however, a data from a large number of short trials is obtained, resulting in data on a true interval scale.[230] Computerized batteries thus have the potential to be more sensitive to subtle changes in performance across time, making this an ideal tool for use in the current study.

For CogState, reliability (intra-class correlation) is 0.77 with very good stability (i.e., low within-subjects standard deviations) and negligible practice effects when testing intervals are greater than 1 week.[231] For healthy individuals (n = 867), stability of performance is robust, particularly compared with that of traditional, paper and pencil neuropsychological measures. Specifically, test-retest scores in a large sample of healthy individuals differed by approximately 2% on average, compared with between 7%-19% for traditional measures.[232] The absence of practice effects is of particular benefit to the current study, as it will allow us to evaluate participants across shorter intervals than are typically suggested when using traditional neurocognitive measures. Indeed, Jansen and colleagues[227] recently cautioned that practice effects obtained with repeated administration of traditional measures may make interpretation of change over time more difficult in studies that rely on such measures as primary outcomes.

It is important to note that CogState is well validated only in samples of children aged 6 years and older. In this way, it is comparable to many other measures of neurocognitive functioning in the selected domains, which lack either tasks suitable for younger children or solid psychometric data. Given that young age at diagnosis is a significant risk factor for neurocognitive decline following treatment for ALL, we acknowledge that the current project will not be able to characterize neurocognitive change and impairment in the youngest cohort of children. However, we believe the project aims are still relevant and

critical to understand the impact of modern therapeutic approaches on neurocognitive functioning in older children. Indeed, in their recent meta-analysis of neurocognitive sequelae in ALL patients from 28 published studies, Campbell and colleagues[198] reported that age at diagnosis did not clearly and consistently moderate neurocognitive outcomes. Therefore, we feel that examining functioning in children aged 6 to 11 years will still provide critical data that will enhance our understanding of the impact of HR B-ALL diagnosis on cognitive functioning over time.

CogState tasks have been used successfully in trials of populations relevant to pediatric cancer patients.[228] Specifically, it has been used to study children with attention deficit hyperactivity disorder, with CogState tasks discriminate between those with and without the diagnosis, and those on and off medication,[233] as well as typically-developing children.[230] In addition, CogState has been used in samples of patients with concussions,[234] HIV/AIDS,[235] pediatric cerebral malaria,[236] and adult cancer patients.[237]

Of particular relevance to this study, a trial of 550 pediatric cancer survivors using CogState in addition to a more comprehensive neuropsychological battery has recently been completed by a study team led by Dr. Kevin Krull, recruiting participants from St. Jude Children's Research Hospital, Northwestern University, and Dana Farber Cancer Institute/Harvard Medical Center. There was some variability across sites as to who administered the measure; most were bachelors level research assistants who have received brief training in administration procedures in a process similar to that used in the current study (personal communication, Kevin Krull, PhD, 2010). Thus, we feel that it is feasible for site based CRAs or other clinic based personnel to use this measure to collect data across a larger number of sites with children who are receiving therapy.

As of March 24, 2011, Dr. Krull had not yet completed an analysis comparing CogState with standard neurocognitive measures. However, Dr. Krull completed a similar study using a sample of long term pediatric ALL and brain tumor survivors and a computerized battery similar to CogState. In that sample, correlations between the computerized measure of attention and memory and traditional measures of attention and memory were robustly significant (personal communication, Kevin Krull, PhD, 2011), ranging from 0.60 (executive functioning) to 0.79 (verbal memory). These values are consistent with the range of correlations typically found between traditional measures used to evaluate the same construct.

The table below lists contains descriptions and other relevant information about the tasks to be utilized in the CogState battery for this study.

Neurocognitive Function	Name of Task	Task Duration	Task Description	Score	Interpretation
Visual motor	Chase Test	1-2 mins	Subject taps tiles quickly and accurately, attempting to follow a visual, colored target	# of correct moves/second	Higher scores reflect better performance
Executive function	Groton Maze-Learning Task	5-7 mins	Subject must complete a hidden maze by following simple clues revealed on the computer	# of errors made across 5 trials	Lower scores reflect better performance
Visual attention	Identification Task	2-3 mins	Subject must indicate whether or not a card is red	Mean log10 reaction time for correct responses	Lower scores reflect better performance
Processing speed	Detection Task	2-3 mins	Subject must quickly indicate when a card has flipped over on the screen	Mean log10 reaction time for correct responses	Lower scores reflect better performance
Working memory	One-back test, Two-back test	4-5 mins	Subject must indicate when a stimuli is the same as the one that preceded it	Arcsine proportion of total items	Higher scores reflect better performance

			(one-back); or is the same as the one two items previously (two-back test)	correct	

16.4.2 Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF[226] is a widely used assessment of executive functioning for children aged 6-18 years. The parent-report version consists of 86 items which map onto 2 broad areas: behavioral regulation and metacognition, as well as 2 validity scales. The Behavioral Regulation domain is further divided into 3 clinical subscales: Inhibit, Shift, and Emotional Control, whereas the Metacognition domain is divided into 5 clinical subscales: Initiate (i.e., beginning a task), Working Memory (i.e., holding information), Plan/Organize (i.e., anticipating future events and developing appropriate strategies), Organization of Materials (i.e., maintaining order in memory), and Monitor. Parents are asked to consider the frequency with which each item has been a problem over the last 6 months, responding on a 3-point Likert scale consisting of "never," "sometimes," and "often." Items were developed to be ecologically-valid behavioral correlates to presumed neurocognitive difficulties with executive functioning; **thus, this measure was selected to provide parent and patient-reported outcomes of problems related to attention, memory, and executive function that occur in everyday life**. Psychometric properties of this measure are strong using normative samples (1419 parents) weighted to match ethnic and gender proportions in the US population. Internal consistency is high (alpha range = 0.73 to 0.90) and test-retest reliability exceeds 0.80 for both measures over intervals from 2 to 4 weeks.[226, 238, 239] Scores are linear transformations of raw scores into T scores (mean = 50, SD = 10); higher scores indicate greater difficulties.

16.4.3 Demographic and Symptom Information

CogState can be programmed to allow input of customized patient data at the time of testing. For this study, the CRA (or other individual administering the computerized testing) should enter each participant's study identification number, gender, race, ethnicity, and age into the computer program. At the first evaluation, the CRA should also ask the parent or guardian accompanying the child to provide information about their highest level of education attained to estimate socioeconomic status (SES), given recent recommendations that this data be collected and included as a potential moderator of outcomes in studies of this kind.[198] Finally, because prior longitudinal work suggests that children experiencing physical complaints at the time of testing perform more poorly on assessments both then and at subsequent evaluations,[227] we also ask participants to report on their current experience of fatigue and nausea on a 5-point Likert scale anchored by (none/not at all and very much).

16.4.4 Feedback to Participants

Real-time scoring is available for the CogState measure; thus, scores for each participant may be generated immediately. CogState is not designed to be a comprehensive measure of neurocognitive functioning; however, problems identified by CogState may indicate that the patient may require a more complete neuropsychological evaluation. Because we anticipate that the individuals administering CogState will most likely not be formally trained in psychological measures or interpretation, we considered whether providing feedback to families about their performance on CogState was advisable. We consulted with COG colleagues who are currently using CogState with pediatric cancer survivors. Although most are using CogState in conjunction with larger, standard neuropsychological batteries, participants who score $\geq$ 1.5 SD below the normative mean in one or more domains are routinely referred for further assessment (personal communication, Kevin Krull, PhD, 2010). Using this guideline, we plan to inform the health care providers of participants who have scored in the bottom 7% (i.e., 1.5 SD below the mean) relative to the standardization sample for CogState, or in the most extreme 7% of scores on the BRIEF, given that extreme scores on either of these measures may reflect significant difficulties that can interfere with learning. Score reports for the BRIEF and CogState are generated automatically by the scoring programs for each measure. When children receive scores at or more extreme than 1.5 SD from

the mean, their health care team will be informed of the results in the form of a letter listing the scores of concern, provided by the correlative study PI (Dr. Kristi Hardy). In this way, the health care team can follow up with families to determine if further assessment is warranted based on whether or not families are observing difficulties in their child's functioning at home or in school, and make a referral as they would normally do when families report concerns of this kind. Moreover, Dr. Kristi Hardy (a licensed psychologist) will provide detailed information about identification and communication of abnormal findings in the study manual.

16.4.5 Recruitment and Data Fidelity:
Limiting this study to computerized assessment of neurocognitive functioning using a single measure, CogState, maximizes the number of participating institutions who otherwise may have difficulty participating or accruing patients on a trial requiring consistent access to psychologists or other professionals trained in neurocognitive assessment procedures. In this way, we hope to avoid the sample bias that has been a critique of many past studies examining neurocognitive function in this population by enrolling *all* eligible patients across COG institutions. We hope to achieve a larger, more representative sample of participants with exceptional medical and demographic diversity than in previous research. We acknowledge that this approach will not replace studies with more comprehensive, psychologist-administered neurocognitive batteries. Rather, we anticipate that this study will compliment and enhance our existing knowledge of neurocognitive processing in HR B-ALL patients by providing a large, diverse sample that has less cultural bias and can be collected at shorter intervals than traditional measures allow.

Data accuracy and fidelity for this project is expected to be strong given the nature of computerized assessment. CogState provides 24-hour, phone-based technical support during the study period. Because data are automatically stored and scored on a secure server, the only manual data entry required for this protocol at each time point will be participants' identification numbers, gender, age, and date of assessment.

16.4.6 Retrospective anesthetic exposure data collection
The instrument to measure the key exposure of interest (anesthesia exposure) is the anesthesia case report form (A-CRF), adapted from the tool utilized in the St. Jude study, a feasible and effective tool for precise and complete data collection. Data for anesthesia exposures will be captured in the A-CRF for each event and will be collected by each COG institutional site CRA, and uploaded into the RAVE system applying COG rigorous data quality assurance systems. Training will be provided to site CRAs via a concise study guide. The study will provide central real time data review of the A-CRF submissions to ensure validity and completeness.

