Supplemental Online Content

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Supplement 1. Trial protocol

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CHILDREN'S ONCOLOGY GROUP

AALL1331

Risk-Stratified Randomized Phase III Testing of Blinatumomab (*IND# 117467*, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

IND Sponsor for Blinatumomab: DCTD, NCI

A Groupwide Phase III Study
Participating Countries: Australia, Canada, New Zealand and United States

STUDY CHAIR

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ABBREVIATIONS

Abbreviation	Term
aGVHD	Acute graft versus host disease
B-ALL	B-Lymphoblastic Leukemia
CR	Complete remission
DFS	Disease free survival
GVHD	Graft vs. host disease
HR	High risk
HSCT	Hematopoietic stem cell transplant
IEM	Isolated extramedullary
IR	Intermediate risk
IS	Immune suppression
LR	Low risk
MRD	Minimal residual disease
PFS	Progression free survival
Ph^+	Philadelphia chromosome positive
TF	Treatment failure
TKI	Tyrosine kinase inhibitor
URD	Unrelated Donor

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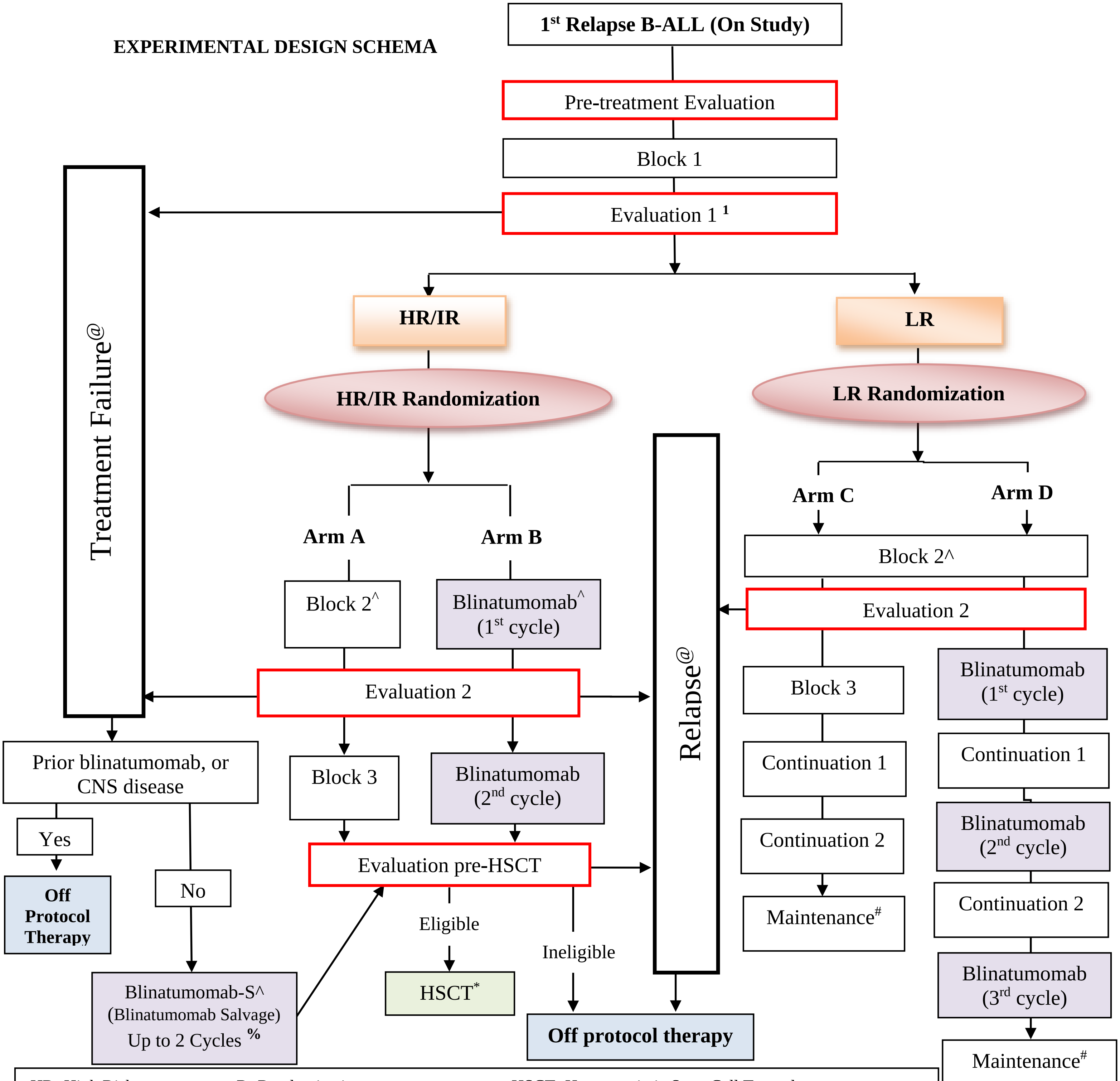
ABSTRACT

AALL1331 is a group wide risk-stratified, randomized Phase III study to test whether incorporation of blinatumomab into the treatment of patients with childhood B-Lymphoblastic Leukemia (B-ALL) at first relapse will improve disease free survival. Blinatumomab is being tested in this population based on its demonstrated safety profile and single agent activity (induction of MRD-negative remissions in children with multiple relapsed refractory B-ALL).

AALL1331 risk stratification is determined based on site of relapse [marrow versus isolated extramedullary (IEM)], time to relapse and minimal residual disease (MRD) status following a uniform first block of chemotherapy. High risk (HR) and intermediate risk (IR) patients will be eligible for randomization to either a control arm with two additional blocks of chemotherapy, or an experimental arm with two blocks of blinatumomab. Both arms will proceed to protocol-specified hematopoietic stem cell transplant (HSCT) that includes a rapid taper of immune suppression for patients with residual disease and no graft vs. host disease (GVHD). Low risk (LR) patients will be eligible for randomization to either a control arm with two blocks of chemotherapy followed by continuation and maintenance chemotherapy, or an experimental arm with one block of chemotherapy, 2 blocks of blinatumomab, each followed by continuation and a third additional block of blinatumomab followed by maintenance.

AALL1331 includes correlative laboratory studies to refine risk stratification, identify new targets for therapy, identify biomarkers to predict response to chemotherapy and blinatumomab, and to link host polymorphisms with various disease characteristics and toxicities.

EXPERIMENTAL DESIGN SCHEMA



HR=High Risk R=Randomization HSCT=Hematopoietic Stem Cell Transplant
IR=Intermediate Risk CR=Complete response LR=Low Risk

@ See Section 3.3 for definitions of treatment failure and relapse.

1 Post Block 1 Evaluation Callback (completed via OPEN)

CNS3 patients receive chemoradiation post Maintenance Cycles 1

* Patient may receive bridge therapy prior to HSCT

^ Patients with persistent testicular involvement after Block 1 will receive testicular radiation (TRT) during designated blocks

% Evaluation pre-HSCT at end of each cycle. See Section 4.7.6 and 4.8.5 for details

+ Patients who achieve remission at end-Block 1 or 2 but are no longer in remission on a subsequent evaluation will be removed from protocol therapy for relapse.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To compare disease free survival (DFS) of HR and IR relapse B-ALL patients who are randomized following Induction Block 1 chemotherapy to receive either two intensive chemotherapy blocks or two 5-week blocks of blinatumomab (HR/IR Randomization).

1.1.2 To compare DFS of LR relapse B-ALL patients who are randomized following Block 1 chemotherapy to receive either chemotherapy alone or chemotherapy plus blinatumomab (LR Randomization).

1.2 Secondary Aims

1.2.1 To compare overall survival (OS) of HR and IR relapse B-ALL patients who are randomized following Induction Block 1 chemotherapy to receive either two intensive chemotherapy blocks or two 5-week blocks of blinatumomab (HR/IR Randomization).

1.2.2 To compare OS of LR relapse B-ALL patients who are randomized following Block 1 chemotherapy to receive either chemotherapy alone or chemotherapy plus blinatumomab (LR Randomization).

1.3 Exploratory Aims

1.3.1 To compare the rates of MRD $\geq$ 0.01% at the end of Block 2 and Block 3 for HR and IR relapse B-ALL patients in HR/IR randomization.

1.3.2 To estimate, for treatment failure (TF) patients not previously receiving blinatumomab, the hematologic complete remission rate (CR), rate of MRD $<$ 0.01%, and proportion able to proceed to hematopoietic stem cell transplant (HSCT) in CR after treatment with blinatumomab.

1.3.3 To assess the feasibility and safety of rapid taper of immune suppression for the subset of HSCT patients with MRD $\geq$ 0.01% pre- and/or post-HSCT with no acute graft versus host disease (aGVHD)

[redacted]

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

Note: This study is not on the CTSU Menu (i.e. it is not posted to the CTSU web site) but is supported by the CTSU Regulatory Office, OPEN and Rave.

3.1.1 Patient Registration

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

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

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

Please see Appendix XIII for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirement s for site registration, submission of regulatory documents and how to check your site’s registration status.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

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

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

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. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on 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

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

See Section 3.1.6 below for details regarding randomization and treatment assignment for patients.

3.1.4 Timing

Informed consent: Except for administration of intrathecal chemotherapy, *informed consent/parental permission* MUST be signed before protocol therapy begins. See Section 3.1.5 for summary of time points to obtain informed consent.

Study enrollment: Study enrollment 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 that 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. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment.

3.1.5 Staged Consent

Informed consent will be obtained at critical stages of treatment for the different groups of patients on this study (see summary table below). Informed consent that describes Block 1 therapy (common to all patients on study) will be obtained before starting treatment. At the end of Block 1 therapy, after LR and IR risk groups have been assigned, subsequent informed consent that describes further therapy will be obtained at the various time points detailed in Table 8 below. Also see Experimental Design Schema

Table 8: Summary of required consents for AALL1331

Consent Form	Time point to Obtain Consent	Population for Consent	Post Induction exclusion criteria
Consent for additional marrow	Before study entry	All potential subjects	
Block 1 consent	Study Entry (Prior to start of Block 1)	All subjects (HR, IR, LR)	
Consent for HR/IR randomization and HSCT	End Block 1 evaluation (prior to start of post-Block 1 therapy)	HR/IR	3.2.5.14
Consent for LR randomization	End Block 1 evaluation (prior to start of Block 2)	LR	3.2.5.14
Consent for salvage therapy and HSCT	Prior to Blinatumomab-S (immediately following treatment failure):	Treatment Failures (TF):	
	• End Block 1	HR/IR	
	• End Block 2	HR/IR on Arm A	

3.1.6 Risk Assignment and Randomization

- End-Block 1 response evaluation (detailed in Section 4.2).

  Risk assignment according to the criteria outlined in Section 3.3 will occur prior to submission of end-Block 1 callback. Consenting IR and HR patients will be randomized according to HR/IR Randomization upon submission of callback. Consenting LR patients will be randomized according to LR Randomization upon submission of callback.

3.1.7 Callback for Randomization

Callback	Timing	Population for Callback	Purpose
Post Block 1 Callback	End Block 1 evaluation*	Consenting LR patients not off protocol therapy after completion of Block 1 therapy. Consenting HR or IR patients not off protocol therapy after completion of Block 1 therapy	Randomize LR patients to either of 2 treatment arms: **Arm C** (Control Arm) or **Arm D** (Experimental Arm). Randomize HR/IR patients to either of 2 treatment arms: **Arm A** (Control Arm) or **Arm B** (Experimental Arm).

*See Section 3.1.10 for timing details

3.1.8 Drug Preparation and Administration

Sites must attest that their drug preparation and administration guidelines comply with the USP. Each site's standard procedure for compounding blinatumomab must be in compliance with USP <797> guidelines (ISO Class 5 or better). Documentation of participating site training with regard to the preparation and administration of blinatumomab must be submitted via RSS as protocol specific requirement at the time of site activation for participation on the trial.

3.1.9 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.

3.1.10 **IMPORTANT NOTE:**

In order to continue to receive protocol therapy, patients will need to begin post-Block 1 therapy according to risk assignment and randomization within a specified time frame (see Section 4.2). If a patient has residual severe non-hematologic toxicities from Block 1 that are likely to preclude beginning post-Block 1 therapy within this time frame, please DO NOT complete end-Block 1 Callback for the patient. This is important to minimize the number of patients who are randomized but are unable to receive post-randomization treatment.

Submission of end-Block 1 Callback must occur within 5 days of response evaluation if patient is not found to be TF (callback data will include local morphologic assessment, central flow MRD result and confirmation of continued eligibility for blinatumomab treatment-see Section 3.2).

3.2 **Patient Eligibility Criteria**

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

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age

Patients ≥1 year and < 31 years of age at the time of relapse will be eligible.

3.2.2 Diagnosis

First relapse of B-ALL with or without extramedullary disease.

Please refer to Section 3.3 for definitions of relapse and criteria for risk classification.

3.2.3 Prior Therapy

Please see Section 4.1.2 for the concomitant therapy restrictions for patients during treatment.

3.2.3.1 No waiting period for patients who relapse while receiving standard Maintenance therapy

3.2.3.2 Patients who relapse on frontline therapy in phases other than Maintenance must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

3.2.3.3 Cytotoxic therapy: At least 14 days since the completion of cytotoxic therapy with the exception of hydroxyurea, which is permitted up to 24 hours prior to the start of protocol therapy, or Maintenance chemotherapy (see Section 3.2.3.1).

3.2.3.4 Biologic (anti-neoplastic) agent: At least 7 days since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

3.2.3.5 Stem cell transplant or rescue: Patient has not had a prior stem cell transplant or rescue.

3.2.3.6 Patient has not had prior treatment with blinatumomab.

3.2.4 Performance Status

Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Please refer to performance status scale at: https://members.childrensoncologygroup.org/_files/protocol/Standard/PerformanceStatusScalesScoring.pdf

3.2.5 Organ Function Requirements

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 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
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.[37]

3.2.5.2 Adequate liver function defined as a direct bilirubin < 3.0 mg/dL.

3.2.5.3 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram.