16.5 **Statistical Design**

16.5.1 Power
The primary objective is to determine the proportion of children aged 6 to < 13 years at time of B-ALL diagnosis that have clinically significant dysfunction at 1 year off therapy for HR B-ALL as assessed with CogState in the following domains: (1) working memory; (2) executive function; (3) visual motor; (4) processing speed; and (5) visual attention. We hypothesize that there will be a significantly higher prevalence of neurocognitive dysfunction in these domains in patients with HR B-ALL at 1 year off therapy compared to the prevalence in the normative population. Each domain will be analyzed separately. For each of the five domains, significant dysfunction will be defined as scores one standard deviation (SD=10) or more below the normative mean (mean=100). For each domain, we expect 14% of the normative proportion will have significant dysfunction (score ≤90). If the prevalence of significant dysfunction in HR B-ALL survivors at 1 year off therapy is 20%, and we enroll 437 children who have assessments at 1 year off therapy, we will have 80% power for establishing a significantly higher prevalence of neurocognitive dysfunction in HR B-ALL survivors compared to the normative population

at 2-sided alpha level of 0.01. Because there are 5 separate domains, the alpha level for each analysis is set to 0.01 according to Bonferroni adjustment to maintain an overall alpha level of 0.05. Assuming that 15% of participants may have missing data due to non-compliance or early death, we plan to enroll 515 children total. As noted below, data from all enrolled participants will be included in the exploratory analyses, even if data from only one time point was collected.

For Aim 2 in which we will assess the decline in neurocognitive functioning over time, given a sample size of 437 patients with 1 year off therapy assessment, we will have 99% power to detect a 0.5 SD (SD=10) decline in the mean of change of score between 1 year off therapy and baseline in a one-sample t-test at 2-sided alpha level of 0.01. The alpha level for the test is similarly adjusted as in aim 1. In the power consideration, the SD for the change of score between 2 time-points is expected to be no more than 14, assuming a SD of 10 for the score at both time-points (as in the normative population) and a non-negative correlation of scores within the same patient.

Of note, HR B-ALL patients, enrolled on this trial, are randomized to receive ITT versus IT methotrexate. CCG 1952, a study that enrolled NCI standard risk patients, also included an ITT versus IT methotrexate randomization. No clinically meaningful differences in neurocognitive functioning were found except for a slightly slower processing speed in the IT MTX group (p=0.04) as well as more patients from the IT MTX group falling into the below-average range compared to the ITT group (19.5% vs. 6.9%; p=0.02). The mean age of the group tested was 4.2 +/- 2.4 years. Currently, more than 60% of those enrolled on COG AALL0232 are > 10 years of age at diagnosis. Thus, with published data and large clinical experience suggesting that in a younger and more vulnerable population, that differences in neurocognitive outcome among the patients receiving triple intrathecal therapy as opposed to intrathecal methotrexate, are not clinically meaningful, comparing neurocognitive outcome among the two groups is not a primary objective of this study.

For each patient the number of anesthetic events, the total cumulative exposure to each anesthetic agent adjusted for weight and the total cumulative duration of anesthesia will be calculated. Our primary outcome of interest is age-adjusted population normative reaction time/processing speed (Cogstate Detection task score) at 1-year off-therapy, controlling for the Detection task score as the first time point. Exposures of interest are the cumulative doses of each primary anesthetic agent as well as the total cumulative duration of anesthesia while on therapy. Multivariable linear regression models will be constructed to determine the association of cumulative anesthetic agents with the primary neurocognitive outcome while adjusting for End of Consolidation score and other key potential covariates (e.g. age at diagnosis, biologic sex, insurance status, intrathecal therapy, high dose methotrexate, neurological adverse events). Secondary models will examine potential effects on the other neurocognitive outcomes listed above. A $p<0.05$ will be considered significant for all comparisons. For the primary model examining the effects of propofol exposure on reaction time/processing speed, a sample of 300 achieves at least 80% power to detect an effect size (f^2) of 0.03 (i.e., a small effect, Cohen 1988) attributable to propofol exposure using an F-test and adjusted for an additional 5 independent variable. [240, 241] The planned sample size of 300 reflects the estimated number of participants for whom data at both the first time point and the 1-year off-therapy time point will be available, accounting for approximately 20% attrition over time.

16.5.2 Accrual

Of the 3300 children (1800 HR B-ALL and 1500 VHR B-ALL) projected to be enrolled on the high risk ALL trial that will be eligible for therapeutic randomization, we anticipate that at least 40% (n = 1320) will be eligible for the neurocognitive protocol. This estimate is based on the age distribution, relapse rates, and prevalence of neurodevelopmental disorders provided in the Spring 2011 progress report for COG AALL0232, a recently closed therapeutic trial also for HR B-ALL patients. Of these, approximately 924 are expected to be enrolled on the parent trial in the first 3.5 years, which is the time frame during

which we would like to accomplish initial accrual for the study. To achieve our enrollment goal of 515 participants for this study, then, we would need to enroll 55.7% of those patients.

To estimate whether an enrollment goal of just over half of eligible patients was realistic, we examined records of active COG protocols involving neurocognitive or quality of life correlative studies of similar scope to the current study. For the recent standard risk B-ALL therapeutic study in COG (AALL0331), almost 90% of eligible patients enrolled on the embedded health related quality of life ancillary study.[242] In addition, over approximately 24 months of active recruitment, 99 sites have obtained IRB-approval and enrolled participants (n = 187) on COG ALTE07C1, a prospective, longitudinal study open to children with CNS tumors enrolled on either ACNS0331 or ACNS0332, which contains a neuropsychologist-dependent battery of approximately 60 minutes (personal communication, Leanne Embry, MD, 2011). Because the current study requires no dedicated support from a neuropsychologist and has lower participant burden, we feel that it is reasonable to meet our accrual goals for this study.

16.5.3 Hypothesis Testing

To analyze data for the primary aim, we will estimate the proportion of individuals with clinically significant dysfunction (score at or below 90) for each domain at the 1 year off therapy time-point and the corresponding 95% CIs for the estimated proportion. One sample test of binomial proportions at 2-sided alpha level of 0.01 will be used to examine if the prevalence of neurocognitive dysfunction is significantly higher than the prevalence of 14% from the normative population. Estimation will also be performed separately by gender.

To evaluate the change in neurocognitive function over time, actual scores for each domain at each time point will be summarized and examined by descriptive statistics and scatter plots. Change in score for a domain from baseline to a later time-point will be calculated and similarly summarized by descriptive statistics. The mean change of score from baseline to a later time-point will be estimated along with its 95% CI. One sample t-test on the change of score will be used to examine if there is significant decline in neurocognitive function from baseline to 1 year off therapy. Linear mixed models using scores from all time-points as outcome will also be used to estimate the change in scores between time-points with adjustment for within-patient correlation of the score by random effects for individual patients. If the change in score over time appears approximately linear in time, linear mixed models assuming time as a continuous covariate will be used to estimate the rate of decline over time and determine whether the rate of decline is significantly higher than zero.

For exploratory analyses on identifying demographic, disease, treatment, and behavior factors that are associated with neurocognitive deficit in each domain, logistic regression models will be used to explore the association between such factors (predictors) and the presence of neurocognitive deficit (outcome variable) or meaningful decline ($\geq$ 0.5 SD) at a particular time point. Non-linear mixed effect models on neurocognitive deficit (presence/absence) at all time-points as outcome variables may also be performed to explore such associations; such non-linear mixed model will adjust for within-patient correlation of neurocognitive deficit by random effect and treat the time-points as fixed effect. For exploratory analyses on identifying factors that are associated with neurocognitive decline over time, linear regression models using change of scores between 2 time-points as outcome variable will be used to examine the association between such factors and neurocognitive decline. Linear mixed models on multiple changes of scores over time from the same patient may also be considered for examining the association between the factors of interest and neurocognitive decline with adjustment for within-patient correlation of multiple changes of scores. For these models, we will employ data from all participants with data collected at any time point.

APPENDIX I: DASATINIB DOSING GUIDELINES

DASATINIB 48 mg/m^2

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (tablet sizes = 5 mg, 20 mg, 50 mg)	Cumulative Weekly Dose
0.31 - 0.37	15 mg (3 x 5 mg tablet)	105 mg/wk
0.38 - 0.45	20 mg (1 x 20 mg tablet)	140 mg/wk
0.46 - 0.57	25 mg (1 x 20 mg and 1 x 5 mg tablets)	175 mg/wk
0.58 - 0.67	30 mg (1 x 20 mg and 2 x 5 mg tablets)	210 mg/wk
0.68 - 0.79	35 mg (1 x 20 mg and 3 x 5 mg tablets)	245 mg/wk
0.80 - 0.87	40 mg (2 x 20 mg tablets)	280 mg/wk
0.88 – 0.98	45 mg (2 x 20 mg and 1 x 5 mg tablets)	315 mg/wk
0.99 – 1.10	50 mg (1 x 50 mg tablet)	350 mg/wk
1.11 - 1.20	55 mg (1 x 50 mg and 1 x 5 mg tablets)	385 mg/wk
1.21-1.29	60 mg (3 x 20 mg tablets)	420 mg/wk
1.30 – 1.40	65 mg (3 x 20 mg and 1 x 5 mg tablets)	455 mg/wk
1.41-1.51	70 mg (1 x 50 mg and 1x 20 mg tablets)	490 mg/wk
1.52 - 1.62	75 mg (1 x 50 mg, 1 x 20 mg, and 1 x 5 mg tablets)	525 mg/wk
1.63 - 1.71	80 mg (4 x 20 mg tablets)	560 mg/wk
1.72 - 1.82	85 mg (4 x 20 mg and 1 x 5 mg tablets)	595 mg/wk
1.83- 1.92	90 mg (1 x 50 mg and 2 x 20 mg tablets)	630 mg/wk
1.93 – 2.03	95 mg (1 x 50 mg, 2 x 20 mg and 1 x 5 mg tablets)	665 mg/wk
2.04 – 2.12	100 mg (2 x 50 mg tablets)	700 mg/wk
2.13 – 2.20	105 mg (2 x 50 mg and 1 x 5 mg tablets)	735 mg/wk
$\geq$ 2.21	110 mg (2 x 50 mg and 2 x 5 mg tablets)	770 mg/wk