3.2.6 Exclusion Criteria

3.2.6.1 Patients with Philadelphia chromosome positive/BCR-ABL1+ ALL are not eligible

3.2.6.2 Patients with Burkitt Leukemia/Lymphoma or mature B-cell leukemia are not eligible

3.2.6.3 Patients with T-Lymphoblastic Leukemia (T-ALL)/Lymphoblastic Lymphoma (T- LL) are not eligible

3.2.6.4 Patients with B-Lymphoblastic Lymphoma (B-LL) are not eligible

3.2.6.5 Patients with known optic nerve and/or retinal involvement are not eligible. Patients who are presenting with visual disturbances should have an ophthalmologic exam and, if indicated, an MRI to determine optic nerve or retinal involvement.

3.2.6.6 Patients known to have one of the following concomitant genetic syndromes: Down syndrome, Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome.

3.2.6.7 Patients with known HIV infection.

3.2.6.8 Patients with known allergy to mitoxantrone, cytarabine, or both etoposide and etoposide phosphate (Etopophos).

3.2.6.9 Lactating females who plan to breastfeed.

3.2.6.10 Patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.

3.2.6.11 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

3.2.6.12

a.) Patients with pre-existing significant central nervous system pathology that would preclude treatment with blinatumomab, including: history of severe brain injury, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination /movement disorder, or autoimmune disease with CNS involvement are not eligible. Patients with a history of cerebrovascular ischemia/hemorrhage with residual deficits are not eligible. (Patients with a history of cerebrovascular ischemia/hemorrhage remain eligible provided all neurologic deficits have resolved)

b.) Patients with uncontrolled seizure disorder are not eligible. (Patients with seizure disorders that do not require antiepileptic drugs, or are well controlled with stable doses of antiepileptic drugs remain eligible.)

3.2.7 Regulatory Requirements

3.2.7.1 All patients and/or their parent or legal guardian must sign a written informed consent.

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

3.3 Definitions

Acute Lymphoblastic Leukemia (ALL)
Bone marrow with > 25% L1 or L2 lymphoblasts (M3 marrow). Patients with > 25% L3 marrow lymphoblasts and/or evidence of c-*myc* translocation are considered to have Burkitt or mature B-cell leukemia and are ineligible for this study.

Definitions of Relapse

RELAPSE:
Any recurrence of disease whether in marrow or extramedullary. Relapse should be confirmed by pathology examination of appropriate tissue.

ISOLATED BONE MARROW RELAPSE: Patients with an M3 marrow at any point after achieving remission without involvement of the CNS and/or testicles. Every effort should be made to confirm morphologic relapse using flow cytometry, FISH and/or cytogenetics.

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 that are, in the opinion of the investigator, more likely due to recurrent CNS leukemia than to alternative causes (e.g., viral infection or chemotherapy toxicity). If any CSF evaluation shows positive cytomorphology and WBC < 5/μL, a second CSF evaluation is recommended 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. Note that AALL1331 excludes patients with known optic nerve and/or retinal involvement (Section 3.2.5.4).

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

ISOLATED EXTRAMEDULLARY (IEM) RELAPSE: CNS and/or testicular relapse with an M1 marrow. The presence of MRD in the bone marrow does NOT exclude IEM.

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

CNS Status:

NOTE: in this protocol "CNS-positive" means meeting the criteria for CNS Relapse (whether isolated CNS or combined relapse) at the time of AALL1331 study entry as listed in the Definitions of Relapse above. CNS 2 status first noted at the time of enrollment for concurrent relapse at another site (i.e. bone marrow) will not be considered 'CNS-positive'.

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 ≥ 5/μL WBCs 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, 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 algorithm should be used to distinguish between CNS 2 and CNS 3 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:

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

Bone Marrow Status:

M1 Marrow: < 5% blasts in a bone marrow aspirate with at least 200 cells counted.

M2 Marrow: 5% - 25% blasts in a bone marrow aspirate with at least 200 cells counted.

M3 Marrow: > 25% blasts in a bone marrow aspirate with at least 200 cells counted.

For **initial remission** an M1 marrow must be achieved.

Treatment Failure: Failure to achieve the following:

	Marrow	CNS	Testicular
End-Block 1 (All patients)	M2 or better	Remission (clearance of CSF blasts, i.e. CNS1)	None; patients with persistent testicular disease will receive testicular radiation in Block 2 (LR and HR/IR randomized to the control arm) or during Blinatumomab Block: Cycle 1 (HR/IR randomized to the experimental arm)
End-Block 2, or End Blinatumomab Block, Cycle 1 (HR/IR only)	M1	Continued remission	Remission (clearance of testicular disease)

NOTE: Patients who achieve remission at end-Block 1 or Block 2 but are no longer in remission on a subsequent evaluation will be removed from protocol therapy for relapse.

Risk Assessment-Post Block 1*:

Low Risk

- Late marrow (≥ 36 months); end-Block 1 MRD < 0.1%
- Late (≥ 18 months) Isolated Extramedullary (IEM), end-Block 1 MRD < 0.1% (or indeterminate MRD)

Intermediate Risk

- Late (≥ 36 months) marrow, end-Block 1 MRD ≥ 0.1%

- Late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%

High Risk

- Early (< 36 months) marrow
- Early (< 18 months) IEM

***** The timing of relapse is measured from the date of initial diagnosis to the date of relapse

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

All eligible patients with first relapse B-ALL who are enrolled on AALL1331 will receive standard chemotherapy during Block 1. All patients will then be risk assessed at the end of Block 1 as either HR, IR, LR or TF. Risk assessment is based on site of relapse, time to relapse, end Block 1 bone marrow morphology and MRD levels. HR and IR patients will be eligible to participate in HR/IR Randomization and LR patients will be eligible to participate in LR Randomization. See summary table below. Treatment failures are those patients whose disease status fails to meet pre-defined response criteria at end-Block 1 or end-Block 2. These patients are eligible to receive up to 2 blocks of blinatumomab if they have not previously received it on study and have no evidence of persistent CNS disease. These patients will also be eligible to continue on to HSCT if they achieve a morphologic CR. Otherwise, they will be removed from protocol therapy. See Section 3.3 for response definition of TF.

Risk Stratification at end Block 1

Risk Group	Definition	Randomization Eligibility	Treatment Arms
High	• Early (< 36 months) marrow • Early (< 18 months) IEM	HR/IR	• Arm A (Control) • Arm B (Experimental)
Intermediate	• Late (≥ 36 months) marrow, end-Block 1 MRD ≥ 0.1% • Late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%	HR/IR	• Arm A (Control) • Arm B (Experimental)
Low	• Late (≥ 36 months) marrow, end-Block 1 MRD < 0.1% • Late (≥ 18 months) IEM, End-Block 1 MRD < 0.1%	LR	• Arm C (Control) • Arm D (Experimental)
Treatment Failure at end Block 1	Failure to achieve the following: • M2 or better • CNS remission (clearance of CSF blasts, i.e. CNS1)	None	• Salvage therapy (TF)

<u>Hospitalization:</u>

Hospitalization is STRONGLY recommended during the first 3 days of the first blinatumomab Cycle and the first 2 days of subsequent blinatumomab cycles in case of a cytokine reaction.

CNS Leukemia
All patients with CNS3 involvement at the time of relapse will receive intrathecal triples (ITT) instead of IT MTX. During Block 1 these patients will receive two additional ITT doses and during Block 2 they will receive one additional ITT dose. For LR patients with CNS3 involvement, AALL1331 will further intensify CNS-directed therapy by replacing lower dose oral MTX (25 mg/m^2 every 6 hours x 4 doses) with intermediate dose IV MTX (1 g/m^2 over 24 hours) during the each of the 2 continuation phases. All of these patients will then receive 1800 cGy cranial radiation and concurrent chemotherapy (including high dose dexamethasone) between and the first and second 12 week blocks of Maintenance. IR and HR patients will proceed to TBI-based HSCT and these patients will also receive a protocol-specified cranial radiation boost as part of their HSCT preparative regimen.

Testicular Leukemia
Patients with suspected isolated testicular relapse or equivocal testicular enlargement with concurrent bone marrow/CNS relapse must have a testicular biopsy performed at baseline. Patients with persistent or equivocal testicular enlargement at the end of Block 1 must have a testicular biopsy. Patients with persistent testicular leukemia at the end of Block 1 are eligible to continue on study and will receive 2400 cGy of testicular radiation during either Block 2 chemotherapy (for LR patients and HR/IR patients randomized to the control arm) or during blinatumomab (for HR/IR patients randomized to the experimental arm and TF.) Patients with extramedullary testicular leukemia that has resolved by end Block 1 will NOT receive testicular irradiation, with the exception of that which may be used in the HSCT preparative regimen for HR/IR patients.

HSCT
All patients enrolled on this protocol, their parents and full siblings should undergo HLA tissue typing as soon as possible after diagnosis of relapse, and should have transplantation consultation and initiation of a donor search. For HR/IR patients, and for TF patients who achieve remission with blinatumomab salvage, the goal of this protocol is to move to transplant within 2 weeks of recovery from the last block/cycle of therapy prior to transplant. Because unrelated donor acquisition can take 8-12 weeks, centers must expedite the donor search process to meet this deadline.

Patient Pill Diary
It is recommended that patients use a Patient Pill Diary to keep track of oral medications.

4.1.1 TREATMENT ASSIGNMENTS

4.1.1.1 HR/IR Randomization

IMPORTANT NOTE:

In order to continue to receive protocol therapy, patients will need to begin post-Block 1 therapy according to risk assignment and randomization within a specified time frame (see Section 4.2). If a patient has residual severe non-hematologic toxicities from Block 1 that are likely to preclude beginning post-Block 1 therapy within this time frame, please DO NOT complete end-Block 1 Callback for the patient. This is important to minimize the number of patients who are randomized but are unable to receive post-randomization treatment.

Following submission of the end-Block 1 callback form HR and IR patients will be randomized to receive treatment on either of 2 treatment arms (see Experimental Design Schema):

- **Arm A (Control Arm)**: Patients receive Block 2 and Block 3 of standard therapy followed by HSCT.

- **Arm B (Experimental Arm)**: Patients receive two 5 week blocks of Blinatumomab, followed by HSCT.

4.1.1.2 **LR Randomization**

Following submission of the end-Block 1 callback form LR patients will be randomized to receive treatment on either of 2 treatment arms (see Experimental Design Schema):

- **Arm C (Control)**: Patients receive Block 2 and Block 3 of standard therapy followed by Continuation 1, Continuation 2, and Maintenance.

- **Arm D (Experimental)**: Patients receive Block 2 of standard therapy followed by a 5-week Blinatumomab Block, Continuation 1, a 5-week Blinatumomab Block, Continuation 2, a 5-week Blinatumomab Block, and Maintenance.

4.1.2 Concomitant Therapy Restrictions

4.1.2.1 **Cytochrome P450 Interactions with Antileukemic Drugs.**

Since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with anti-leukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes.[38] Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsants. 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 anti-leukemic 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	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS

voriconazole, ketoconazole)		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.[39,40]

For a more complete list of CYP3A4/5 Inhibitors and Inducers, go to: http://medicine.iupui.edu/flockhart/

4.1.2.2 **Possible Drug Interactions with 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://members.childrensoncologygroup.org/prot/reference_materials.asp

4.2 Block 1 (All patients) - 4 Weeks Duration

Block 1 therapy is common to all patients on study. See Experimental Design Schema. The therapy delivery map (TDM) for Block 1 is in APPENDIX II-A.

4.2.1 Disease Evaluation Pre-Treatment

See Section 7.0, Evaluations/Material and Data to be Accessioned

4.2.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.2.3 Block 1 Chemotherapy

Dexamethasone: PO (may be given IV)
Days: 1-5, 15-19
Dose: 10 mg/m²/dose (Total daily dose: 20 mg/m²/day, divided BID; dose capped at 40 mg per day)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days: 1, 8, 15, 22
Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Pegaspargase: IV over 1-2 hours
Days: 3, 17
Dose: 2500 International Units/m²/dose
Administer through the tubing of a rapidly infusing solution of D_5W or 0.9% NaCl

MitoXANTRONE: IV over 15-30 minutes, administered through the tubing of a rapidly infusing solution of D_5W or 0.9% NaCl.
Days: 1, 2
Dose: 10 mg/m²

Methotrexate: Intrathecal (IT) - CNS 1/2 PATIENTS ONLY
Days: 1, 8
Note: For CNS2 patients continue weekly IT until 2 clear CSF samples (CNS1) are obtained.

Age-based dosing:

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

Intrathecal Triple Therapy (ITT) - ANY PATIENT WITH CNS3 AT THE TIME OF RELAPSE
Days 1, 8, 15, and 22.

Age-based dosing:

Age (yrs)	Dose (mg)		
1 - 1.99	MTX: 8	HC: 8	ARAC: 16
2 - 2.99	MTX: 10	HC: 10	ARAC: 20
3 - 8.99	MTX: 12	HC: 12	ARAC: 24
≥ 9	MTX: 15	HC: 15	ARAC: 30

4.2.4 Disease Evaluation End Block 1

- The end-Induction evaluation should occur no earlier than Day 29 (± 1 day).
- The evaluation may be delayed no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- See Sections 7.1 and 13.0 for details on specimen acquisition, handling and shipping.

4.2.5 Research Studies Block 1

See Section 7.2 for a full list of research studies.

4.2.6 HLA Tissue Typing for Hematopoietic Stem Cell Transplant

All patients enrolled on this protocol, their parents and full siblings should undergo HLA tissue typing as soon as possible after diagnosis of relapse, and should have transplantation consultation and initiation of a donor search. The goal of this protocol is to initiate transplantation within 2 weeks of recovery from Block 3. Since unrelated donor acquisition can take 8-12 weeks, centers must expedite the search process to meet this timeframe.

4.2.7 Risk Assessment following Block 1

Following completion of Block 1, patients will be risk assessed based on end-Block 1 criteria outlined in Section 3.3, as HR, IR, LR, or TF.

IMPORTANT NOTE:

In order to continue to receive protocol therapy, patients will need to begin post-Block 1 therapy according to risk assignment and randomization within a specified time frame (see below). If a patient has residual severe non-hematologic toxicities from Block 1 that are likely to preclude beginning post-Block 1 therapy within this time frame, please DO NOT complete end-Block 1 Callback for the patient. This is important to minimize the number of patients who are randomized but are unable to receive post-randomization treatment.

Post-Block 1 treatment should begin after receipt of risk assignment and submission of end-Block 1 Callback (no callback submission for Post Block 1 TF patients) as soon as clinically acceptable to the treating institution. Patients should have time for full or partial recovery (judged by the treating institution) from any toxicities experienced in the prior course(s) of therapy before proceeding to the next course. However, treatment must begin according to time frames below for patients to continue to receive protocol therapy.**HR B-ALL or IR B-ALL patients with M1 marrow- Eligible for the HR/IR Randomization**

- For HR/IR B-ALL patients randomized to **Arm A**, Block 2 (Section 4.3, APPENDIX II-B) therapy should proceed with Day 1 vincristine and dexamethasone without awaiting count recovery (no later than 5 days after risk assignment). It is recommended, but not required, that proceeding with Day 8 IV methotrexate treatment await count recovery to ANC $\geq$ 500/µL and platelets $\geq$ 50,000/µL. Day 8 treatment must begin no later than 14 days after giving the Day 1 vincristine and dexamethasone to continue to receive protocol therapy.
- For HR/IR B-ALL patients randomized to **Arm B**, Blinatumomab Block - Cycle 1 (Section 4.5, APPENDIX II-D) starts when ANC $\geq$ 500/µL and platelets $\geq$ 50,000/µL (awaiting count recovery is recommended, but not required). Treatment must begin no later than 14 days after risk assignment for patient to continue to receive protocol therapy.

HR B-ALL or IR B-ALL patients with M2 marrow- Eligible for the HR/IR Randomization:

- For HR/IR B-ALL patients randomized to **Arm A**, Block 2 (Section 4.3, APPENDIX II-B) starts without awaiting count recovery (no later than 5 days after risk assignment).
- For HR/IR B-ALL patients randomized to **Arm B**, Blinatumomab Block - Cycle 1 (Section 4.5, APPENDIX II-D) starts without awaiting count recovery (no later than 5 days after risk assignment).

LR B-ALL Eligible for the LR Randomization

- All LR B-ALL patients (**Arm C and Arm D**) will receive Block 2 therapy (Section 4.3, APPENDIX II-B) and should proceed with Day 1 vincristine and dexamethasone without awaiting count recovery (no later than 5 days after risk assignment). It is recommended, but not required, that proceeding with Day 8 IV methotrexate treatment await count recovery to ANC $\geq$ 500/µL and platelets $\geq$ 50,000/µL. Day 8 treatment must begin no later than 14 days after giving the Day 1 vincristine and dexamethasone to continue to receive protocol therapy.

Treatment failures Post-Block 1 (see Section 3.3. for definition) have the option to receive up to two 5 week cycles of Blinatumomab (Sections 4.7, 4.8 and APPENDIX II-F, and II-G respectively) and continue on to HSCT after achieving morphologic CR.

- TF patients with residual CNS disease (CNS2/3) regardless of marrow status should be removed from protocol therapy.
- TF patients with M3 marrow disease and no residual CNS disease (CNS1) should proceed to Blinatumomab-S Cycle 1 without awaiting count recovery (no later than 5 days after risk assignment).

NOTE: If residual non-hematologic toxicities prevent a patient from beginning post Block-1 treatment within the time frames noted above, then the patient should be removed from protocol therapy.

4.3 Block 2 (HR/IR and LR Patients: Post-randomization) – 4 weeks duration

Block 2 therapy is for HR/IR patients, randomized to the control arm (**Arm A**) and all LR patients post LR randomization (**Arm C and Arm D**). See Experimental Design Schema.

The Therapy Delivery Map (TDM) for Block 2 is in APPENDIX II-B.

END-BLOCK 1 CALLBACK OCCURS PRIOR TO STARTING BLOCK 2 THERAPY. PLEASE SEE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON STAGED CONSENT, AND APPROPRIATE TIMING TO OBTAIN INFORMED CONSENT.

4.3.1 Criteria to Begin Block 2 Therapy

Block 2 should begin after receipt of risk assignment and submission of the appropriate end-Block 1 Callback as soon as clinically acceptable to the treating institution. Patients should have time for full or partial recovery (judged by the treating institution) from any toxicities experienced in the prior course(s) of therapy before proceeding to the next course. To continue to receive protocol therapy, however, Block 2 must begin no later than 5 days after risk assignment. Count recovery is not required to proceed to Block 2.

4.3.2 Testicular Radiation Therapy (TRT)

Patients with persistent testicular leukemia at the end of Block 1 are eligible to continue on study and will receive 2400 cGy of testicular radiation during either Block 2 chemotherapy (HR/IR patients randomized to the control arm, and all LR patients) or during the first cycle of Blinatumomab (for HR/IR patients randomized to the experimental arm).

- Patients with extramedullary testicular leukemia that has resolved by end Block 1 will NOT receive testicular irradiation with the exception of that which may be used in the HSCT preparative regimen.
- See Section 14.2 for detailed testicular radiation guidelines

4.3.3 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

Dosing should be based on actual BSA.

4.3.4 Block 2 Chemotherapy

Dexamethasone: PO (may be given IV)
Days: 1-5
Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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)

Intermediate Dose Methotrexate (ID MTX): IV over 36 hours
Day: 8
Dose: 1000 mg/m²/dose
Given as a 100 mg/m^2 bolus over 30 minutes followed by 900 mg/m^2 over 35.5 hours.

Be certain that the ID MTX infusion is completed in the 36 hour period. **Even if the infusion is not complete at this time point, it must be stopped.**

Leucovorin rescue: See below.

Suggested hydration and alkalinization for IDMTX: Prehydrate with D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m^2/hour to achieve a urine specific gravity ≤ 1.010 and pH between 7 and 8. Ringers Lactate may be bused as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity ≤ 1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m^2 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 using D 5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour throughout IDMTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is < 0.25 μM.

Timing of ID MTX:
- For patients beginning Block 2 with **M1** marrow, it is recommended to await count recovery to an ANC ≥ 500/μL and platelets ≥ 50,000/μL prior to beginning Day 8 IV methotrexate.
- Patients beginning Block 2 with **M2** marrow should proceed without awaiting count recovery.
- To continue to receive protocol therapy, all patients must begin Day 8 IV methotrexate no later than 14 days after risk assignment.

Leucovorin: PO/IV
Day: 9, 10
Dose: 15 mg/m^2/dose every 6 hours beginning **48 hrs** after the **START** of ID MTX infusion.

- If 48 hr methotrexate level is ≤ 0.5 μM, do not give more than two doses of leucovorin (48 and 54 hours).

- If MTX level at 48 hours is > 0.5 μM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 μM.

See Section 5.8 for ID MTX/LCV rescue and infusion guidelines.

Methotrexate: Intrathecal (IT) – CNS1/2 PATIENTS ONLY
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

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).

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 8, 22

Age-based dosing:

Age (yrs)	Dose
1 to < 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

When ITT therapy and ID MTX are scheduled for the same day, deliver the ITT 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).

Pegaspargase: IV over 1-2 hours
Administer 4 hours after completion of Day 8 IV MTX. (Day 9 or 10)
Dose: 2500 International Units/m^2/dose

Cyclophosphamide: IV over 15-30 minutes (see note below)
Days: 15-19
Dose: 440 mg/m^2/dose

Etoposide: IV over 1-2 hours (see note below)
Days: 15-19
Dose: 100 mg/m^2/dose

NOTE: Await count recovery to ANC ≥ 500/μL and platelets ≥ 50,000/μL prior to beginning Day 15 IV cyclophosphamide and etoposide.

4.3.5 Disease Evaluation End Block 2

- The End Block 2 disease evaluation should not be done earlier than Day 29 (± 1 day);

- The evaluation may be delayed no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- See Sections 7.1 and 13.0 for details on specimen acquisition, handling and shipping.

4.3.6 Following Completion of Block 2:

a. HR/IR B-ALL patients post-Block 2:
For HR/IR B-ALL patients randomized to **Arm A**, Block 3 (Section 4.4, APPENDIX II-C) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

b. HR/IR B-ALL Treatment Failures post-Block 2:
TF patients (see Section 3.3 for definition) have the option to receive up to two 5 week cycles of Blinatumomab (Sections 4.7, 4.8, and APPENDICES II-F and II-G respectively) and continue on to HSCT after achieving morphologic CR.
*HR/IR patients who are considered to be in relapse at end Block 2 are removed from protocol therapy (see Section 3.3 for definition)

c. For LR B-ALL patients post-Block 2:
- **Arm C**, Block 3 (Section 4.4, APPENDIX II-C) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.
- **Arm D**, therapy with Blinatumomab Block Cycle 1 (Section 4.7, APPENDIX II-M) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.4 Block 3 (**HR/IR Patients** on **Arm A**; **LR Patients** on **Arm C**) - 4 weeks

Block 3 therapy is for all HR/IR patients randomized to the control arm (**Arm A**), and LR patients randomized to the control arm (**Arm C**). See Experimental Design Schema.

The Therapy Delivery Map (TDM) for Block 3 is in APPENDIX II-C.

4.4.1 Criteria to Begin Block 3 Therapy

Start when ANC ≥ 500/µL and platelets ≥ 50,000/µL

4.4.2 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.4.3 Block 3 Chemotherapy

Dexamethasone: PO (may be given IV)
Days: 1-5
Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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)

Cytarabine: IV over 3 hours
Days: 1, 2, 8, 9
Dose: 3000 mg/m^2/dose Q12H

Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose of cytarabine and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2-4 hour schedule.

Erwinia L-asparaginase: IM
Day: 2, 4, 9, 11, 23
Dose: 25, 000 International Units/m^2/dose

- Erwinia asparaginase should be given 4 hours after the last cytarabine infusion on Days 2 and 9.
- Erwinia asparaginase should be given 4 hours after the MTX infusion is complete on Day 23.
- If Erwinia asparaginase is not available, a single dose of Pegaspargase should be substituted 4 hours after the last cytarabine dose is complete on Day 9, and no asparaginase is given on Day 23.

Methotrexate: Intrathecal (IT)
Day: 1 **FOR ALL PATIENTS**
Day 22: **CNS1/2 PATIENTS 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

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).

NOTE: Await count recovery to ANC ≥ 500/μL and platelets ≥ 50,000/μL prior to beginning Day 22 IV Methotrexate and intrathecal chemotherapy.

Triple Intrathecal Therapy (ITT) -
CNS3 PATIENTS ONLY
Day: 22

Age-based dosing:

Age (yrs)	Dose		
1 to < 1.99	MTX: 8 mg	HC: 8 mg	ARAC: 16 mg
2 to < 2.99	MTX: 10 mg	HC: 10 mg	ARAC: 20 mg
3 to < 8.99	MTX: 12 mg	HC: 12 mg	ARAC: 24 mg
≥ 9	MTX: 15 mg	HC: 15 mg	ARAC: 30 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).

Intermediate Dose Methotrexate: IV over 36 hours
Day: 22
Dose 1000 mg/m²/dose

See Sections 4.3.4 and 5.8 for ID MTX/LCV rescue and infusion guidelines

Leucovorin: PO/IV
Days: 23, 24
Dose: 15 mg/m^2/dose beginning **48 hrs** after the **START** of ID MTX infusion.

- If 48 hr methotrexate level is ≤ 0.5 µM, do not give more than two doses of leucovorin (48 and 54 hours).
- If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.

See Section 5.8 for ID MTX/LCV rescue and infusion guidelines.

4.4.4 Disease Evaluation End Block 3 (HR/IR Patients ONLY):

- The End Block 3 disease evaluation should not be done earlier than Day 29 (± 1 day);
- The evaluation may be delayed no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- See Sections 7.1 and 13.0 for details on specimen acquisition, handling and shipping.

Notes regarding End Block 3 Disease Assessment:

- BM assessment should be coordinated so that patients begin their preparative regimens no later than 2 weeks from BM documentation of CR.
- If delays > 14 days are required for donor timing or other reasons, patients may receive up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment is required to document remission and MRD status within 14 days of starting the HSCT preparative regimen.
- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

4.4.5 Following completion of Block 3:

a. HR/IR B-ALL patients:
Arm A, should proceed to HSCT as soon as possible after count recovery (ANC ≥ 500/µL and platelets ≥ 50,000/µL). See Section 4.9. Patients may receive up to 6 weeks of bridging maintenance therapy prior to HSCT as described in Section 4.10.

b. For LR B-ALL patients:
Arm C, Continuation 1 (Section 4.11, APPENDIX II-I) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.5 Blinatumomab Block: Cycle 1 (HR/IR Patients in Arm B) - 5 weeks

The therapy described in this section is for the 1st cycle of therapy with Blinatumomab in the HR/IR randomization. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab Block: Cycle 1 (**Arm B**) is in APPENDIX II-D.

NOTE: Hospitalization is STRONGLY recommended during the first 3 days of this cycle in case of a cytokine reaction.

END BLOCK 1 CALLBACK OCCURS PRIOR TO STARTING BLINATUMOMAB BLOCK: CYCLE 1 THERAPY. PLEASE SEE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON STAGED CONSENT, AND APPROPRIATE TIMING TO OBTAIN INFORMED CONSENT.

4.5.1 Criteria to Begin Blinatumomab Block: Cycle 1

Blinatumomab Cycle 1 should begin after receipt of risk assignment and submission of end- Block 1 Callback as soon as clinically acceptable to the treating institution. Patients should have time for full or partial recovery (judged by the treating institution) from any toxicities experienced in the prior course(s) of therapy before proceeding to the next course.

For patients beginning Blinatumomab Cycle 1 with M1 marrow, it is recommended to await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL. To continue to receive protocol therapy, M1 patients must begin Blinatumomab Cycle 1 no later than 14 days after risk assignment.

For patients beginning Blinatumomab Cycle 1 with M2 marrow, it is recommended to proceed without awaiting count recovery. To continue to receive protocol therapy, M2 patients must begin Blinatumomab Cycle 1 no later than 5 days after Callback.

4.5.2 Testicular Radiation Therapy (TRT)

- Patients with persistent testicular leukemia at the end of Block 1 are eligible to continue on study and will receive 2400 cGy of testicular radiation during the 1st cycle of Blinatumomab (for HR/IR patients randomized to the experimental arm).
- Patients with extramedullary testicular leukemia that has resolved by end-Block 1 will NOT receive testicular irradiation with the exception of that which may be used in the HSCT preparative regimen.
- See Section 14.2 for detailed testicular radiation guidelines.