DASATINIB 60 mg/m²

Body Surface Area (m²)*	Daily Dose (d) for 7 days (tablet sizes = 5 mg, 20 mg, 50 mg)	Cumulative Weekly Dose
0.31 - 0.37	20 mg (1 x 20 mg tablet)	140 mg/wk
0.38 - 0.45	25 mg (1 x 20 mg and 1 x 5 mg tablets)	175 mg/wk
0.46 - 0.54	30 mg (1 x 20 mg and 2 x 5 mg tablets)	210 mg/wk
0.55 - 0.62	35 mg (1 x 20 mg and 3 x 5 mg tablets)	245 mg/wk
0.63 - 0.70	40 mg (2 x 20 mg tablets)	280 mg/wk
0.71 - 0.79	45 mg (2 x 20 mg and 1 x 5 mg tablets)	315 mg/wk
0.80 - 0.87	50 mg (1 x 50 mg tablets)	350 mg/wk
0.88 - 0.95	55 mg (1 x 50 mg and 1 x 5 mg tablets)	385 mg/wk
0.96 - 1.04	60 mg (3 x 20 mg tablets)	420 mg/wk
1.05-1.12	65 mg (3 x 20 mg and 1 x 5 mg tablets)	455 mg/wk
1.13 - 1.20	70 mg (1 x 50 mg and 1 x 20 mg tablets)	490 mg/wk
1.21-1.29	75 mg (1 x 50 mg, 1x 20 mg and 1 x 5 mg tablets)	525 mg/wk
1.30 - 1.37	80 mg (4 x 20 mg tablets)	560 mg/wk
1.38 - 1.45	85 mg (4 x 20 mg and 1 x 5 mg tablets)	595 mg/wk
1.46 - 1.53	90 mg (1 x 50 mg and 2 x 20 mg tablets)	630 mg/wk
1.54 - 1.62	95 mg (1 x 50 mg, 2 x 20 mg and 1 x 5 mg tablets)	665 mg/wk
1.63 - 1.70	100 mg (2 x 50 mg tablets)	700 mg/wk
1.71 - 1.79	105 mg (2 x 50 mg and 1 x 5 mg tablets)	735 mg/wk
1.80 - 1.87	110 mg (2 x 50 mg and 2 x 5 mg tablets)	770 mg/wk
1.88 - 1.95	115 mg (2 x 50 mg and 3 x 5 mg tablets)	805 mg/wk
1.96 - 2.04	120 mg (2 x 50 mg and 1 x 20 mg tablets)	840 mg/wk
2.05 - 2.12	125 mg (2 x 50 mg, 1 x 20 mg and 1 x 5 mg tablets)	875 mg/wk
2.13 - 2.2	130 mg (2 x 50 mg, 1 x 20 mg tablets, and 2 x 5 mg tablets)	910 mg/wk
2.21 - 2.29	135 mg (2 x 50 mg, 1 x 20 mg tablets, and 3 x 5 mg tablets)	945 mg/wk
≥2.3	140 mg (2 x 50 mg and 2 x 20 mg tablets)	980 mg/wk

APPENDIX II: 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 (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.33 - 0.38	½ tab / d x 6	150 mg/wk
0.39 - 0.44	½ tab / d x 7	175 mg/wk
0.45 - 0.50	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.51 - 0.56	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.57 - 0.62	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.63 - 0.68	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.69 - 0.74	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.75 - 0.80	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.81 - 0.86	1 tab / d x 7	350 mg/wk
0.87 - 0.92	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.93 - 0.98	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.99 - 1.04	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
1.05 - 1.10	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
1.11 - 1.16	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
1.17 - 1.22	1½ tab / d x 6; 1 tab / d x 1	500 mg/wk
1.23 - 1.27	1½ tab / d x 7	525 mg/wk
1.28 - 1.33	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.34 - 1.39	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.40 - 1.45	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.46 - 1.51	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.52 - 1.57	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.58 - 1.63	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.64 - 1.69	2 tab / d x 7	700 mg/wk
1.70 - 1.75	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.76 - 1.81	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.82 - 1.87	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.88 - 1.93	2½ tab / d x 4; 2 tab / d x 3	800 mg/wk
1.94 - 1.99	2½ tab / d x 5; 2 tab / d x 2	825 mg/wk
2.00 - 2.05	2½ tab / d x 6; 2 tab / d x 1	850 mg/wk
2.06 - 2.11	2½ tab/ d x 7	875 mg/wk
2.12 - 2.17	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
2.18 - 2.23	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
2.24 - 2.29	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
2.30 - 2.35	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
2.36 - 2.41	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
2.42 - 2.47	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
2.48 - 2.52	3 tab/ d x 7	1050 mg/wk
2.53 - 2.58	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
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 (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
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 III: THIOGUANINE DOSING GUIDELINES

THIOGUANINE 60 mg/m²

Body Surface Area (m^2)*	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

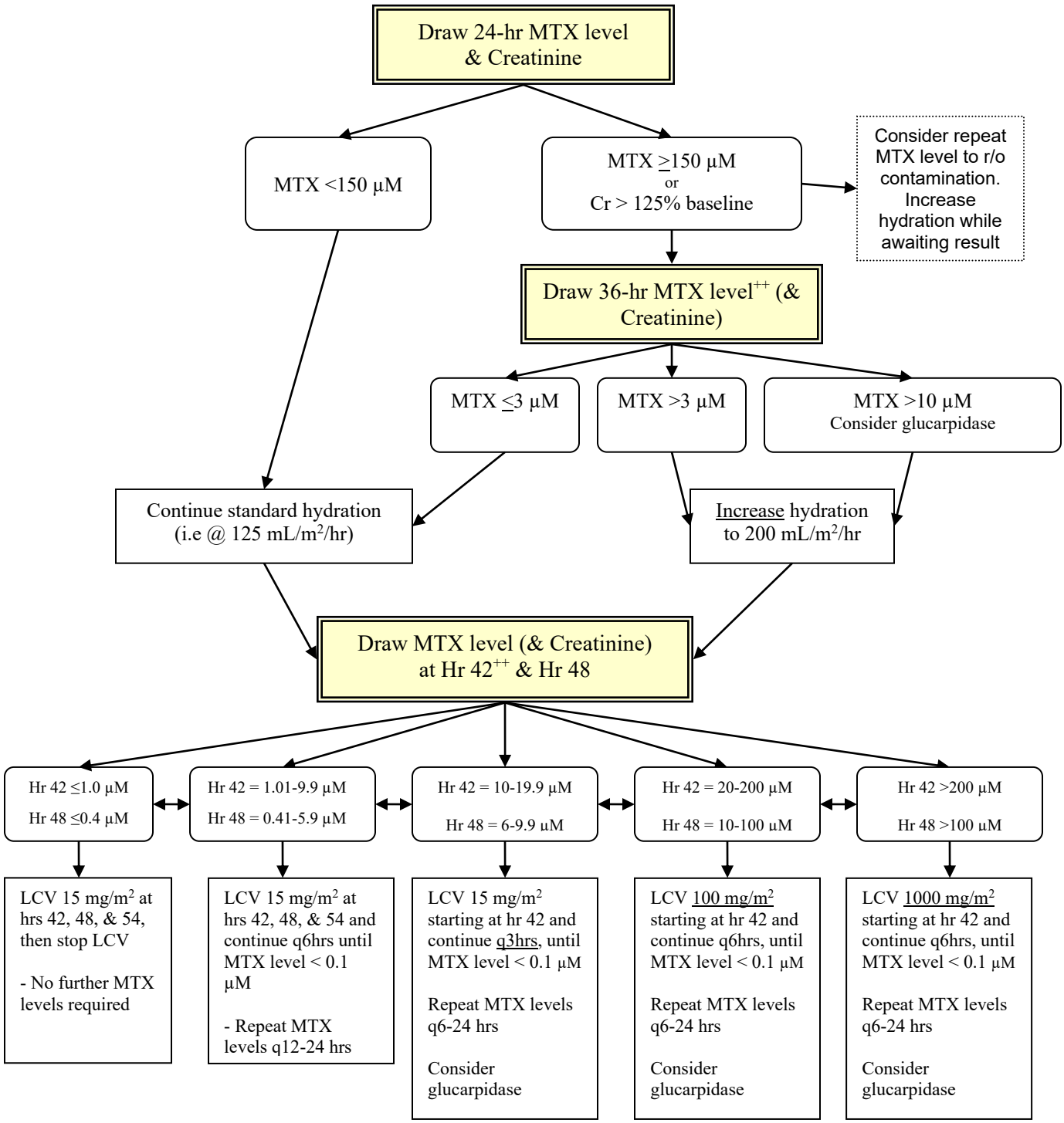
Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 40 mg)	Cumulative Weekly Dose
2.36 – 2.40	3½ tab / d x 6; 4 tab / d x 1	1000 mg/wk
2.41 – 2.45	3½ tab / d x 5; 4 tab / d x 2	1020 mg/wk
2.46 – 2.49	3½ tab / d x 4; 4 tab / d x 3	1040 mg/wk
2.50 – 2.54	4 tab / d x 4; 3½ tab / d x 3	1060 mg/wk
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 IV-A: HIGH DOSE METHOTREXATE FLOW CHART

(Non-Down syndrome Patients ONLY – See Appendix IV-B for Down syndrome)

(Please refer to Section 5.8 for complete details; all levels are timed from the start of the HD MTX infusion)