4.5.3 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA. There is no maximum dosing

4.5.4 Blinatumomab Block: Cycle 1 Chemotherapy

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1-28
Dose: 15 µg/m²/day
***. IV bag will be changed every 24-48 hours**

Dexamethasone: PO/IV
Day: 1
Dose: Prior to day 1 therapy -

- A single dose of 10 mg/m^2/dose will be administered 6 to 12 hours prior to initiation of the blinatumomab infusion.
- A single dose of 5 mg/m^2/dose will be administered within 30 minutes prior to the start of the blinatumomab infusion

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
Day: 15, 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

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 15, 29

Age-based dosing:

Age (yrs)	Dose
1 to < 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

4.5.5 Disease Evaluation End-Blinatumomab Block: Cycle 1

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.

- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

4.5.6 Following completion of Blinatumomab Block: Cycle 1 (Arm B)

a. For HR/IR B-ALL patients randomized to Arm B:
Blinatumomab Block Cycle 2 (Section 4.6, APPENDIX II-E) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

b. Treatment Failures post-Blinatumomab Block:
Patients with a TF post Blinatumomab Block: Cycle 1 (see Section 3.3. for definition) will be taken off protocol therapy.

4.6 Blinatumomab Block: Cycle 2 (HR/IR Patients in Arm B) - 5 weeks

The therapy described in this section is for the 2nd cycle of therapy with blinatumomab on Arm B. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab Block: Cycle 2 (Arm B) is in APPENDIX II-E.

NOTE: Hospitalization is STRONGLY recommended during the first 2 days of this cycle in case of a cytokine reaction.

4.6.1 Criteria to Begin Blinatumomab Block: Cycle 2

- Do not start Blinatumomab Cycle 2 before Day 36 after beginning of Cycle 1.
- Begin Blinatumomab Block: Cycle 2 therapy when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.6.2 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA.

4.6.3 Blinatumomab Block: Cycle 2 Administration Guidelines

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1-28
Dose: 15 µg/m²/day

* **IV bag will be changed every 24-48 hours**

Dexamethasone: PO/IV
Day: 1
Dose: Prior to day 1 therapy -

- A single dose of 10 mg/m²/dose will be administered 6 to 12 hours prior to initiation of the blinatumomab infusion.
- A single dose of 5 mg/m²/dose will be administered within 30 minutes prior to the start of the blinatumomab infusion

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Methotrexate: Intrathecal (IT) - **CNS1/2 PATIENTS ONLY**
Days: 8, 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

Triple Intrathecal Therapy (ITT) - **CNS3 PATIENTS ONLY**
Days: 8, 29

Age-based dosing**:**

Age (yrs)	Dose		
1 to < 1.99	MTX: 8 mg	HC: 8 mg	ARAC: 16 mg
2 to < 2.99	MTX: 10 mg	HC: 10 mg	ARAC: 20 mg
3 to < 8.99	MTX: 12 mg	HC: 12 mg	ARAC: 24 mg
≥ 9	MTX: 15 mg	HC: 15 mg	ARAC: 30 mg

4.6.4 Disease Evaluation End-Blinatumomab Block: Cycle 2

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

Notes regarding End Block 3 Disease Assessment:

- BM assessment should be coordinated so that patients begin their preparative regimens no later than 2 weeks from BM documentation of CR.
- If delays > 14 days are required for donor timing or other reasons, patients may receive up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment is required to document remission and MRD status within 14 days of starting the HSCT preparative regimen.
- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

4.6.5 Following completion of Blinatumomab Block: Cycle 2 (Arm B):

- Patients will continue on to HSCT (See Section 4.9).Patients may receive up to 6 weeks of bridging maintenance therapy prior to HSCT as described in Section 4.10.
- Treatment Failures post-Blinatumomab Block: Cycle 2 (see Section 3.3. for definition) will be taken off protocol therapy.

4.7 Blinatumomab-S: Cycle 1 (Treatment Failures) - 5 weeks

Patients classified as treatment failures after Block 1 or Block 2 treatment (see Section 3.3 for definitions) who have not previously received blinatumomab on study and who are without evidence of CNS disease will have the option to be non-randomly assigned treatment with up to 2 blocks of salvage blinatumomab (Blinatumomab-S), and continue on study with HSCT therapy if a morphologic CR is achieved. **Note that blinatumomab dosing in Blinatumomab-S cycles differs from dosing in Blinatumomab Block cycles** (See Section 4.7.4.) The schedule below describes treatment for the 1st cycle only. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab-S: Cycle 1 is in APPENDIX II-F.

NOTE: Hospitalization is STRONGLY recommended during the first 3 days of this cycle in case of a cytokine reaction.

OBTAIN INFORMED CONSENT PRIOR TO INITIATING THE FIRST CYCLE OF SALVAGE THERAPY. PLEASE SEE THE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON TIMING TO OBTAIN INFORMED CONSENT.

4.7.1 Criteria to Begin Blinatumomab-S: Cycle 1

- None

4.7.2 Testicular Radiation Therapy (TRT)

- All Treatment Failures on the basis of M3 marrow at the end of Block 1 who also have persistent testicular leukemia will receive 2400 cGy of testicular radiation during the 1st cycle of salvage blinatumomab.
- Patients with extramedullary testicular leukemia that has resolved by end Block 1 will NOT receive testicular irradiation with the exception of that which may be used in the HSCT preparative regimen for HR/IR patients.
- See Section 14.2 for detailed radiation guidelines.

4.7.3 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA.

4.7.4 Blinatumomab-S: Cycle 1 Chemotherapy Guidelines

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1-28
Dose: 5 µg/m²/day (Days 1-7) followed by 15 µg/m²/day (Days 8-28)

* **IV bag will be changed every 24-48 hours**

Dexamethasone: PO/IV
Dose: Prior to day 1 therapy -

- A single dose of 10 mg/m^2/dose will be administered 6 to 12 hours prior to initiation of the blinatumomab infusion.
- A single dose of 5 mg/m^2/dose will be administered within 30 minutes prior to the start of the blinatumomab infusion

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Methotrexate: Intrathecal (IT)
Day: 15

Age-based dosing**:**

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

4.7.5 Disease Evaluation End Blinatumomab-S Cycle 1:

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

4.7.6 Following completion of Blinatumomab-S: Cycle 1:

a. Patients with M1 marrow after Blinatumomab-S Cycle 1:

- Such patients proceed to HSCT on study as soon as possible after count recovery (ANC ≥ 500/µL and platelets ≥ 50,000/µL). See Section 4.9.
- Patients should begin their preparative regimens no later than 2 weeks from BM documentation of CR.
- If delays > 14 days are required for donor timing or other reasons, patients may receive Blinatumomab-S Cycle 2 as described in Section 4.8 or up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment will be needed to document remission and MRD status within 14 days of starting the HSCT preparative regimen.

- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

b. Patients with M2/M3 marrow after Blinatumomab-S: Cycle 1
Such patients proceed to Blinatumomab-S: Cycle 2 (Section 4.8, APPENDIX II-G) without awaiting count recovery.

4.8 **Blinatumomab-S: Cycle 2 (Treatment Failures) - 5 weeks**

Blinatumomab-S: Cycle 2 is for patients with M2/M3 marrow after completion of Blinatumomab-S: Cycle 1. Patients who are M1 after completion of Blinatumomab-S: Cycle 1 and have delays >14 days before initiating HSCT may also receive treatment on Blinatumomab-S: Cycle 2 (See Section 4.7.6). **Note that blinatumomab dosing in Blinatumomab-S cycles differs from dosing in Blinatumomab Block cycles** (See Section 4.8.3.)

The schedule below describes treatment for the 2nd cycle only. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab-S: Cycle 2 is in APPENDIX II-G.

NOTE: Hospitalization is STRONGLY recommended during the first 2 days of this cycle in case of a cytokine reaction.

4.8.1 Criteria to Begin Blinatumomab-S: Cycle 2

Do not start Blinatumomab-S: Cycle 2 before Day 36 after beginning of Cycle 1.

4.8.2 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA.

4.8.3 Blinatumomab-S: Cycle 2 Chemotherapy

Blinatumomab: IV; Continuous Infusion over 28 days*

Days: 1-28

Dose: 15 μg/m²/day (Days 1-28)

* **IV bag will be changed every 24-48 hours**

Dexamethasone: PO/IV

Dose: Prior to day 1 therapy -

- A single dose of 10 mg/m^2/dose will be administered 6 to 12 hours prior to initiation of the blinatumomab infusion.

- A single dose of 5 mg/m^2/dose will be administered within 30 minutes prior to the start of the blinatumomab infusion

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Methotrexate: Intrathecal (IT)
Day: 15

Age-based dosing**:**

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

4.8.4 Disease Evaluation End-Blinatumomab-S: Cycle 2

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

4.8.5 Following completion of Blinatumomab-S: Cycle 2:

a. Patients with M1 marrow after Blinatumomab-S Cycle 2:

- Such patients proceed to HSCT on study as soon as possible after count recovery (ANC ≥ 500/µL and platelets ≥ 50,000/µL). See Section 4.9.
- Patients should begin their preparative regimens no later than 2 weeks from BM documentation of CR.
- If delays > 14 days are required for donor timing or other reasons, patients may receive Blinatumomab-S Cycle 2 as described in Section 4.8 or up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment will be needed to document remission and MRD status within 14 days of starting the HSCT preparative regimen.
- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

b. Patients with M2/M3 marrow after Blinatumomab-S Cycle 2
Remove from protocol therapy.

4.9 Hematopoietic Stem Cell Transplant

All transplants performed on COG trials must occur at COG-accredited HSCT programs with the exception of adolescents/adults being treated on COG trials who are referred to an adult transplant facility. See the COG Administrative Policy 3.3 regarding the agreement requirements for these cases.

4.9.1 Overview

Stem cell transplantation in this study will be utilized in patients with HR/IR relapse ALL (see Section 3.3 for risk definitions).

All patients enrolled on this protocol and their full siblings should undergo HLA tissue typing as soon as possible after diagnosis of relapse. All high-risk patients should have transplantation consultation and initiation of a donor search early while undergoing their initial Block 1 therapy. It is recommended that all intermediate-risk patients also undergo transplantation consultation as soon as possible after Block 1 therapy, so that a donor search can be initiated immediately if they are noted to be MRD+ after initial induction. The goal of this protocol is to move to transplantation within 2 weeks of recovery from the final consolidation cycle or completion of salvage blinatumomab therapy. As unrelated donor acquisition can take 8-12 weeks, to meet this deadline centers must expedite the search process. Please see Section 7.1c for details of required evaluations.

Patients going on to HSCT will undergo an extensive pre-transplant evaluation to assess remission status, assure adequate organ system function, and document freedom from active viral, bacterial, and fungal infection. Patients should begin their preparative regimen no later than 2 weeks after obtaining the BM aspiration scheduled after recovery from their final consolidation cycle or completion of salvage blinatumomab therapy. If transplantation is delayed by 14 days for donor timing or other reasons, patients may receive up to 6 weeks of bridging maintenance therapy as described in Section 4.10, Appendix II-H. For patients who receive bridging therapy, a repeat BM assessment will be needed to document remission and MRD status within 14 days of starting the HSCT preparative regimen. Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

Patients will receive 1 of 3 designated preparative regimens (cyclophosphamide/total body irradiation (TBI) [cy/TBI] alone or with thiotepa or etoposide). Fludarabine will be added to cy/TBI for cord blood recipients. GVHD prophylaxis varies slightly according to stem cell source.

Patients who are high risk for relapse (MRD+ pre-HSCT with no evidence of GVHD by Day +55, or with + MRD post BMT) are eligible for early taper of immune suppression. The intent of the protocol will be for patients to undergo TBI-based myeloablative conditioning. If patients are not eligible for a myeloablative regimen and either do not undergo HSCT or undergo a reduced intensity procedure, limited data will be collected regarding post transplant survival and relapse.

4.9.1.1 **Eligibility Criteria for Hematopoietic Stem Cell Transplant (HSCT)**

Patients who have an appropriately matched stem cell source (see Section 4.9.1.5) and who meet one of the following criteria:

1. Patients with HR relapse:
   - Early (< 36 months) marrow
   - Early (< 18 months) IEM
2. Patients with IR relapse with persistent MRD:
   - Late (≥ 36 months) marrow, end-Block 1 MRD ≥ 0.1%
   - Late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%
3. Patients with treatment failure (TF) who achieve a morphological CR after receiving blinatumomab.
4. Patients who achieve a morphological remission (< 5% blasts) and maintain the remission through the BM assessment prior to transplant. (Patients who achieve a remission and relapse prior to HSCT can go to HSCT later, but as they have met a study endpoint, this procedure will be as per center preference and the patient will only be followed for survival.)

4.9.1.2 **Exclusion Criteria for Hematopoietic Stem Cell Transplant (HSCT)**

Interval development of significant pathology that would preclude HSCT including the following infectious and organ system pathologies:

1. Infections
   Patients with uncontrolled fungal, bacterial or viral infections are excluded.
   Patients acquiring fungal disease during induction therapy may proceed if they have a significant response to antifungal therapy with no or minimal evidence of active disease remaining by CT evaluation.
2. Organ Function Requirements for HSCT
   Must meet the criteria for renal, biliary and cardiac function as outlined in Section 3.2.4. In addition, must have adequate pulmonary function defined as anFEV_1, FVC, and DLCO (corrected for Hgb) ≥ 60% by pulmonary function tests (PFTs).

   For children who are unable to cooperate for PFTs, the criteria are: no evidence of dyspnea at rest, no exercise intolerance, and not requiring supplemental oxygen therapy.
3. Performance Status
   Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Please refer to performance status scale at:
   https://members.childrensoncologygroup.org/_files/protocol/Standard/PerformanceStatusScalesScoring.pdf

4.9.1.3 **Eligibility for Accelerated Taper of Immune Suppression**

a. Patients who are MRD+ (≥ 0.01%) within 2 weeks of beginning HSCT preparative regimen who do not have any evidence of aGVHD by Day +55 post HSCT (pre-MRD+ group)

b. Patients who are MRD- (< 0.01%) within 2 weeks of beginning HSCT preparative regimen but are found to be MRD+ (≥ 0.01%) on peri-engraftment (Day +28-55) or Day +100 marrow who do not have any evidence of aGVHD by Day +55 (peri-engraftment group) or Day +100 (Day +100 group)

4.9.1.3.1 **Adjustment of TBI/chemotherapy During the Preparative Regimen**. The full dose of preparative regimen TBI and chemotherapy agents will be administered unless patients have a life threatening reaction thought likely to occur again with continued administration and an appropriate substitution cannot be made (i.e. etopophos for etoposide).

4.9.1.4 **Dose Adjustment of Chemotherapy for Patients Whose Weight Exceeds > 125% Ideal Body Weight (IBW)**

Chemotherapy given during the preparative regimen (thiotepa, cyclophosphamide, and etoposide) will be dosed based on actual weight for patients ≤ 125% IBW. Those > 125% IBW will be dosed based upon adjusted ideal body weight as follows:

Adjusted ideal body weight = IBW + 0.25 (Actual weight – IBW).

The following formulas for pediatric and adult IBW calculations are recommended, but IBW may be calculated according to institutional standard operating procedures (SOPs).

Recommended Ideal Body Weight Calculation for Children Age 1- 17 years

$$\text{IBW} = \frac{\text{Height (cm)}^2 \times 1.65}{1000}$$

Recommended Ideal Body Weight Calculation for Adults (Height >5 feet/60 inches)

IBW (females) = (cm ÷ 2.54 – 60) x 2.3 kg + 45.5 kg

IBW (males) = (cm ÷ 2.54 – 60) x 2.3 kg + 50 kg

4.9.1.5 **Stem Cell Source Requirements**

Molecular typing at high resolution of HLA A, B, C, and DRB1 is required, and DQB1 suggested, for all bone marrow or peripheral blood stem cell (PBSC) donors who are either unrelated or related but not matched siblings (i.e. matched parent, partially mismatched sibling, etc.). For matched sibling donors and cord blood units, intermediate level matching of class I antigens is acceptable, but allele level typing is required for DRB1 and encouraged for class I antigens and DQB1.

Hierarchy of stem cell choices is as follows:

1) Preferred: Genotypically HLA matched siblings

2) If genotypically matched sibling is not available, the following are equally acceptable:

   a) **Unrelated or "other" related (non-genotypically matched) donors** must be matched at 8/8 or 7/8 alleles (HLA-A, B, C and DRB1 at high resolution).

   b) **Unrelated Cord blood units** must be matched at 4/6, 5/6, or 6/6 antigens (HLA A, B [intermediate), and DRB1 [high resolution]). Published data show lower non-relapse mortality when patients receive units matched at 8/8, 7/8, or 6/8 alleles (HLA-A, B, C and DRB1 at high resolution), therefore allele-level typing is strongly encouraged. Use of cords matched at 5/8 or 4/8 alleles leads to more TRM, but are acceptable if better matches are not available. It is recommended that units matching at the 3/8 allele level be avoided if possible. Minimum pre-thaw cell dose of $3x10^7$ nucleated cells/kg recipient weight is required. Two cords may be used if this cell dose is not achieved with a single unit. The two units must each match the recipient at a minimum of 4/6 antigens and must match each other at a minimum of 3/6 antigens.

   NOTE: Centers using unlicensed cord blood must consent the patient on the NMDP cord blood IND protocol or other cord blood IND protocols as appropriate in order to use such units on this study

3) Use of Peripheral Blood Stem Cells (PBSC)
   Bone marrow should be requested from allogeneic donors. PBSC is allowed only if the donor is unable or unwilling to give marrow.

4.9.1.5.1 Recommended minimum cell doses:
HPC-M cell dose should be at least 1×10^8 TNC/kg
HPC-A cell dose should be at least 2×10^6 CD34/kg

4.9.1.6 **Preparative Regimens**

Preparative regimens allowed on this protocol are standard regimens used in ASCT0431 for related and unrelated BM/PBSC recipients and BMT CTN 0501 for cord blood recipients. ASCT0431 designated TBI 1200cGy/thiotepa/cyclophosphamide, but also allowed a variation substituting VP-16 for thiotepa and a second variation substituting a slightly higher TBI dose (1320cGy) for thiotepa. BMT CTN 0501 used TBI 1320/cyclophosphamide/fludarabine for all patients.

4.9.2 Preparative Regimen Administration

4.9.2.1 **TBI Administration**
Fractionated TBI will be administered according to protocol guidelines (see Section 14.5 for radiotherapy guidelines). TBI may be delivered from either linear accelerator or Cobalt sources.

4.9.2.2 **Thiotepa Administration** (for centers choosing the thiotepa-containing regimen).

- Thiotepa will be administered intravenously. To minimize skin toxicity, frequent bathing (minimum 2-3x daily) is required on the days of thiotepa administration as per center standard.
- See above for dose modification if weight exceeds 125% of IBW

4.9.2.3 **Cyclophosphamide Administration**

- Cyclophosphamide will be administered intravenously.
- Hyperhydration and maintenance of significant urine output after administration is required. Mesna administration is encouraged, but not required.
- Recommended mesna dosing: 360 mg/m^2 during cyclophosphamide followed by 120 mg/m^2/hour for 24 hours after each dose. Institutional standards or protocols for mesna administration may also be used.
- See above for dose modification if weight exceeds 125% of IBW

4.9.2.4 **Etoposide Administration** (for centers choosing etoposide regimen)

- Patients should be given 1.5X maintenance fluids during etoposide administration to minimize the risk of hypotension.
- Etopophos substitution is allowed.
- See above for dose modification if weight exceeds 125% of IBW

4.9.2.5 **Fludarabine Administration**

- Fludarabine will be administered over 30-60 minutes each day.
- Fludarabine will not be adjusted for body weight.

4.9.3 Preparative Regimen Administration Tables

4.9.3.1 TBI 1200/thiotepa/cyclophosphamide Regimen (related and unrelated BM/PBSC)

Treatment	Route	Dose	Days	Notes
TBI		200 cGy BID	Day -8, -7, & -6	May deliver 1200 cGy fractionated TBI over 4 days per center preference
Thiotepa	IV	5 mg/kg/day	Day -5 & -4	
Cyclophosphamide	IV	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.3.2 TBI 1200/etoposide/cyclophosphamide Regimen (related and unrelated BM/PBSC)

Drug/Treatment	Route	Dose	Days	Notes
TBI		200 cGy BID	Day -7, -6, & -5	May deliver 1200 cGy fractionated TBI over 4 days per center preference
Etoposide	IV	1500 mg/m^2	Day -4	
Cyclophosphamide	IV	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.3.3 TBI 1320/cyclophosphamide Regimen (related and unrelated BM/PBSC)

Treatment	Route	Dose	Days	Notes
TBI		165 cGy BID	Day -7, -6, -5, & -4	Total dose must be 1320 cCy
Cyclophosphamide	IV	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.3.4 TBI 1320/fludarabine/cyclophosphamide Regimen (related and unrelated cord blood)

Treatment	Route	Dose	Days	Notes
Fludarabine	IV	25 mg/m^2/day	Day -10, -9, -8	
TBI		165 cGy BID	Day -7, -6, -5, & -4	Total dose must be 1320 cCy
Cyclophosphamide	IV	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.4 Sanctuary Site Therapy (see Section 14.0)

Prior to transplant, designated patients with extramedullary relapse must receive cranial or testicular radiotherapy boosting in addition to the doses of TBI associated with the preparative regimen. The cranial boost and/or testicular boosts should be given over 3 days prior to the beginning of TBI.

4.9.4.1 **Radiotherapy boost for patients with CNS leukemia (CNS3) at relapse**:

Patients with CNS3 involvement at the time relapse with or without a history of prior CNS leukemia and/or radiotherapy will receive a cranial radiotherapy boost just prior to TBI (3 doses, maximum 200 cGy daily: total dose to cranial axis =

1800 cGy (unless alternative TBI dose given in which case the dose will be 1920 cGy). If the patient is ≤ 3 years at the time of transplant, centers may elect not to give a boost because of developmental concerns. If the patient has CNS1 or CNS2 status at relapse, no boost will be given.

4.9.4.2 **Testicular boost for patients with testicular leukemia at relapse:** The only patients that will receive a testicular boost prior to TBI (3 daily doses, 200 cGy fractions, total 600 cGy) are IR/HR/TF patients with extramedullary testicular leukemia at the time of relapse that DID resolve by end Block 1, since those without resolution have already received 2400 cGy of testicular radiation.

4.9.4.3 **Prophylactic testicular boosting**: Prophylactic testicular boosting of 400 cGy for patients without testicular relapse is allowed, but not part of the designated therapy.

4.9.5 Growth Factor Administration

Filgrastim (G-CSF) at a dose of 5 micrograms/kg/day given IV or subcutaneously is required for recipients of cord blood starting at day +1 and continuing until patients are fully engrafted. G-CSF is generally not necessary for BM/PBSC recipients and is not recommended, unless engraftment is delayed.

4.9.6 GVHD Prophylaxis

GVHD prophylaxis will consist of tacrolimus/methotrexate (TAC/MTX) for recipients of related and unrelated donor BM/PBSC and cyclosporine and mycophenylate mofetil (CYA/MMF) for cord blood recipients. Substitution of CYA for TAC or TAC for CYA according to center preference is allowed.

Drug	Route*	Dose	Days	Important Notes
BM Recipient				
Tacrolimus (TAC)	IV	0.02 mg/kg/day cont infusion	Begin Day -3	Target concentration 8-12 ng/mL
Methotrexate (MTX)	IV	5 mg/m^2 sib donor 10mg/m^2 URD^	+1, +3, &+6 sibs +1, +3, +6, +11 URD	
Cord Recipient				
Cyclosporine A (CYA)	IV	Varies by age, adjusted to target	Begin Day -3	Target concentration 200-400 ng/mL
Mycophenylate mofetil (MMF)	IV	≥50 kg: 1000 mg q8h < 50kg: 15mg/kg q8h	Begin Day -3	

* All drugs may be switched to PO after engraftment when patients are able to tolerate and absorb PO medications.

^ URD, unrelated donor

4.9.6.1 **Tacrolimus Administration, Monitoring and Dose Adjustments (related or unrelated BM/PBSC)**

Tacrolimus should be administered by continuous IV infusion until patients are able to take PO. Serum tacrolimus troughs and serum magnesium, potassium, and creatinine should be drawn at least twice per week while hospitalized, then as per good clinical practice thereafter unless a change in medication (e.g. use of concomitant CYP3A4 inhibitors) or renal function might result in an acute change in level.

At that point, concentrations will be measured as clinically indicated. Concentrations sent when dosing by continuous infusion are not true trough concentrations, however, the same target range of drug concentration will be used for both continuous IV and bolus PO routes of administration.

When converting patients at a therapeutic tacrolimus level from IV to PO formulation, multiply total daily IV dose times 4 and administer in 2 divided oral doses per day, every 12 hours (e.g., 1 mg of IV tacrolimus per day equates to 4 mg of PO tacrolimus per day). The oral dose should be administered 8-12 hours after the end of the tacrolimus continuous infusion.[41]

The target serum trough concentration for tacrolimus is 8-12 ng/mL. Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level.

4.9.6.2 **Methotrexate Administration, Monitoring and Dose Adjustments (related or unrelated BM/PBSC)**

For patients receiving sibling donors, methotrexate should be given at a dose of 5 mg/m^2 on Days +1, 3, and 6 after transplant. For patients receiving unrelated BM or PBSC, methotrexate should be given at a dose of 10 mg/m^2 on Days +1, 3, and 6, and 11. All doses of methotrexate should be administered as scheduled if possible, but centers may modify or hold methotrexate for significant toxicity (see Section 5.8 for methotrexate dose modification guidelines).

4.9.6.3 **Leucovorin Administration**

Leucovorin may be given at the physician's discretion for patients at risk for methotrexate toxicity. Patients at risk for methotrexate toxicity include those with extravascular fluid collections (ascites, pleural effusions) or with decreased renal function (see Section 5.8).

4.9.6.4 **Cyclosporine Administration, Monitoring and Dose Adjustments (related and unrelated cord blood)**

Cyclosporine should be administered by IV infusion until patients are able to take PO. Cyclosporine levels as well as serum magnesium, potassium, and creatinine levels should be drawn at least twice per week while hospitalized, then weekly or monthly thereafter unless a change in medication (e.g. use of concomitant CYP3A4 inhibitors) or renal function might result in an acute change in level. At that point, levels will be measured as clinically indicated. When converting patients at a therapeutic tacrolimus level from IV to PO formulation, multiply the IV dose times 2.5 if using the modified formulation (i.e., Neoral or Gengraf) or times 3 if using the non-modified formulation (i.e., SandIMMUNE).

The target serum trough concentration for cyclosporine is 200-350 ng/mL. Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level.

4.9.6.5 **Mycophenylate Mofetil (MMF) Administration and Dose Adjustments (related and unrelated cord blood)**

MMF should be given at a dose of 1 gram IV q8 hours for patients ≥ 50kg or 15 mg/kg IV q8 hours for patients < 50 kg beginning the morning of Day -3. MMF should be given IV until patient can tolerate oral medications. MMF should be dosed upon actual body weight.

The FDA has determined that a REMS (Risk Evaluation and Mitigation Strategy) program is necessary to ensure the benefits of mycophenolate outweigh the risks of first trimester pregnancy loss and congenital malformations associated with mycophenolate use during pregnancy. Mycophenolate REMS is a program to tell doctors, nurses, pharmacists and patients about the risks of taking mycophenolate during pregnancy. Providers and patients (females of child-bearing potential) are required to enroll in the program. The program also contains important information about patient education and reporting details for pregnancy. Providers and patients are required to sign acknowledgement forms prior to initiating therapy. Please refer to the website for additional information (https://www.mycophenolaterems.com/). If ≤ Grade 1 acute GVHD, MMF will be discontinued by Day +30. For patients with > Grade 1 acute GVHD, the MMF taper will be per institutional protocols. Patients may transition to PO formulations at a 1:1 IV to PO conversion when clinically appropriate. Refer to Section 5.13 for dose adjustments based on serum drug levels.