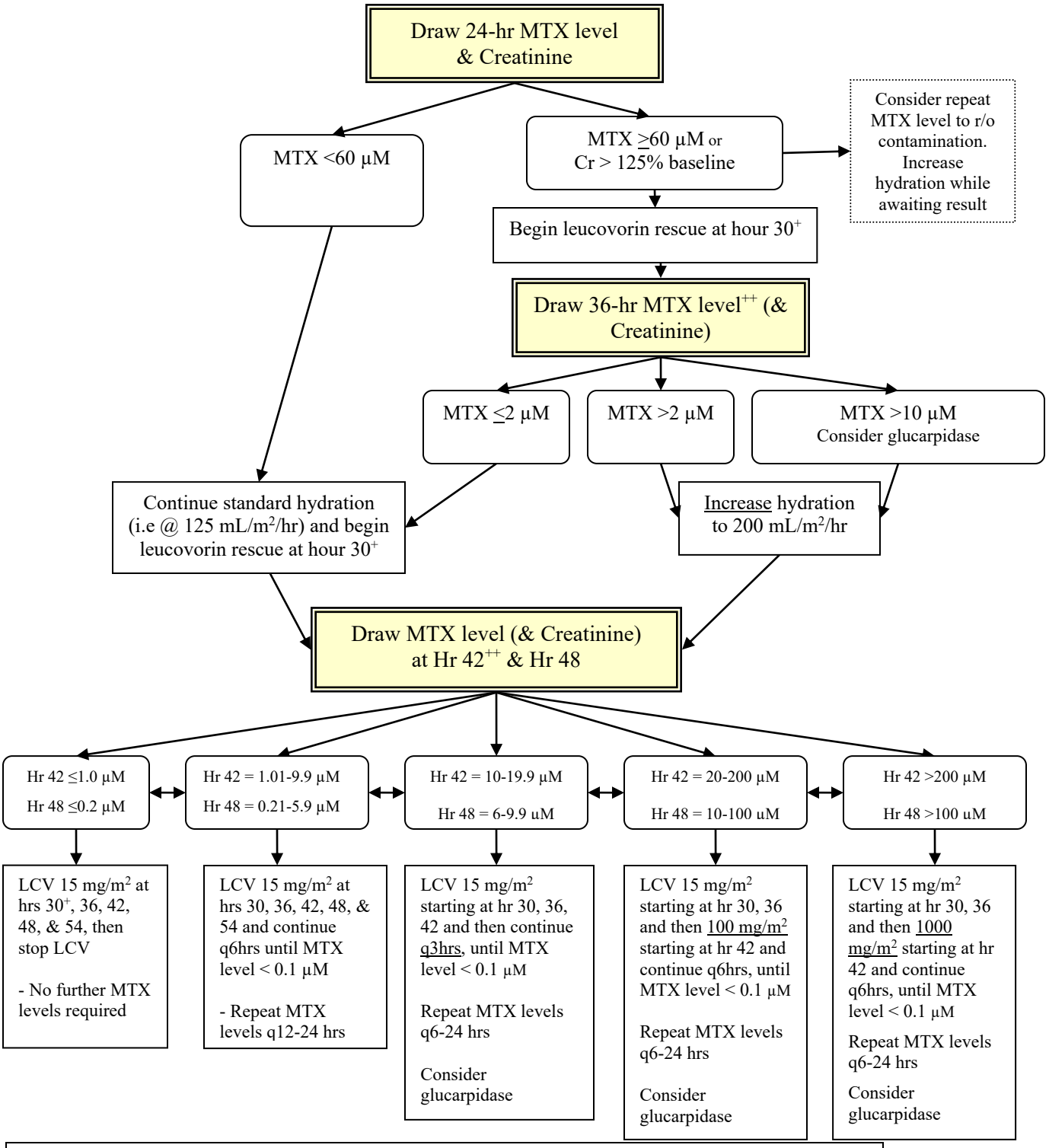


++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of **≤1.0** and/or **≤ 0.4 µM** at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

APPENDIX IV-B: INTERMEDIATE DOSE METHOTREXATE FLOW CHART

(Down syndrome Patients ONLY).

(Please refer to Section 5.8 for complete details; all levels are timed from the start of the ID MTX infusion)



+ If the first cycle of ID MTX is tolerated, defined as no delayed clearance, no treatment delay due to myelosuppression, no mucositis of Grade 2 or higher, and no nephrotoxicity (pre-treatment serum creatinine >1.5x baseline or GFR creatinine clearance < 65 mL/minute/1.73m^2), subsequent cycles of ID MTX should be followed by leucovorin 15 mg/m^2 PO/IV q 6h beginning **36 hrs** after the start of the infusion for a minimum of 4 doses if 48 hour plasma MTX is < 0.2 µM.

++ 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 **≤1.0** and/or **≤ 0.2 µM** at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

APPENDIX V: OSTEONECROSIS STUDY DRUG LEVELS

Completed July 2016

Blood for levels of methotrexate, asparaginase and dexamethasone will be collected at 4 time points during treatment. **Blood draws should occur only at these time points relative to scheduled drug administration so they accurately reflect relevant drug exposures.** Blood can be collected from a central line.

Collection Time	Necessary drug administration information	Specimens (Blood)	Tube*#	Ship to	Studies to be done
Day 1 of Consolidation (to be drawn approx. 3 weeks after Induction "Day 4" PEG-ASP).	• Dose (IU/m^2), • Date and time of Induction "Day 4" PEG-ASP	8-10 mL	Use 1 x 10 mL red top tube (preferred) **or** Use 2 x 6 mL red top tubes*#	St. Jude	Serum anti-asparaginase antibodies, albumin, and asparaginase activity
Day 22 of Consolidation (to be drawn approx. 7 days after Consolidation "Day 15" PEG-ASP).	• Dose (IU/m^2) • Date and time of Consolidation "Day 15" PEG-ASP	8-10 mL	Use 1 x 10 mL red top tube (preferred) **or** Use 2 x 6 mL red top tubes*#	St. Jude	Serum anti-asparaginase antibodies, albumin, and asparaginase activity
Day 8 of Delayed Intensification (to be drawn as soon after Day 7 dexamethasone dose as possible)	• Dose (mg/m^2), • Date and time of Day 7-last dexamethasone dose; and • Dose (IU/m^2), • Date and time of DI "Day 4" PEG-ASP	8-10 mL	Use 1 x 10 mL red top tube (preferred) **or** Use 2 x 6 mL red top tubes*#	St. Jude	Serum dexamethasone, anti-asparaginase antibodies, albumin, and asparaginase activity
Day 22 of Interim Maintenance II –**VHR Only** (to be drawn BEFORE the Day 22 PEG ASP)	• Dose (mg/m^2), • Date and time of Day 21- last methotrexate dose; and • Dose (IU/m^2), • Date and time of IM II "Day 2" PEG-ASP	8-10 mL (to be drawn BEFORE the Day 22 PEG-ASP)	Use 1 x 10 mL red top tube (preferred) **or** Use 2 x 6 mL red top tubes*#	St. Jude	Serum methotrexate, anti-asparaginase antibodies, albumin, and asparaginase activity

*Immediately after being drawn, the red top tubes should not be inverted, but rather sit upright for at least 30–60 minutes to help with coagulation. Do not freeze; ship with cold pack or wet ice, do not ship on dry ice.

#Special instructions for trans-oceanic sites (e.g. New Zealand, Australia) for which overnight delivery is not possible: Immediately after being drawn, the red top tubes should not be inverted, but rather sit upright for at least 30–60 minutes to help with coagulation. Then centrifuge each sample, separate the serum and transfer serum into capped small polypropylene tube(s), freeze the sera, and batch-send the samples on dry ice at your convenience. Contact the St. Jude laboratory for tubes if needed.

Ship samples by overnight express delivery (specify Saturday delivery if shipping on Friday) within 24 hours to:

Clinical Pharmacokinetics Laboratory
St. Jude Children's Research Hospital
Dept. of Pharmaceutical Sciences
262 Danny Thomas Pl. MS-313
Chili's Care Center, Room I-5411
Memphis, TN 38105
Phone: 901-595-2242
Fax: 901-595-3341
Email: mary.relling@stjude.org

See the Osteonecrosis Study Summary Sheet on the AALL1131 protocol webpage for courier information.

APPENDIX VI: YOUTH INFORMATION SHEETS
INFORMATION SHEET REGARDING RESEARCH STUDY AALL1131
(for children from 7 through 12 years of age)

(*High Risk B-Lymphoblastic Leukemia*)

1 We have been talking with you about B-Lymphoblastic Leukemia or B-ALL. B-ALL is a type of cancer that 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 High Risk B-ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat High Risk B-ALL and reduce the bad effects of the anticancer drugs. We will do this by trying different ways to treat High Risk B-ALL and seeing which one works better. 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 receive a treatment called chemotherapy. Chemotherapy is medicine that kills cancer. Some of the children who are part of this study will get the usual treatment doctors use for B-ALL. Some of the children will get extra chemotherapy that is new and some will get less chemotherapy. Sometimes X-ray treatments are also given to help kill cancer that is in the brain and/or testicles (if you are a boy) or to keep the cancer from moving into the brain. The chemotherapy you get will be decided by chance, like flipping a coin for "heads" or "tails". You will have regular blood tests and several bone marrow tests and spinal taps during your treatment. These tests help doctors in deciding the most appropriate treatment for your B-ALL. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much. We will also give some other drugs that will help patients cope with some of the side effects of the treatment. We will continue to closely look at how treatment affects patients on this study, to make sure patients get the best treatment with the least side effects.

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 getting rid of the cancer for as long as possible, and with fewer bad effects; 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. There is a risk that you will have more bad effects from the medicines if you are treated with any of the additional treatments along with the usual medicines. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

6 Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7 We are asking your permission to collect additional bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. This sample would be taken when other standard bone marrow tests are being performed, and will not involve any extra procedure. You can still take part in this study even if you don't allow us to collect the extra bone marrow sample for research.