4.9.7 Standard Taper of Immune Suppression

This applies to all patients who are MRD negative pre- and at all times post-transplant who have not developed aGVHD requiring systemic therapy. (Patients who develop significant aGVHD will be tapered at the discretion of the transplant center.)

Drug	Stem Cell Source	Taper Schedule
Tacrolimus	Matched Sibling BM/PBSC	Start Day +42 over 8 weeks, off by Day +98
Tacrolimus	Unrelated Donor BM/PBSC	Start Day +100 off by Day +180
Cyclosporine	Unrelated Cord	Start Day +100 off by Day +180
Mycophenylate Mofetil	Unrelated Cord	Continue until Day +45 or 7 days after engraftment, whichever day is later. Stop without a taper.

4.9.8 Accelerated Taper of Immune Suppression

See Section 4.9.1 for eligibility requirements.

4.9.8.1 Taper for patients who are MRD positive pre-HSCT with no aGVHD by Day +55 and for patients who are MRD positive > 0.01% by flow cytometry at their peri-engraftment BM test (approx. Day +30)

Drug	Stem Cell Source	Taper Schedule
Tacrolimus	Matched Sibling BM/PBSC	Taper already started by Day +42. At Day +55 increase rate of taper to complete taper by Day +70
Tacrolimus	Unrelated Donor BM/PBSC	Start Day+55 off by Day +100
Cyclosporine	Unrelated Cord	Start Day+55 off by Day +100
Mycophenylate Mofetil	Unrelated Cord	Continue until Day +45 or 7 days after engraftment, whichever day is later. Stop without a taper.

4.9.8.2 Taper for patients who are MRD negative pre- HSCT with no aGVHD by Day +55 who are MRD positive > 0.01% by flow cytometry at their Day +100 test.

Drug	Stem Cell Source	Taper Schedule
Tacrolimus	Matched Sibling BM/PBSC	Taper already started by Day +42 and pt should be off immune suppression. Stop tacrolimus without taper if still on medication.
Tacrolimus	Unrelated Donor BM/PBSC	Taper over 2-3 weeks as soon as MRD report is received.
Cyclosporine	Unrelated Cord	Taper over 2-3 weeks as soon as MRD report is received.
Mycophenylate Mofetil	Unrelated Cord	Should be off this medication.

4.10 Bridging Maintenance Therapy (All HR/IR Patients, as required) – up to 6 weeks

This therapy is for all HR/IR patients who have completed either Blocks 2 and 3 of chemotherapy or both cycles of blinatumomab and due to stem cell source or facility scheduling issues have a lag time > 2 weeks after count recovery prior to starting HSCT therapy. Patients should start bridging therapy when clinically able after meeting count requirements and continue until approximately one week prior to beginning the transplant preparative regimen.

The Therapy Delivery Map (TDM) for Bridging therapy is in Appendix II-H.

4.10.1 Criteria to Begin Bridging Maintenance Therapy

Start when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.10.2 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

Dosing should be based on actual BSA.

4.10.3 Bridging Maintenance Chemotherapy Guidelines

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

Mercaptopurine: PO
Days: 1-42
Dose: 75 mg/m^2/dose*

Other Considerations:

- *See Section 5.9 for suggested starting dose based on TPMT status (if status is known)
- Administer in the evening on an empty stomach (at least 1 hour before or two (2) hours after food or drink except water).
- Adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible

Methotrexate: PO
Days: 1, 8, 15, 22, 29, 36
Dose: 20 mg/m^2/dose

Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water).

4.11 Continuation 1/Continuation 2 (All LR Patients) - 8 weeks

The therapy described in this section is for all LR patients in either **Arm C** or **Arm D** and represents therapy given during Continuation 1 and Continuation 2. See Experimental Design Schema.

The therapy delivery map for Continuation 1 and Continuation 2 is in APPENDIX II-I.

4.11.1 Criteria to Begin and During Continuation Therapy

a. Begin Continuation when ANC ≥ 500/μL and platelets ≥ 50,000/μL.

b. All Patients should have ANC ≥ 500/μL and platelets ≥ 50,000/μL prior to starting therapy on Days 22 and 42.

- If at Day 22 the ANC is < 500/μL and platelets < 50,000/μL, it is permissible to delay the divided dose oral methotrexate (ddMTX) (25 mg/m^2/dose for CNS1/2) or ID MTX (for CNS3) by 14 days. Omit the Day 29 standard dose oral methotrexate (20 mg/m^2/dose) in this case.
- If counts are not recovered after one (1) week, omit the ddMTX and ID MTX for this cycle and resume with the Day 29 standard dose MTX.

4.11.2 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.11.3 Continuation 1/Continuation 2 Chemotherapy Guidelines

Dexamethasone: PO (may be given IV)
Days: 1-5
Dose: 3 mg/m^2/dose (Total daily dose: 6 mg/m^2/day, divided BID)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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)

Methotrexate: Intrathecal (IT) –**CNS1/2 PATIENTS ONLY**
Days: 1, 43

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).

Triple Intrathecal Therapy (ITT) - **CNS3 PATIENTS ONLY**
Days 1, 43

Age-based dosing**:**

Age (yrs)	Dose
1 to < 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

When ITT therapy and ID MTX are scheduled for the same day, deliver the ITT 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: PO
Days: 1-42
Dose: 75 mg/m²/dose*

Other Considerations:

- ***See** Section 5.9 for suggested starting dose based on TPMT status, if known
- Administer in the evening on an empty stomach (at least 1 hour before or two (2) hours after food or drink except water).
- Adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible

Methotrexate: PO
Days: 8, 15, 29, 36
Dose: 20 mg/m^2/dose

Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water).

Divided Dose Methotrexate (dd MTX): PO - CNS1/2 PATIENTS ONLY
Day: 22
Dose: 25 mg/m^2/dose Q6H x4 doses

Other Considerations:
- ANC must be ≥ 500/µL and platelets must be ≥ 50 000/µL prior to Day 22 therapy.
- Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water).

Leucovorin: PO
Day: 24
Dose: 10 mg/m^2/dose for 2 doses 6 hours apart beginning **48 hrs** after the **START** of Day 22 Methotrexate

Intermediate Dose Methotrexate (ID MTX): IV over 36 hours - CNS3 PATIENTS ONLY
Day: 22
Dose: 1000 mg/m²/dose
Given as a 100 mg/m^2 bolus over 30 minutes followed by 900 mg/m^2 over 35.5 hours.

Be certain that the ID MTX infusion is completed in the 36 hour period. **Even if the infusion is not complete at this time point, it must be stopped.**

Leucovorin rescue: See below.

Suggested hydration and alkalinization for IDMTX: Prehydrate with D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m^2/hour to achieve a urine specific gravity ≤ 1.010 and pH between 7 and 8. Ringers Lactate may be bused as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity ≤ 1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m^2 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 using D 5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour throughout IDMTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is < 0.25 µM.

Timing of ID MTX
ANC must be ≥ 500/µL and platelets must be ≥ 50 000/µL prior to ID MTX.

Leucovorin: PO/IV
Days: 23, 24
Dose: 15 mg/m^2/dose every 6 hours beginning **48 hrs** after the **START** of ID MTX infusion.

- If 48 hr methotrexate level is ≤ 0.5 µM, do not give more than two doses of leucovorin (48 and 54 hours).
- If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.

See Section 5.8 for ID MTX/LCV rescue and infusion guidelines.

Cyclophosphamide: IV over 15-30 minutes
Days: 42, 49
Dose: 300 mg/m²/dose (see note below)

Etoposide: IV over 1-2 hours
Days: 42, 49
Dose: 150 mg/m²/dose

Note: ANC must be ≥ 500/µL and platelets must be ≥ 50,000/µL prior to Day 42 therapy. Once the Day 42 cyclophosphamide/etoposide is given, the Day 49 cyclophosphamide/etoposide doses should be given regardless of blood counts (hold only for presumed or proven significant infection).

Thioguanine: PO
Days 42-48.
Dose: 40 mg/m^2/dose/once daily

Other Considerations:
- Administer in the evening on an empty stomach (at least 1 hour before or two (2) hours after food or drink except water).
- Adjust daily dose using the dosing nomogram in Appendix IV to attain a weekly cumulative dose as close to 280 mg/m^2/week as possible.
- An oral suspension can also be compounded for patients who cannot swallow pills. The compounded oral suspension is recommended for patients with a BSA between 0.27 and 0.48 m^2. (see Section 6.18)

Cytarabine: IV/SQ
Days: 43-46, 50-53
Dose: 50 mg/m^2/dose

4.11.4 Following Continuation 1:

a. LR B-ALL patients randomized to the control arm (**Arm C**) will receive Continuation 2 (Section 4.11, APPENDIX II-I) when ANC ≥ 500/µL and platelets ≥50,000/µL.

b. LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Blinatumomab Block: Cycle 2 (**Arm D**) - (Section 4.13, APPENDIX II-N) when ANC ≥ 500/µL and platelets ≥50,000/µL.

4.11.5 Following Continuation 2:

a. LR B-ALL patients randomized to the control arm (**Arm C**) will receive Maintenance Cycle 1 therapy (Section 4.12, Appendix II-J) when ANC ≥ 500/µL and platelets ≥50,000/µL.

b. LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Blinatumomab Block: Cycle 3 (**Arm D**) - (Section 4.13, APPENDIX II-N) when ANC ≥ 500/µL and platelets ≥50,000/µL.

4.12 Maintenance Cycle 1 (All LR patients) – 12 weeks

Maintenance Cycle 1 therapy is for common for all LR B-ALL patients randomized to either **Arm C** or **Arm D**. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for Maintenance Cycle 1 is in Appendix II-J.

CNS3 patients ONLY are to be given Chemoradiation (Section 4.13, Appendix II-K) BETWEEN Maintenance Cycle 1 and subsequent Maintenance cycles (Maintenance-Post Cycle 1, Section 4.14, Appendix II-L).

All other patients receive **Maintenance-Post Cycle 1 treatment** (Section 4.14, Appendix II-L) immediately following Maintenance Cycle 1.

4.12.1 Criteria to Begin Maintenance Therapy

- Maintenance begins when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50 000/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. Triple Intrathecal therapy (ITT), vincristine and prednisone will be delivered as scheduled, despite myelosuppression.

4.12.2 Duration of Cycles in Maintenance Therapy

- **Maintenance consists of 12-week cycles repeated until total duration of therapy is 2 years from start of Block 1 therapy for both male and female patients.**
- Therapy may be stopped on anniversary date if the 5-day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

4.12.3 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.
Dosing should be based on actual BSA.

4.12.4 Maintenance Chemotherapy Cycles

Dexamethasone: PO (may be given IV)
Days: 1-5, 29-33, & 57-61
Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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)

Mercaptopurine: PO
Days: 1-84
Dose: 75 mg/m²/dose*

Other Considerations:
- ***See Section 5.9** for suggested starting dose based on TPMT status, if known
- Administer in the evening on an empty stomach (at least 1 hour before or two (2) hours after food or drink except water).
- Adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Day: 1

Age-based dosing:

Age (yrs)	Dose
1 to < 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
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

Methotrexate: PO
Days: 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78
Dose: 20 mg/m^2/dose

4.12.5 Following Maintenance Cycle 1:

- **ONLY** CNS3 will receive Chemoradiation (see Section 4.13, APPENDIX II-K) prior to moving on to subsequent Maintenance cycles (Maintenance-Post Cycle 1, Section 4.14, APPENDIX II-L).
- All other patients in both Arm C and Arm D will continue on to **Maintenance-Post Cycle 1** (Section 4.14, APPENDIX II-L).

4.13 Maintenance Chemoradiation - 3 weeks

The CNS-directed therapy described in this section is for LR B-ALL CNS3 Patients ONLY (Patients with late B-ALL isolated CNS3 or CNS3 combined relapse).

The Therapy Delivery Map for this additional CNS-directed therapy during Maintenance is in APPENDIX II-K.

4.13.1 Criteria to Begin Maintenance Chemoradiation

Start when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.13.2 Cranial Radiation Therapy

Cranial radiation will be administered during this phase of therapy, which is between the 1st and 2nd cycles of Maintenance therapy. Patients with CNS3 and isolated CNS relapse will receive 1800 cGy cranial radiation to the brain in 10 daily fractions along with concurrent chemotherapy. See Section 14.1 for details on cranial irradiation.

4.13.3 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.13.4 Chemotherapy Guidelines for Maintenance Chemoradiation

Dexamethasone: PO (may be given IV)
Days: 1-7, 15-21
Dose: 5 mg/m²/dose (Total daily dose: 10 mg/m²/day, divided BID; dose capped at 40 mg per day)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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)

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

4.13.5 Following Maintenance Chemoradiation:

- All patients will continue on to Maintenance-Post Cycle 1 (see Section 4.14, APPENDIX II-L).

4.14 **Maintenance-Post Cycle 1 (All LR patients)**

Maintenance-Post Cycle 1 therapy is common for all LR B-ALL patients randomized to either **Arm C** or **Arm D**. See Experimental Design Schema.

NOTE: CNS3 and Isolated CNS Relapse ONLY are to be given Chemoradiation (see Section 4.13, APPENDIX II-K) between Maintenance Cycle 1 and subsequent Maintenance cycles (Maintenance-Post Cycle 1). All other patients receive Maintenance-Post Cycle 1 immediately following Maintenance Cycle 1.

4.14.1 Criteria to Continue Maintenance Therapy

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. Triple Intrathecal therapy, vincristine and prednisone will be delivered as scheduled, despite myelosuppression.

4.14.2 Duration of Cycles in Maintenance Chemotherapy

- **Maintenance consists of 12-week cycles repeated until total duration of therapy is 2 years from start of Block 1 therapy for both male and female patients.**
- Therapy may be **s**topped on anniversary date if the 5-day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

4.14.3 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.14.4 Chemotherapy Guidelines for Maintenance-Post Cycle 1

Dexamethasone: PO (may be given IV)

Days: 1-5, 29-33, &57-61

Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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)

Mercaptopurine: PO
Days: 1-42
Dose: 75 mg/m^2/dose*

Other Considerations:

- ***See** Section 5.9 for suggested starting dose based on TPMT status (if status is known)
- Administer in the evening on an empty stomach (at least 1 hour before or two (2) hours after food or drink except water).
- Adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible

Methotrexate: PO - CNS3 PATIENTS ONLY
Day: 1
Dose: 20 mg/m^2/dose

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
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

Methotrexate: PO
Days: 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78
Dose: 20 mg/m^2/dose

4.15 Blinatumomab Block: Cycle 1 (Patients in Arm D) - 5 weeks

The therapy described in this section is for the 1st cycle of therapy with Blinatumomab on **Arm D**. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab Block: Cycle 1 (Arm D) is in APPENDIX II-M.