INFORMATION SHEET REGARDING RESEARCH STUDY
(for teens from 13 through 17 years of age)

(*High Risk B Lymphoblastic Leukemia*)

1 We have been talking with you about Acute Lymphoblastic Leukemia or B-ALL. B-ALL is a type of cancer that 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 High Risk B-ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat High Risk B-ALL and reduce the bad effects of the anticancer drugs. We will do this by trying different ways to treat High Risk B-ALL and seeing which one works better. 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 receive a treatment called chemotherapy. Chemotherapy is medicine that kills cancer. Some of the children and teens who are part of this study will get the usual treatment doctors use for B-ALL, some will get extra chemotherapy and some will get less chemotherapy. Sometimes X-ray treatments are also given to help kill cancer that is in the brain and/or testicles (if you are a boy) 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. These tests help doctors in deciding the most appropriate treatment for your B-ALL according to your risk group. The chemotherapy you get will be decided by chance, like flipping a coin for "heads" or "tails". Some children and teens that are part of this study will get treatment that is usual for HR B-ALL, with intrathecal methotrexate or intrathecal methotrexate, hydrocortisone and cytarabine (triple intrathecals) in the different phases of treatment. Some children and teens that are part of this study will get usual HR B-ALL treatment throughout all phases of treatment; some will get treated with drugs usually used to treat B-ALL (etoposide and cyclophosphamide) during the phase of treatment called Consolidation and Delayed Intensification.

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 getting rid of the cancer for as long as possible, and with fewer bad effects; 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. There is a risk that you will have more bad effects from the medicines if you are treated with triple intrathecals along with the usual medicines. We do not know this for sure which is why we are doing this study. Other things may happen to you that we don't yet know about.

6 Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7 We are asking your permission to collect additional bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. This sample would be taken when other standard bone marrow tests are being performed, and will not involve any extra procedure. You can still be treated on this study even if you don't allow us to collect the extra bone marrow sample for research.

APPENDIX VII: PHYSICIAN GUIDE FOR PATIENT EDUCATION ON REQUIRED RESEARCH TESTS

Required Research Study Tests

A number of factors will be used to identify which risk group subjects belong to and will be used to make treatment decisions on this study. These factors include the results of the research tests, as well as age and the presence or absence of leukemia cells in the spinal fluid or brain. Because you signed a consent form to take part in the ALL Classification Study AALL08B1 or APEC14B1 (*if available for ALL patients*), extra tests will be done on leukemia cells obtained before therapy was started as well as during Induction. These will require additional blood and bone marrow to be taken at times when blood and bone marrow are already being collected.

Please note:

- For subjects with Down syndrome enrolled on this study before the start of Induction therapy, the research tests are also required on this trial but will be **not** be used to determine post-Induction treatment.
- For subjects with Down syndrome who received Induction therapy on AALL0932, you will have had the same research tests performed but on that trial, the results of these tests were used at the end of Induction therapy to help decide that you are classified as having DS HR B-ALL.
- For subjects who received Induction therapy on AALL0932 and who do not have Down syndrome, you will have had the same research tests performed and on that trial, the results of these tests were used at the end of Induction therapy to help decide that you are classified as having High Risk (HR) B-ALL

Fluorescence In Situ Hybridization (FISH)

The tests that are done on leukemia cells obtained before the start of treatment will look for specific changes that are present in the chromosomes of your leukemia cells, but not in your normal body cells. A chromosome is the part of the cell that contains genetic information. Changes in the chromosomes of the leukemia cells are almost always present at the time B-ALL is diagnosed. Some of these changes are associated with a better response to treatment and higher leukemia cure rate, others are associated with a worse response to treatment and lower leukemia cure rate, and some don't have any clear effect on leukemia response or cure. A sample of your leukemia cells will be sent to a laboratory at your hospital or another hospital that has been approved by the COG to do these tests. The tests will look for certain chromosome changes using tests called fluorescence in situ hybridization (FISH). The results of these FISH tests will be used to help decide whether you are classified as having HR or VHR B-ALL. The treatment that is given after Induction therapy is completed will be stronger for those with VHR B-ALL than for Subjects with HR B-ALL.

Minimal Residual Disease (MRD)

The tests performed during Induction will measure low numbers of remaining leukemia cells called minimal residual disease (MRD). For subjects enrolled in this study, the blood and bone marrow samples will be sent to a COG-approved flow laboratory that will measure the MRD using a special test called flow cytometry. These laboratories have performed MRD tests for over 10,000 subjects with ALL enrolled in COG ALL studies since 2004, and the level of MRD present has been shown to be very predictive of how well treatment works. We have found that subjects with higher levels of MRD have lower cure rates overall than do subjects with lower levels of MRD. The MRD tests have not been approved by the FDA, so that for the purposes of this study the FDA considers the MRD test to be investigational. We will measure MRD present in your bone marrow (Day 29) during Induction therapy,

which will give study doctors important information on how quickly your leukemia is responding to treatment.

From past studies COG researchers know that subjects with ALL that responds quickly to treatment (have lower levels of MRD in the blood at Day 8 and the bone marrow at Day 29) have higher cure rates than those with ALL that responds more slowly to treatment and have higher levels of MRD at these times. We also know from past studies that using stronger treatment after the first 4 to 5 weeks of Induction therapy can increase the chance that subjects with a slower response (and higher MRD levels) are cured. Because of this, the results of the MRD test in the blood and bone marrow will be used to help decide whether you are classified as having HR B-ALL or VHR B-ALL at the end of Induction therapy. Subjects with VHR B-ALL will get stronger treatment after Induction therapy is completed than subjects with HR B-ALL. If you were not enrolled on this study, your doctor might or might not use MRD testing to determine what your treatment should be after Induction therapy is completed, but MRD testing is required for participation on this study. Researchers will also learn more about how well MRD tests predict cure rates from studying subjects on this study.

In the past, early response to treatment was determined based on the number of blasts remaining in the bone marrow at Day 8 or Day 15 of Induction therapy along with the levels of MRD present in the bone marrow at Day 29 of Induction. Because recent COG ALL studies have shown that combining MRD measurements from blood (Day 8) and bone marrow (Day 29) is very accurate in predicting how likely subjects are to be cured of ALL, those subjects enrolled in this study will not be required to have bone marrow tests performed on Day 8 or Day 15 of Induction.

Risks of Using These Research Tests

This study requires FISH testing, MRD and LDA testing. The results of these tests will be used to help determine whether your leukemia is considered HR B-ALL or VHR B-ALL at the end of Induction treatment. For subjects with Down syndrome who received Induction on AALL0932, results of these tests were used to help decide that your leukemia is DS HR B-ALL. This grouping will determine the strength of the treatment that you receive during the next phases of chemotherapy treatment.

Because no test is perfectly accurate, there is a small risk that these tests might not be accurate and that you might be assigned incorrectly to the HR B-ALL or VHR B-ALL groups. If you are incorrectly assigned to the VHR B-ALL group then you might receive stronger treatment than is needed. Having stronger treatment may increase the risk of having side effects. If you are incorrectly assigned to the HR B-ALL group then you might receive less treatment than is needed. Having less treatment may increase the chance that the leukemia comes back (relapses). For subjects with Down syndrome who received Induction on AALL0932, if you were incorrectly classified as DS HR B-ALL then on this study you might receive stronger treatment than is needed. Having stronger treatment may increase the risk of having side effects.

The FISH tests look for changes that are present in a high percentage of leukemia cells. Because of this, it is very unlikely, but not impossible, that a mistake might be made and a change said to be present when it is really not there, or a change not detected when it really is there. While it is not possible to know this risk with certainty, we believe that the chance of an incorrect test result is less than 3%.

Most of the time, the MRD results are clearly higher or lower than the values that are used to call them positive or negative. However, in a small number of cases, the MRD value that is measured might be very close to the cutoff value, increasing the chance that there could be a mistake. While it is not possible to know this risk with certainty, only about 1% to 3% of results in past studies were near this cutoff. It is important to know that the tests used in the past to determine how quickly the leukemia was responding to treatment (counting the percentage of leukemia cells left in the bone marrow at Day 8 and Day 15 of Induction therapy) also could be inaccurate. COG studies have shown that the MRD tests are a more accurate way to predict the chance of relapse than the older methods of counting leukemia cells under the microscope.

APPENDIX VIII: CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at:
https://ctep.cancer.gov/investigatorResources/default.htm.
For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov .

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements For AALL1131 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

APPENDIX IX: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Cytarabine (by vein)

Drugs that may interact with cytarabine
• Clozapine, digoxin, flucytosine, leflunomide

Food and supplements that may interact with cytarabine*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Cyclophosphamide

Drugs that may interact with cyclophosphamide
• Allopurinol • Chloramphenicol • Cyclosporine • Digoxin • Etanercept • Hydrochlorothiazide • Indomethacin • Nevirapine • Pentostatin • Warfarin

Food and supplements that may interact with cyclophosphamide*
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Dasatinib

Drugs that may interact with dasatinib
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, rifapentin, telithromycin • Antidepressants and antipsychotics o Aripiprazole, nefazodone, fluvoxamine • Antifungals o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir • Anti-seizure medications o Carbamazepine, oxcarbazepine, fosphenytoin, phenobarbital, phenytoin, primidone • Heart burn and anti-reflux medications o Esomeprazole, cimetidine, famotidine, lansoprazole, nizatidine, omeprazole, pantoprazole, ranitidine • Heart medications o Amiodarone, diltiazem, dronedarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Aprepitant, bosentan, conivaptan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, modafinil, natalizumab, netupitant

Food and supplements that may interact with dasatinib*
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Daunorubicin

Drugs that may interact with daunorubicin
• Some antibiotics and antifungals (clarithromycin, erythromycin, itraconazole, ketoconazole) • Some antiepileptics (carbamazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (darunavir, lopinavir; nelfinavir, ritonavir, saquinavir, telaprevir, tenofovir, tipranavir) • Some heart medications (amiodarone, carvedilol, digoxin, dronedarone, nicardipine, propranolol, verapamil) • Other agents, such as atorvastatin, clozapine, cyclosporine, dexamethasone, ivacaftor, leflunomide, natalizumab, nefazodone, progesterone, rifampin, tacrolimus, tofacitinib, and trazodone

Food and supplements that may interact with daunorubicin*
• Echinacea • Grapefruit, grapefruit juice, Seville oranges, star fruit • St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Dexamethasone

Drugs that may interact with dexamethasone
• Antibiotics o Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine • Antifungals o Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine, sirolimus, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, amlodipine, dronedenarone, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: o Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Doxorubicin

Drugs that may interact with doxorubicin
• Some antiepileptics (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (stavudine, zidovudine) • Other agents, such as clozapine, cyclosporine, verapamil, and warfarin

Food and supplements that may interact with doxorubicin*
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Etoposide

Drugs that may interact with etoposide

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Aripiprazole, clozapine, nefazodone
• Antifungals
  ○ Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib
• Anti-rejection medications
  ○ Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  ○ Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  ○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  ○ Amiodarone, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Aprepitant, atovaquone, bosentan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, sitaxentan

Food and supplements that may interact with etoposide*

• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Leucovorin

Drugs that may interact with leucovorin
○ Some antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone)

Food and supplements that may interact with leucovorin*
• Folic acid

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Mercaptopurine

Drugs that may interact with mercaptopurine
○ Artiritis medications: leflunomide, tofacitinib ○ Other medications, such as allopurinol, azathioprine, clozapine, febuxostat, natalizumab, olsalazine, sulfasalazine, warfarin

Food and supplements that may interact with mercaptopurine*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Methotrexate (by mouth or by vein)

Drugs that may interact with methotrexate*
• Some antibiotics (amoxicillin, Bactrim, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline) • Some anti-inflammatory drugs (aspirin, acetaminophen, ibuprofen, naproxen, ketorolac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, retinoids, theophylline, warfarin

Food and supplements that may interact with methotrexate**

- Alcohol
- Echinacea
- Some vitamins, including those that contain folic acid or high doses of vitamin C

** Sometimes these drugs are used with methotrexate on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Pegaspargase

Drugs that may interact with pegaspargase
○ Leflunomide, natalizumab, tofacitinib

Food and supplements that may interact with pegaspargase*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Prednisone

Drugs that may interact with prednisone
• Arthritis medications ○ Leflunomide, tofacitinib • Antiretrovirals and antivirals ○ Boceprevir, ritonavir, telaprevir • Anti-seizure medications ○ Phenobarbital, phenytoin, primidone • Growth hormones • Heart medications ○ Diltiazem, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: ○ Aprepitant, aripiprazole, aspirin, cyclosporine, deferasirox, ibuprofen, itraconazole, mifepristone, natalizumab, rifampin, warfarin

Food and supplements that may interact with prednisone*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Thioguanine

Drugs that may interact with thioguanine
○ Arthritis medications: leflunomide, tofacitinib ○ Other medications, such as allopurinol, clozapine, natalizumab, olsalazine, sulfasalazine

Food and supplements that may interact with thioguanine*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Vincristine

Drugs that may interact with vincristine
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Aripiprazole, nefazodone, trazodone • Antifungals o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tocilizumab, tofacitinib • Anti-rejection medications o Cyclosporine, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, digoxin, dronedenarone, propranolol, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vincristine*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

APPENDIX X: CYP3A4 SUBSTRATES, INHIBITORS AND INDUCERS

This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5] alfentanil[4,5] amiodarone[4] aprepitant/fosaprepitant atorvastatin[5] axitinib bortezomib bosutinib[5] budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] eletriptan[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] fentanyl[4] gefitinib haloperidol imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor ketoconazole lansoprazole lapatinib losartan lovastatin[5]	atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine graperfruit[3] grapefruit juice[3] idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	aprepitant conivaptan crizotinib cyclosporine diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit[3] grapefruit juice[3] imatinib isavuconazole mifepristone nilotinib verapamil	barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort	bosentan dabrafenib efavirenz etravirine modafinil nafcillin rifapentin

lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen temsirolimus teniposide tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 5.10 and Section 6.6 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX XI: NCI/DCTD COLLABORATIVE AGREEMENT LANGUAGE

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).-Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

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

   Email: ncicteppubs@mail.nih.gov

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

APPENDIX XII: PH LIKE DETERMINATION ASSAY

Description of populations for testing

Previous studies by the Children's Oncology Group (COG) and others have identified a subtype of newly diagnosed and relapsed B-progenitor acute lymphoblastic leukemia (B-ALL) characterized by a Philadelphia chromosome-like (Ph-like or *BCR-ABL1*-like) gene expression profile (GEP) similar to Ph+ ALL but lacking a *BCR-ABL1* fusion.[74, 97] The frequency of the Ph- like ALL gene expression signature is approximately 10% in childhood standard risk (SR) B- ALL and 15% in high risk (HR) B-ALL[77], and is three to four times more common than Ph+ ALL, with a worse prognosis compared to patients without this phenotype.[243] Genomic profiling studies have identified genetic alterations that activate kinase signaling in this subset of patients.[77, 80] Many of the identified rearrangements involve fusion of kinase genes (*ABL1, ABL2, CSF1R, JAK2,* and *PDGFRB, CRLF2,* and *EPOR*) to a host of other genes that appear to induce malignant transformation that may be attenuated with specific tyrosine kinase inhibitors (TKIs). It is therefore hypothesized that the treatment outcome of patients with a characterized lesion will be improved with addition of specific TKIs to chemotherapy.[77, 244] These major discoveries in the genomics of Ph-like ALL have led to this protocol, AALL1131, being amended in order to incorporate testing to identify relevant NCI HR patients who would be amenable to treatment with TKIs in an attempt to lower the high rate of treatment failure and death in HR patients with B-ALL.

We published detailed genomic analyses of 1725 B-ALL patients 0-39 years old.[80] All cases had GEP performed using Affymetrix U133 Plus 2.0 arrays, and 264 (15.3%) had Ph-like ALL. The prevalence of Ph-like ALL increased with age: 10% among young children with standard risk (SR) ALL, 13% in high risk ALL, 21% in adolescents, and 27% in young adults 21-39 years. Ph-like ALL was associated poor outcome with 5-year rates of 58% EFS and 73% OS for high-risk non-adolescents, 41% EFS and 66% OS for adolescents, and 24% EFS and 26% OS for young adults. Next generation sequencing was performed in 154 Ph-like patients; 91% of which had genomic alterations activating kinase signaling, including 73.9% with lesions eligible for the clinical trials discussed below: 50% with *CRLF2* rearrangements (*CRLF2-R*; 42% *P2RY8-CRLF2* fusion and 58% *IGH-CRLF2*), 12.6% with ABL class (*ABL1*, *ABL2*, *CSF1R*, *PDGFRB*) gene fusions, 7.4% with *JAK2* fusions, and 3.9% with erythropoietin receptor gene rearrangements (*EPOR*-R). The Willman lab used data from this and other studies to establish and validate a rapid assay to identify patients with Ph-like ALL and/or the above genomic rearrangements. This assay quantifies the expression of 8 genes on a Taqman based low density array (LDA) card. Via successive iteration, the Gastier-Foster team at Nationwide Children's Hospital (NCH) have developed a panel of multiplex RT-PCR (mPCR) assays that can identify a total of 41 TK gene fusions. These assays are performed in a CAP/CLIA-certified laboratory and are available for both research and clinical use. Positive results are confirmed by repeat PCR and bidirectional Sanger sequencing of amplified products.

We have now used the LDA card to screen three large cohorts of ALL patients, including two from AALL1131 (1389 patients in cohort 1 and 961 patients in cohort 2) and a cohort of 1023 SR ALL patients from COG AALL0331. As detailed below, there were very few ABL class lesions detected in the SR cohort, thus we will only be screening NCI HR patients enrolled at diagnosis on AALL1131 for the Ph-like signature using the LDA card for this study. The AALL1131 NCI HR patients with these genomic alterations will comprise the historical controls treated without TKI, to which we will later compare outcome of those treated with chemotherapy plus TKI.

Technical Description of Assay

We have now fully developed the downstream testing algorithm that will be used to characterize Ph-like ALL patients identified by LDA (Figure 1). The LDA screening assay (the "device") is a multi-analyte, quantitative RT-PCR (qPCR) assay coupled with a proprietary mathematical algorithm to determine the "Ph-like" status of a sample (as either positive or negative). The preferred platform for performing the

qPCR is the low density array (LDA) microfluidic card manufactured by Life Technologies™ Corporation, a brand of Thermo Fisher Scientific. This platform utilizes the TaqMan® technology for determining quantitative gene expression levels, in which two primers and a non-overlapping labeled probe are responsible for generating and detecting products at each of 40 amplification cycles.