NOTE: Hospitalization is STRONGLY recommended during the first 3 days of this cycle in case of a cytokine reaction.

END- BLOCK 1 CALLBACK OCCURS PRIOR TO STARTING BLINATUMOMAB BLOCK: CYCLE 1 THERAPY. PLEASE SEE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON STAGED CONSENT, AND APPROPRIATE TIMING TO OBTAIN CONSENT.

4.15.1 Criteria to Begin Blinatumomab

Start when ANC ≥ 500/µL and platelets ≥ 50,000/µL

4.15.2 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA. There is no maximum dosing.

4.15.3 Blinatumomab Block: Cycle 1 (Patients in Arm D) Chemotherapy

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1-28
Dose: 15 µg/m²/day
***. IV bag will be changed every 24-48 hours**

Dexamethasone: PO/IV
Day: 1
Dose: Prior to day 1 therapy -

- A single dose of 10 mg/m²/dose will be administered 6 to 12 hours prior to initiation of the blinatumomab infusion.

- A single dose of 5 mg/m^2/dose will be administered within 30 minutes prior to the start of the blinatumomab infusion

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
Day: 8, 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

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 8, 29

Age-based dosing:

Age (yrs)	Dose
1 to < 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 to < 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 to < 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

4.15.4 Following Blinatumomab Block: Cycle 1 (Arm D)

The next phase of therapy is Continuation 1 (Section 4.11, APPENDIX II-I).

4.16 **Blinatumomab Block: Cycle 2/3 (**LR Patients in **Arm D) - 5 weeks**
The therapy described in this section is therapy given during Blinatumomab Block Cycle 2 and Blinatumomab Block Cycle 3. Do not start Blinatumomab Cycle 2 before Day 56 after beginning of Continuation 1. Do not start Blinatumomab Cycle 3 before Day 56 after beginning of Continuation 2. See Experimental Design Schema.

NOTE: Hospitalization is STRONGLY recommended during the first 2 days of these cycles in case of a cytokine reaction.

4.16.1 Criteria to Begin Blinatumomab Block: Cycle 2/3
Start when ANC ≥ 500/µL and platelets ≥ 50,000/µL

4.16.2 General Chemotherapy Guidelines
See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA. There is no maximum dosing.

4.16.3 Blinatumomab Block: Cycle 2/3: Chemotherapy Guidelines

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1-28
Dose: 15 µg/m²/day
***. IV bag will be changed every 24-48 hours**

Dexamethasone: PO/IV
Day: 1
Dose: Prior to day 1 therapy -

- A single dose of 10 mg/m^2/dose will be administered 6 to 12 hours prior to initiation of the blinatumomab infusion.
- A single dose of 5 mg/m^2/dose will be administered within 30 minutes prior to the start of the blinatumomab infusion

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed

4.16.4 Following Blinatumomab Block Cycle 2:
LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Continuation 2- (Section 4.11, APPENDIX II-I)

4.16.5 Following Blinatumomab Block Cycle 3:

LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Maintenance Cycle 1 therapy- (Section 4.12, Appendix II-J.)

5.0 DOSE MODIFICATIONS FOR TOXICITIES

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

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

Allergy

Local Allergic Reactions (inflammation at injection site, swelling): Note these recommendations only apply when the asparaginase product is administered intramuscularly. Continue asparaginase administration in the presence of Grade 1 allergy as defined by CTCAE v4.0 (transient flushing or rash; drug fever < 38ºC).

Systemic Allergic Reactions: In the event of Grade 1 reactions, characterized by transient flushing or rash and drug fever < 38ºC, without the need for treatment with antihistamines or steroids, the dose of asparaginase being administered intravenously may be continued with close observation.

Discontinuation is recommended for Grade 2 or higher allergic reactions as defined by CTCAE v4.0, which require medical intervention

Note: Premedication with antihistamines to decrease the risk of overt allergy symptoms is strongly discouraged since anti-histamine use may mask the appearance of systemic allergy. Systemic allergy is frequently associated with the presence of asparaginase neutralizing antibodies, which render asparaginase therapy ineffective. In the event of a Grade 2 or higher systemic or recurrent local allergic reaction, *Erwinia* asparaginase should be substituted.

Anaphylaxis

Discontinue pegaspargase if the patient develops Grade 3 anaphylaxis as defined by CTCAE v4.0 (symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; allergy-related edema/angioedema; hypotension). If this occurs, *Erwinia* asparaginase 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.[67,68] 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.[69] Current COG trials have adopted pegaspargase as the preparation of choice, based on the results of CCG 1962.[70] COG AALL07P2 showed that *Erwinia* asparaginase was well tolerated and achieved nadir serum asparaginase activity at both 48 and 72 hours after dosing that was similar to that achieved with pegaspargase. Based on these and other data, the FDA approved *Erwinia* asparaginase for use following allergy to pegaspargase, with a dose of 25,000 IU/m^2 x 6 doses IM on a Monday/Wednesday/Friday schedule substituted for a single dose of pegaspargase.

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

Phase(s) of Treatment	Drug(s)	Replacement Schedule for Erwinia asparaginase#
Block 1/Block 2	One or more doses of pegaspargase (2,500 IU/m^2)	25,000 IU/m^2/dose IM^ M/W/F x 6 doses for each dose of pegaspargase.
Chemoradiation	Pegaspargase (2,500 IU/m^2)	25,000 IU/m^2/dose IM^ M/W/F x 6 doses for each dose of pegaspargase.

#If a patient develops a Grade 3 or higher anaphylaxis to Erwinia, discontinue future asparaginase therapy. Consider discontinuation for severe Grade 2 or higher allergic reactions
***** qod: every other day
^Erwinia asparaginase may be administered intravenously to patients who are enrolled in a separate clinical trial evaluating IV Erwinia asparaginase, or if FDA approval is expanded to include IV administration.

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: Discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until symptoms and signs subside, and amylase/lipase levels return to normal and then resumed. Grade 3-4 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, which is not catheter-related, consider evaluation for inherited predisposition to thrombosis.

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

Centers may elect to discontinue pegaspargase and switch to erwinia asparaginase based upon laboratory evidence of silent inactivation of asparaginase activity in the absence of clinical symptoms of hypersensitivity at their discretion.

5.2 Blinatumomab

The most frequent serious adverse events noted in patients treated with blinatumomab to date are disorders of the nervous system, both peripheral and central, and systemic cytokine release syndrome (CRS). Both categories of events are more likely to occur within the first week of treatment with blinatumomab, and both categories of events are usually reversible and able to be managed with attentive supportive care.

AEs related to blinatumomab that require treatment interruption (according to table below) and do not resolve to CTCAE ≤ Grade 1 within 14 days will require permanent discontinuation of blinatumomab treatment. If the patient is eligible to continue protocol therapy (chemotherapy and/or HSCT), then the patient may, at the discretion of the investigator and family, continue to receive protocol therapy. Otherwise, the patient will be off protocol therapy.

In the case that the AE(s) **DO resolve within 14 days**, blinatumomab treatment may resume at a **reduced dose of 5 µg/m2/day** to complete the 28 day course (not counting the duration of treatment interruption). **NOTE**: For Grade 4 Nervous System/Psychiatric and thromboembolic AEs, blinatumomab must be permanently discontinued.

For patients who had experienced a ≥ Grade 2 Neurologic Systems and Psychiatric AE related to blinatumomab, **no dose escalation beyond 5 µg/m^2/day will be permitted** for subsequent cycles. For patients who experienced other AEs related to blinatumomab, subsequent cycles will begin at the reduced dose of 5 µg/m2/day, **but may escalate to 15 µg/m2/day** after 7 days if there are no significant blinatumomab-related AEs.

A **second AE** that requires interruption **will require permanent discontinuation** of treatment and the patient will be off protocol therapy.

The resumption of the infusion at the reduced dose should be accompanied by **dexamethasone premedication** as indicated in the relevant subsection of Section 4.0, should be performed in the hospital under supervision of the investigator and patients should be observed for at least 72 hours after the start of the next infusion before considering discharge to the outpatient setting.

Table: Dose modifications for Adverse Events (AE) Possibly, Probably or Definitely Related to Blinatumomab:

Category: AE (CTCAE v4.03)	AE Grade	Stop Infusion?	Supportive Care (in addition to institutional guidelines)*	Restart allowed (with premeds) if Gr 1 within 14 days?	Restarting dose (mcg/m2/day)	Escalation to 15 mcg/m2/day after 7 days in subsequent cycle allowed?
Nervous system/ Psychiatric[1]: All (other than seizure)	1	N		-	-	-
	2, 3	Y	DEX, CNS	Y	5	N
	4	Y	DEX, CNS	N	-	-
Nervous system: Seizure	1,2,3	Y	SZ, DEX, CNS	Y	5	N
	4	Y	SZ, DEX, CNS	N		
Immune system[2]: Cytokine release syndrome, allergic reaction, anaphylaxis and General: Infusion related reaction	1	N		-	-	-
	2,3	Y	DEX	Y	5	Y
	4	Y	DEX	N	-	-
Blood and lymphatic system[3]: Disseminated intravascular coagulation, hemolysis, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura	1,2	N		-	-	-
	3,4	Y		Y	5	Y
Blood and lymphatic system[4]: All others (lymphopenia, neutropenia, anemia, thrombocytopenia, etc.)	1,2,3,4	N		-	-	-
Vascular: Thromboembolic event	1	N		-	-	-
	2, 3	Y		Y	5	Y
	4	Y		N	-	-
Investigations[5,6], Metabolism and Nutrition: All **(if not considered clinically relevant or responding to routine medical management)**	1,2,3,4	N		-	-	-
Investigations[5,6], Metabolism and Nutrition: All **(if clinically relevant and not responding to routine medical management)**	1,2	N		-	-	-
	3,4	Y		Y	5	Y
All other AE	1,2	N		-	-	-
	3,4	Y		Y	5	Y

<u>**Table Footnotes:**</u>

[1] Most AEs in the psychiatric disorders category are unlikely to be caused by blinatumomab and generally require supportive care rather than dose modification or discontinuation of blinatumomab (e.g., Insomnia, Depression, Anxiety). Psychiatric AEs that may reflect underlying central nervous system toxicity (e.g., Confusion, Delirium, Hallucinations, Psychosis) are of greater interest, particularly if accompanied by other AEs in the nervous system disorders category.

[2] Close monitoring of fluid status by intake and output should be undertaken for the first week of blinatumomab infusion. Efforts to keep patients balanced between intake and output should be maintained, even if diuretic therapy (furosemide or similar) is needed to do this. Careful attention to fluid status may prevent deterioration from capillary leak, however even with meticulous attention some patients will experience pulmonary edema and require more aggressive respiratory support. Treating physicians should use their clinical judgment and institutional standards for whatever supportive care measures are needed during this period of time.

[3] In the first days of treatment, transient DIC-like pictures may develop. Because patients are at risk for capillary leak syndrome and cytokine release syndrome, appropriate supportive care with dexamethasone (described above), blood products and factors (packed red cells, platelets, cryoprecipitate, fresh frozen plasma), vitamin K, and/or albumin should be considered according to institutional standards of care. Particularly in the first week of infusion, when the risk of capillary leak and cytokine release is more prominent, appropriate use of blood products and factors is preferred if laboratory indications suggest the need for replacement, as large volumes of crystalloid fluids tend to exacerbate the capillary leak.

[4] In the first days of treatment, a rapid transient drop in platelets, neutrophils and/or hemoglobin may be observed. These effects are not necessarily cytokine-mediated. Counts typically recover to baseline during treatment, and usually within two weeks of starting blinatumomab. Transfusion of blood and platelets should be performed according to appropriate institutional standards.

[5] In the first days of treatment, transient increases in transaminases up to over 1000 U/L may develop. These have generally returned to baseline in the 1st week of treatment.

[6] Decrease in serum immunoglobulins have been observed in patients treated with blinatumomab. Intravenous immunoglobulin should be administered according to institutional standards, but is recommended for any patient with a total IgG level below 400. Immunoglobulin must not be administered through the line through which blinatumomab is actively being infused.

* <u>Definitions of supportive care abbreviations:</u>

DEX: Dexamethasone should be administered at a total daily dose of at least 0.2-0.4 mg/kg/day (maximum 24 mg per day) administered preferably intravenous divided 3-4 times daily for 4 days. The dose should then be tapered over up to 3-4 days or as clinically indicated.

SZ: Appropriate imaging should be performed to evaluate for possible hemorrhage or thrombosis, and other diagnostic procedures should be performed as clinically appropriate. Prophylactic anticonvulsant treatment with a therapeutic dose of institutional standard agents (e.g., lorazepam, phenytoin, levetiracetam) should be administered if seizures develop, and continued throughout the blinatumomab infusion. Anti-convulsant therapy should be considered starting at least 24-48 hours prior to any subsequent blinatumomab infusions, and continuing for the remainder of those treatment cycles. Diagnostic measures to exclude potential infectious causes should be conducted once the patient has stabilized (i.e., a lumbar puncture to evaluate for bacterial, viral or fungal sources should be performed). Any identified pathology should be treated as clinically appropriate.

CNS: A daily finger-nose-finger or writing sample test is recommended according to age-appropriate activities for patients. In adults treated with blinatumomab, it has been found that a daily handwriting sample can often predict future nervous system toxicity before the clinical toxicity develops. In case of a change in finger-nose-finger or handwriting test it is recommended to start dexamethasone on the schedule above to prevent

5.3 Cyclophosphamide

Hematuria: Omit in the presence of macroscopic hematuria. If there is a history of previous significant hematuria, hydrate before cyclophosphamide until specific gravity is < 1.010 and hydrate at 125 mL/m^2/hr for 24 hours after dose. Monitor for adequate urine output as per institution guidelines. Give IV mesna at a total dose that is 60% of the cyclophosphamide dose divided to 3 doses (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.