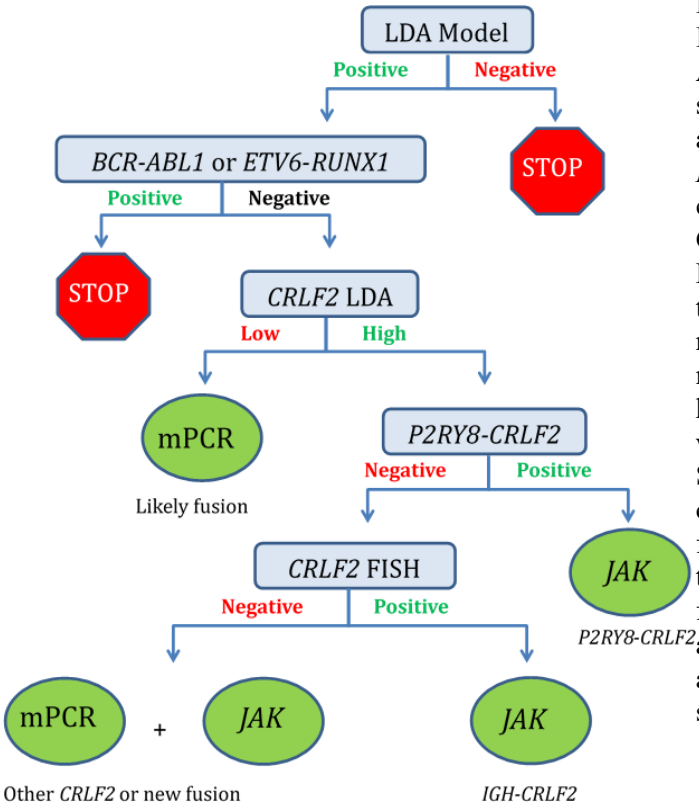


Figure 1. Algorithm for Testing Patients for Ph-like Events. A flow chart for processing samples is shown. Samples that are positive by LDA are excluded if they have *BCR-ABL1* or *ETV6-RUNX1*. Remaining samples are evaluated for the presence of high CRLF2. Those that are positive by either FISH or *P2RY8-CRLF2* PCR continue testing for JAK mutations. Those that are negative for *CRLF2* fusions are tested by multiplex PCR and Archer sequencing for kinase-associated fusions and confirmed with singleplex PCR and bi-directional Sanger sequencing. The high CRLF2 cases that are negative for detectable fusions also continue for JAK mutation testing (in the event that a new *CRLF2* fusion might exist). All Ph-like cases that are negative for all assays are then analyzed by research level next generation sequencing.

To summarize the testing algorithm, all NCI HR patients will be tested via LDA and those with a score ≥0.5 (range of possible scores is 0-0.99) are considered positive. Any cases with *BCR-ABL1* or *ETV6-RUNX1* (RQ-PCR assays for both are included on the LDA card) are excluded from further testing, because the targetable lesion has been identified (*BCR-ABL1*) or we know that concomitant targetable kinase activating lesions occur rarely, if at all (*ETV6-RUNX1*; unpublished data). *CRLF2* is one of the 8 genes that define Ph-like ALL, and *P2RY8-CRLF2* is also tested for on the LDA card. Cases that are Ph-like and $CRLF2_{high}$, but negative for *P2RY8-CRLF2* undergo fluorescence in situ hybridization (FISH) testing to detect other *CRLF2*-rearrangements (almost all of which are *IGH-CRLF2*). All *CRLF2*-rearranged cases undergo JAK mutation testing by targeted amplification and sequencing. Ph-like ALL cases that are $CRLF2_{low}$ move directly to mPCR testing for gene fusions, as do cases that are Ph-like and $CRLF2_{high}$ that do not have *CRLF2*-R (about 10-15% of $CRLF2_{high}$, 40% of which have kinase fusions).

In the discovery phase of our studies, Ph-like cases without identified lesions have undergone RNA sequencing (RNAseq), with whole genome sequencing also performed on selected cases. Funded under the NCI Director's Challenge and the NCI Strategic Partnerships to Evaluate Cancer Gene Signatures (SPECS) Programs, Dr. Willman's laboratory first discovered Ph-like ALL through analysis of microarray-derived gene expression profiles (GEP; using Affymetrix U133.0_Plus_2 arrays that interrogate expression using 54,675 probe sets) using predictive analysis of microarray (PAM) analysis and other statistical approaches. Using extensive supervised learning methods and leave-one-out cross-validation on appropriately designed training and test sets, the Willman laboratory has identified a limited set of genes whose quantitative expression in ALL blasts is highly predictive of Ph-like ALL. Assays for

this limited set of genes, initially identified on microarrays, were converted to measurement in direct quantitative RT-PCR assays on a clinically validated diagnostic platform (low density array (LDA) cards). With a predictive statistical algorithm, these assays can rapidly identify Ph-like ALL vs. non-Ph-Like ALL patients with very high sensitivity and specificity. The top two predictive models [one including the expression of 8 genes and the second a larger set of 15 genes (inclusive of the first 8 genes)] were able to predict Ph-like ALL in an independent test set with a high degree of sensitivity (98.1%) and specificity (88.7%). Furthermore, this assay and algorithm have successfully identified many of the Ph-like ALL patients with potentially targetable kinase fusions to date, despite a highly heterogeneous spectrum of underlying genomic lesions associated with Ph-like ALL[80], including many new kinase fusions not present in the original training set (unpublished data). To confirm the clinical utility and diagnostic accuracy of the LDA screening assay in a CLIA-approved laboratory, we retrospectively analyzed 780 high-risk B-precursor ALL patients enrolled in COG High Risk ALL Clinical Trials P9906 and AALL0232 and examined correlations between the Ph-like ALL phenotype and clinical outcome. The ~25% of patients that were predicted to have Ph-like ALL by the LDA card had a significantly worse EFS than other high-risk ALL patients and were greater than three times more likely to die (Loh, Blood, 2013).[106] The specific Ph-like features factored heavily in these poor outcome results, and each of the major potentially targetable classes was significantly associated with an increased risk of treatment failure and death.

These LDA screening studies led to the ultimate identification of 21 Ph-like ALL patients with underlying kinase fusions involving *ABL1*, *ABL2*, *CSF1R* or *PDGFRB* (Figure 2A), 12 cases (Figure 2B) with fusions involving *EPOR* (n=5) or *JAK2* (n=7), and 45 cases (Figure 2C) with *CRLF2* genomic rearrangements and JAK point mutations. Patients with Ph-like ALL who had *CRLF2* rearrangements, about of half of whom have *JAK* point mutations (Figure 2C) also had very poor outcomes.

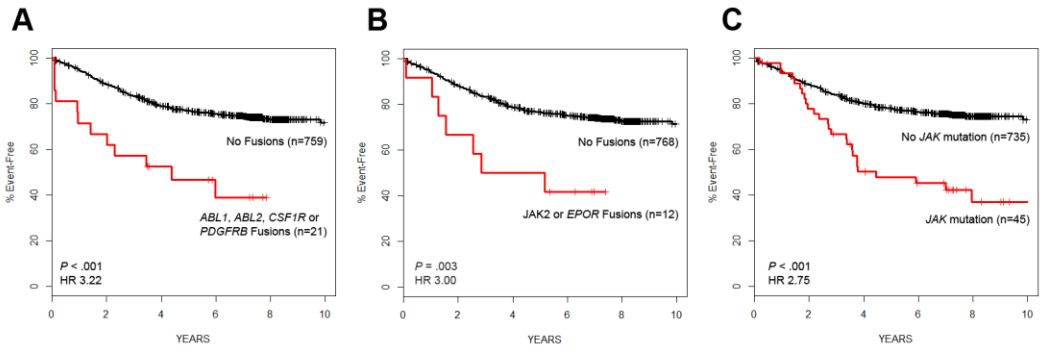


Figure 2. Event-free Survival of Ph-like Events in AALL0232 and P9906. **A.** Outcome of tyrosine kinase fusions (*ABL1*, *ABL2*, *CSF1R* and *PDGFRB*). **B.** Outcome of *EPOR* or *JAK2* fusions. **C.** Outcome of *JAK1* or *JAK2* point mutations. Note: There is no overlap among the cases with JAK mutations vs JAK fusions.

Specimens and processing

Diagnostic bone marrow and peripheral blood samples will be submitted as per usual protocol (either AALL08B1 or APEC14B1 (*if available for ALL patients*)) to Nationwide Children's Hospital. Samples will be processed after initial blast count is determined and nucleic acids will be extracted. The test material for these assays is cDNA generated from total RNA that has been isolated from samples of leukemic peripheral blood or bone marrow with at least 25% leukemia blasts present. In the event that a sample with less than 25% blasts is submitted for analysis and is Ph-like negative, the result will be considered unsatisfactory. A Ph-like positive result will be considered satisfactory. In brief, one microgram of total RNA is converted to cDNA and then diluted to a volume of 50 µL with distilled water. This diluted cDNA is mixed with an equal volume of an amplification cocktail (also known as master

mix) containing Taq polymerase, salts, buffers and dNTPs for performing PCR reactions. A control QT-PCR assay to assess expression of *EEF2* will be performed. Once a sample is identified to be suitable for the LDA assay, the sample will be batched and shipped (samples are shippedtwice weekly) to the University of New Mexico, where the LDA assay will be run. The University of New Mexico will utilize an algorithm (Figure 1 above) to determine which samples who will require additional downstream testing and clinical research forms have been designed for eRDE data entry and transmittal to Nationwide Children's Hospital. Once received by Nationwide Children's Hospital, the appropriate molecular testing will be performed using a combination of qualitative RT-PCR and RNA sequencing. Regardless of methodology, a singleplex RT-PCR followed by bidirectional sequencing will be performed to confirm all results priorto entry into the eRDE. Local institutions will have access to the relevant results of this testing that will potentially make patients eligible to enroll in clinical trials testing dasatinib + chemotherapy if positive for an ABL-class fusion (AALL1131), or ruxolitinib + chemotherapy (AALL1521) if positive for a CRLF2 or JAK/STAT pathway lesion. Currently the 3' fusion partners that will be eligible for dasatinib on AALL1131 include *ABL1*, *ABL2, PDGFRB*, and *CSF1R*, as all have extensive data demonstrating in vitro response to imatinib or dasatinib.[80]

Description of Additional Methodologies for Actionable Fusion Identification

Following our retrospective studies, the testing algorithm (Figure 1) was assessed prospectively for 6 months in early 2016 to optimize the workflow and data management. There are a wide variety of ABL-class (currently at least 13 *ABL1* fusions, 3 *ABL2* fusions, 3 *CSF1R* fusions, and 8 *PDGFRB* fusions, many of which have a variety of different breakpoints) and *JAK2* fusions (21 known currently), which are initially identified using a series of multiplex and singleplex (MP/SP) RT-PCR assays (Table 1). Confirmatory bi-directional Sanger sequencing is then performed and *patients are only eligible to enroll in the AALL1131 dasatinib arm (or AALL1521) if an in-frame fusion transcript is identified by Sanger sequencing*. When this screening strategy was activated in real-time in August of 2016, we knew that the number of fusion partners and breakpoints was likely to expand as more patients were analyzed.

Table 1. Currently available fusions identified by the MP/SP assay at Nationwide (note: the dasatinib sensitive arm only allows enrollment of *ABL1, ABL2, PDGFRB*, and *CSF1R* fusions)

ABL1 Fusions	
5' gene	3' gene
NUP214	*ABL1*
*ETV6***	
ZMIZ1	
RCSD1	
RANBP2	
FOXP1	
NUP153	
SFPQ	
SPTAN1	
LSM14A	
CENPC	
SNX2	

JAK Fusions	
5' gene	3' gene
*BCR***	*JAK2*
STRN3	
PAX5	
ATF7IP	
EBF1	
ETV6	
TERF2	
*SSBP2***	
PCM1	
ZNF274	
RFX3	

Kinase Fusions	
5' gene	3' gene
ZC3HAV1	*ABL2*
PAG1	
RCSD1	
EBF1	*PDGFRB*
TNIP1	
ETV6	
ZEB2	
ATF7IP	
AGGF1	
ETV6	*NTRK3*
MYB	*TYK2*
SSBP2	*CSF1R*
TBL1XR1	
HOOK3	*FGFR1*

**Includes alternate breakpoints

While we expected that the AALL1131 screening strategy would miss some kinase fusions, a lower than expected detection rate led the ALL committee to strategize using more advanced technologies to improve the initial identification of alternate transcript breakpoints and novel 5' fusion partners, resulting in implementation of Archer® sequencing technologies as a screening measure. To identify as many targetable kinase fusions as possible prior to the end of AALL1131 induction therapy, all LDA positive

patients requiring downstream molecular testing started having MultiPlex (MP)/SinglePlex (SP)-RT-PCR performed in parallel with Archer® sequencing since April 3, 2017. As before, all positive results from the MP/SP-PCR or Archer screening studies then undergo SP RT-PCR with bi-directional Sanger sequencing and *patients are only eligible to enroll in the AALL1131 dasatinib arm (or AALL1521) if an in-frame fusion transcript is identified by Sanger sequencing*. Thus implementation of new screening strategies has not altered the trial eligibility rules. It has become clear that that by using Archer or similar RNA based technologies, our strategy will enable us to identify fusions in a higher percentage of cases, allowing patients to enroll on the post-induction dasatinib arm of AALL1131. These RNA sequence-based technologies are planned to replace MP RT-PCR testing due to higher sensitivity and ability to detect fusions with known 5' partners that have alternative splice forms and fusions with previously unknown 5' partners. We anticipate that as the study progresses and unbiased RNA-sequencing becomes a standard clinical assay, implementation of full RNA-sequencing will allow for the highest detection rate of targetable fusions. Regardless of methodology, all testing will be performed in a CAP/CLIA certified laboratory. The Archer FusionPlex® Pan-Heme capture kit (currently used version but we anticipate this kit will continue to be updated and we will use newer versions of these kits as they are validated) has been extensively validated by Nationwide Children's Hospital for the detection of known and novel fusions in B-ALL. Detailed information about the technical specifications of the kit can be found at (http://archerdx.com/fusionplex-assays/fusionplex-pan-heme-kit?mid=nav). In short, the kit is an Anchored MultiPlex PCR-based next-generation sequencing (NGS) assay that generates target-enriched libraries containing over 199 genes, including *ABL1, ABL2, CSF1R, JAK2*, *PDGFRB*, *EPOR*, and others related to lymphoid and myeloid malignancies. The chemistry utilizes unidirectional gene-specific primers (GSPs) to amplify into molecular barcodes ligated onto cDNA fragment ends, enabling the identification of both known and novel fusions. The Archer® Analysis software then uses the molecular barcodes for duplicated read binning, error correction, and read deduplication to support multiplex data analysis and confident fusion detection, reporting both sequencing metrics and number of unique observations supporting the called fusion variants. While the Archer® assay is capable of fusion quantitation, the software validation has been limited to qualitative assessment of fusions and will not be used to measure minimum residual disease (MRD) in subsequent samples. Although the assay requires a minimal amount of RNA (20 ng); the sample must be of good quality as determined by a preliminary internal test of cDNA with an *EEF2* housekeeping gene.

The Archer®sequencing technology will provide enriched and unbiased screens for the ABL-class fusions and as well as *EPOR* rearrangements and other fusions by capturing splice variants and novel partners that might not otherwise be identified using the current mPCR RT-PCR strategy that is based on specific primer design. It should be noted that although the kit contains the *CRLF2* gene that is rearranged in many Ph-like ALL patients, alterations and fusions of this gene are also present in non-primary leukemic cell populations, and will therefore be quantitatively screened for by LDA (see above). Any potential fusion identified by any RNA sequencing based methodology will subsequently be confirmed by SP RT-PCR of the fusion followed by bidirectional Sanger sequencing to confirm the presence of an in-frame fusion that retained the kinase domain of the 3' partner. Importantly, risk assignment to the dasatinib arm will only be possible if the fusion is verified using bidirectional Sanger sequencing. It should be noted that inclusion of Archer® technologies into the current downstream pipeline necessitated updating the algorithm to ensure that results could be obtained by Day 29 (or Day 35) of induction. This is largely due to the additional time required to prepare samples for next generation sequencing. We will therefore begin processing samples for the Archer assay upon receiving results of the LDA screening. Any case determined to be LDA positive (Ph-like), *CRLF2*$_{high}$ with a >4.0 ΔC_t value that is also negative for the *P2RY8-CRLF2* fusion will immediately be put in the queue for Archer® testing (Figure 3). The Archer® platform cannot detect *CRLF2* rearrangements and detects a subset of *EPOR* truncating alterations.

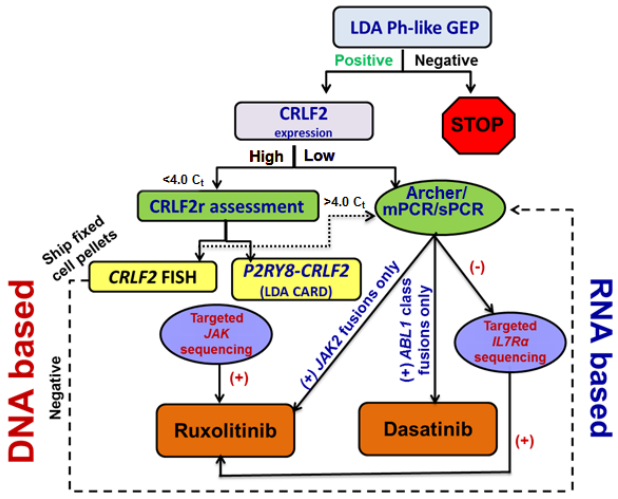


Figure 3. Updated Downstream Testing Algorithm for LDA- positive Samples (additional dotted arrow for assessment of >4 ΔC_t by Archer®)

Scoring procedures/criteria for positive/cut points

A summary of the algorithm used to identify patients who are Ph-like is depicted in Figure 1. An LDA score of > 0.5 (range of possible scores 0.0-0.99) without the presence of *BCR-ABL1* or *ETV6/RUNX1* will indicate that additional molecular testing is required. If the patient overexpresses CRLF2 with a delta Ct (ΔC_t) of < 6.0 and is *P2RY8-CRLF2* positive, additional JAK point mutation analyses will be performed. If the *P2RY8-CRLF2* is negative, confirmatory FISH will be performed to determine disruption of *CRLF2*; however 96% of patients with a CRLF2 delta Ct < 4.0 have been shown in multiple analyses to have a *CRLF2* rearrangement, generally associated with *IgH* fusion. However, *CRLF2* rearranged patients are not the focus of the AALL1131 protocol and will not be further discussed here.

Expected population and distribution

We have now used the LDA card to screen three large cohorts of ALL patients, including two from AALL1131 (1389 patients in cohort 1 and 961 patients in cohort 2) and a cohort of 1023 SR ALL patients from COG AALL0331 (See Table 2 below). The relevant AALL1131 patients will comprise the historical controls treated without TKI, to which we will later compare outcome of those treated with chemotherapy plus TKI. Based on the largely negative results from the SR ALL patients, we will only subject NCI HR patients to this screening process.

Table 2. Incidence of Ph-like genetic lesions screened in retrospective cohorts.

	AALL1131 #1 N=1389	**AALL1131 #2** N=961	**AALL0331 SR ALL** N=1023
Ph-like, no *BCR-ABL1* or *ETV6-RUNX1*	285 (20.5%)	187 (19.5%)	146 (14.3%)
$CRLF2_{high}$	155 (54.4% of Ph-like)	96 (51.3% of Ph-like)	84 (57.1% of Ph-like)
P2RY8-CRLF2	61 (39%)	36 (37.5%)	36 (42.9%)
IGH-CRLF2	61 (39%)	27 (29%)*	4 (4.8%)
Total *CRFL2*-R	122 (79%)	64 (68.9%)**	40 (47.6%)
CRLF2-R +JAK_{mut}	56/122 (46%)	16/64 (25%)	13/40 (32.5%)
$CRLF2_{low}$	130 (45.6% of Ph-like)	91 (48.7% of Ph-like)	62 (42.5% of Ph-like)
ABL class fusion	40 (30.4%)	9 (9.9%)	2 (3.2%)
JAK2 fusion	14 (10.8%)	6 (6.6%)	1 (1.6%)
EPOR-R	11 (8.5%)	Pending	Pending
NTRK3 fusion	1 (0.8%)	0	1 (1.6%)

*FISH not done for 3 *P2RY8-*$CRLF2_{neg}$ cases; **One *CRLF2*-R with unknown partner

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