5.4 Cytarabine (ARAC)

ARAC Syndrome: Do not withhold ARAC for fever if it is likely to have been caused by the ARAC. Obtain blood cultures if a central line is present. For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis. Note that steroid eye drops should be administered routinely with high dose (3000 mg/m^2/dose) ARAC.

Myelosuppression: Do not interrupt high dose (3000 mg/m^2/dose) ARAC, once started, for uncomplicated myelosuppression; do hold for proven or presumed serious infection and do not make up missed doses during Block 3.

Once Continuation 1 and 2 have started, do not interrupt for uncomplicated myelosuppression; do hold for proven or presumed serious infection.

Renal Dysfunction: Adequate renal function (defined as creatinine within normal range) is required for the administration of high dose (3000 mg/m^2/dose) ARAC. Creatinine clearance (CrCl) should be measured for patients with elevated creatinine or suspected renal insufficiency. For CrCl < 60 mL/min/1.73 m^2, hold pending recovery and omit if recovery requires > 3 weeks.

5.5 Anthracycline-Mitoxantrone

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

Note: use the following updated term to report decreases in the EF or SF: *cardiac disorders-others*

Hyperbilirubinemia:[42]

Direct Bili	% Dose Reduction
< 1.2 mg/dL	Full dose
1.2 – 3.0 mg/dL	50%
3.1 – 5.0 mg/dL	75%
> 5.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

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

5.6 Etoposide

Allergic Reaction: Premedicate with diphenhydramine (1-2 mg/kg slow IV push, maximum dose is 50 mg). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension. Etoposide phosphate is a water soluble prodrug that does not contain polysorbate 80 and polyethyleneglycol, the solubilizing agent in etoposide that may induce allergic reactions and hypotension. Etoposide phosphate is rapidly converted to etoposide *in vivo* and provides total drug exposure, as represented by AUC (0-infinity), that is statistically indistinguishable from that measured for etoposide at equimolar doses.

Hypotension: If diastolic or systolic blood pressure (BP) falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of NS 10 mL/kg if BP fails to recover or falls further. Stop infusion if BP does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% NaCl at 10 mL/kg/hr for 2 hours prior to any subsequent infusion.

Renal Insufficiency: If renal function decreases, adjust etoposide as follows: CrCl 10-50 mL/min/1.73 m^2, decrease dose by 25%; if CrCl < 10 mL/min/1.73 m^2, decrease dose by 50%.

Hyperbilirubinemia: If direct bilirubin is > 2 mg/dL, decrease dose by 50%. If direct bilirubin is > 5 mg/dL, hold etoposide.

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 may be administered in an attempt to reduce the risk of worsening already existent myelosuppression (ANC < 500/µL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

Dose modifications following an episode of acute neurotoxicity:
Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.[43-45] 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.[45-50] 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,[51] include fewer doses of IT MTX, with an acceptably low frequency of CNS relapse, but the backbone of the BFM therapies is not the same as those currently used by the Children's Oncology Group. The exclusive use of IT ARAC has not been studied or described in the context of ALL therapy nor can one demonstrate the safety of omitting multiple doses of IT therapy without concomitant use of cranial irradiation or high dose methotrexate.

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

Following an acute neurotoxic event, a history and physical exam should guide the differential diagnosis. A neurology consult may be of value and should be considered. Seizures and other transient events may be linked to fever, infection, encephalitis, meningitis, hypertension, electrolyte disturbance, hypoglycemia, trauma, intracranial hemorrhage or thrombosis, narcotic withdrawal, illicit drug use, or other causes in addition to the direct side effects of chemotherapy. Appropriate laboratory studies may include, but are not limited to, blood cultures, a CBC, electrolytes, including glucose, calcium, magnesium and phosphorus, renal and liver function studies and/or an examination of the CSF. Imaging studies may include a CT scan and/or an MRI. The CT is commonly normal, in the absence of stroke, but if calcifications are present, this finding may be indicative of a more severe mineralizing leukoencephalopathy.[52] 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.[53-55] 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.[56] For patients who return to their "pre-event" status, without residual deficits of physical or neurologic exam, there are few data to support or guide therapeutic interventions. It is reasonable to hold the next dose of IT therapy, or, substitute IT Ara-C for 1 dose of IT MTX, or triple IT therapy. It is also reasonable to include leucovorin rescue at a dose of 5 mg/m^2 q 12 hrs x 2 doses beginning 48 hours after the LP. This pattern of rescue was associated with a clear diminution in the incidence of acute neurotoxicity in one case series.[56] 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.[57-60] 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.[61-64] At doses thought to be therapeutic, side effects have included nystagmus, nausea and vomiting, distorted vision, ataxia, and dizziness. In addition, Hollander et al [65] 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 Intermediate-Dose Methotrexate (ID MTX) and Leucovorin Rescue

[*Please note that* ***IDMTX*** *refers to* IV *MTX* ***1000 mg/m²*** ***given over 36*** **hrs**]

5.8.1 ID MTX Infusion Guidelines

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 0.5 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: to start at least 6 hours prior to commencement of intravenous methotrexate. **Fluid:** D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m^2/hour. 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 ≤ 1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Hour 0: MTX 100 mg/m^2 IV mixed in a final volume of 65 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L and infused over 30 minutes. This is followed, immediately, by MTX 900 mg/m^2 mixed in a final volume of 2935 mL/m^2 D5 ¼ NS with 30 mEq $NaHCO_3$/L given by continuous IV infusion over 35.5 hours at 125 mL/m^2/hr. Be certain that the ID MTX infusion is completed in the 36 hour period. **Note, even if the infusion is not complete at this time point, it must be stopped.**

Recommended Posthydration: Continue hydration using D 5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour (3 L/m^2/day) throughout IDMTX infusion, and for a minimum of 48 hours after its completion. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 µM.

Leucovorin rescue: 15 mg/m^2 PO/IV at 48 and 54 **hrs** after the start of the MTX infusion. If 48 hr methotrexate level is ≤ 0.5 µM, then only two doses of leucovorin are administered (at 48 and 54 hours). If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.

Hour 48: Check plasma methotrexate level at 48 hours after start of the methotrexate infusion. If the level is ≤ 0.5 µM, then do not give more than two doses of leucovorin (48 and 54 hours). If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.

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 (> 100% in 24 hours), assure appropriate urine pH and urine volume as above and consider glucarpidase If urine output fails to continue at 80% of the fluid intake, consider furosemide or acetazolamide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see below).

48 hr MTX level	Leucovorin Rescue
≤ 0.5 µM	Continue 15 mg/m^2 IV/PO q 6hrs for 2 doses.
0.5 – 1 µM	Increase to 15 mg/m^2 q 6 hrs until MTX level < 0.1 µM (draw q 6-24 hrs).

1 – 5 μM	Increase to 15 mg/m^2 q 3 hrs until MTX level < 0.1 μM (draw q 6-24 hrs).
5 – 10 μM	Increase to 100 mg/m^2 q 6hrs until MTX level < 0.1 μM (draw q 6-24 hrs).
> 10 μM	Increase to 1000 mg/m^2 q 6hrs until MTX level < 0.1 μM (draw q 6-24 hrs). Consider glucarpidase.

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 there is a rising creatinine (> 100% in 24 hours) or the 48 hour methotrexate level is > 10 μ/l consider using glucarpidase. If renal function does not recover, omit MTX. Do not give ID 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™).[66,67] To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue will remain on study.

Stop leucovorin 2 hours before administering glucarpidase as it is a competitive substrate and may compete with MTX for glucarpidase binding sites.

Dose of glucarpidase: 50 units/kg administered by intravenous bolus over 5 minutes. Reconstitute each vial with 1 mL sodium chloride 0.9% (do not further dilute). Each vial contains 1000 units/mL (after reconstitution) and round dose up to vial size. No further dose is required.

Maintaining alkalinization of urine with sodium bicarbonate is essential to maintain urinary pH > 7.

It is essential that patients are NOT co-prescribed the following medicines which reduce MTX excretion: NSAIDS, aspirin, ciprofloxacin, co-trimoxazole, penicillin, probenecid, omeprazole.

Two hours after administration of glucarpidase, leucovorin should be administered at a dose of 250 mg/m^2 every 6 hours by IV bolus (maximum rate: 160 mg/min) for up to 48 hours and then decreased based on plasma MTX concentrations to 15mg/m^2 intravenously or orally every 6 hours until the plasma MTX concentration is < 0.2 μM.

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 2 to 4 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3-4 mucositis, attempt to decrease the number of leucovorin doses to 2. 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.

See Section 5.13 for dose modifications when MTX is used post HSCT.

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

During Continuation:

a) ANC ≥ 750/µL and < 1000/µL and/or platelets ≥ 75 000/µL and < 100 000/µL: Do not modify dose but recheck CBC in 1 week. If during subsequent 4 weeks CBCs, ANC remains ≥ 750/µL and platelets remain ≥ 75 000/µL, continue at 100% doses and monitor CBC weekly.

b) ANC ≥ 500/µL and < 750/µL and and/or platelets ≥ 50 000/µL and < 75 000/µL: Reduce dose to 50% of original dose until ANC recovers to ≥ 750/µL and platelets recover to ≥ 75 000/µL. Increase dose approximately every 2 weeks, first to 75% of the original dose and then to full dose, provided ANC remains ≥ 750/µL and platelets remain ≥ 75 000/µL.

c) ANC < 500/µL and/or platelets < 50 000/µL:
Discontinue dose until ANC is ≥ 750/µL and platelets are ≥ 75 000/µL. Restart mercaptopurine and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-week intervals provided ANC remains ≥ 750/µL and platelets remain ≥ 75 000/µL. Consider a marrow evaluation in the face of persistent or prolonged neutropenia.

Prolonged cytopenia is defined as ANC < 750/µL and/or platelets < 75 000/µL after withholding therapy for > 2 weeks. Perform a bone marrow examination after 2 weeks of withholding chemotherapy, if no recovery is apparent. If monocyte count is increasing or viral myelosuppression is clinically suspected, the bone marrow examination may be postponed for 1-2 weeks and omitted if ANC and platelets fully recover by the 4th week after therapy is withheld.

If patient develops severe or unexpected myelosuppression, i.e., doesn't tolerate at least half dose MP, 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 6-MP and MTX simultaneously.

Consider discontinuing TMP/SMX as per COG Supportive care Guidelines at:
https://members.childrensoncologygroup.org/prot/reference_materials.asp.

If neutrophil count falls below 500/µL or if platelet count falls below 50 000/µL on > 2 occasions during Maintenance, perform thiopurine pharmacology testing as described below. Should therapy be withheld for myelosuppression or elevated transaminase, do not "make up" that week. Resume therapy at the correct point, chronologically.

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 weekly during Continuation 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.

For dose modifications when MTX is given for GVHD prophylaxis see Section 5.13.3.

Thiopurine Pharmacology Testing 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).[68-71] 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 6-MP (10 to 30 mg/m^2/day 3 days per week). About 35% of heterozygotes require a lower dose of 6-MP to avoid dose-limiting myelosuppression.[72]

There are now CLIA certified tests for TPMT genotype and phenotype, and for thiopurine metabolites (6-methyl mercaptopurine [6-MMP] and 6-TGN) measurements. Only 3 SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide.[68,73-76] 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 patients who have received full dose thiopurine therapy during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status
- TPMT genotyping will be informative in all patients, if at least 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 patient is *homozygous deficient* for TPMT, the thiopurine dose should be *reduced to* 10-20 mg/m^2/day 3 days per week. If the patient is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30%-50%. Do not increase the dose in response to a high ANC for 4 weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are not often necessary.

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

5.10 Steroids (Dexamethasone)

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) prior to Maintenance therapy. Consider omitting Maintenance steroid for osteonecrosis Grade 1 (clinically asymptomatic, radiographic finding only). Omit Maintenance steroid for osteonecrosis Grade 2 or greater, and notify study chair. Consider resuming Maintenance steroid after 6 months if joint symptoms have resolved and if MRI findings have significantly improved or normalized.

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

Inability to use oral doses:
For dexamethasone, substitute the IV preparation mg for mg.

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, consider switching to an equivalent dose of prednisone.

5.11 PO 6-Thioguanine (TG)

Continuation:
Oral TG will be held for suspected or proven serious infection.

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

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[77,78]:

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

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.

5.13 Stem Cell Transplant Regimen Agents

5.13.1 Tacrolimus

Tacrolimus commonly causes mild/moderate hypertension and alopecia and less commonly kidney or liver dysfunction, transplant associated microangiopathy (TAM), and neurological changes associated with significant hypertension. When trough levels are kept in the therapeutic range and patients receive adequate hydration and magnesium replacement, most of these side effects can be minimized. Hypertension should be managed with single or combination antihypertensive therapy. Tacrolimus should be held for severe toxicities thought to be related to its administration (significant neurological changes/malignant hypertension, TAM, kidney failure, etc.). Other immune suppressive medications may be substituted if tacrolimus is not tolerated (MMF, cyclosporine, etc.).

5.13.2 Cyclosporine

Cyclosporine commonly causes mild/moderate hypertension and less commonly kidney or liver dysfunction, TAM, and neurological changes associated with significant hypertension. When trough levels are kept in the therapeutic range and patients receive adequate hydration and magnesium replacement, most of these side effects can be minimized. Hypertension should be managed with single or combination antihypertensive therapy. Cyclosporine should be held for severe toxicities thought to be related to its administration (significant neurological changes/malignant hypertension, TAM, kidney failure, etc.). Other immune suppressive medications may be substituted if cyclosporine is not tolerated

5.13.3 Methotrexate

The most common acute side-effects of methotrexate include delay of count recovery, worsened mucositis, and kidney and liver damage (can contribute to VOD). Toxicity is directly related to the length of exposure to the drug. While methotrexate is generally excreted rapidly, delayed excretion of methotrexate occurs with decreased renal function and in circumstances where patients have third-space fluid collections (pulmonary effusions, ascites, joint effusions, etc.). The attending transplant physician should assess each patient prior to delivery of each dose and decide whether full dose methotrexate should be administered. Guidelines for modification of methotrexate dosing are listed in the tables below.

Table 5.13.3.1: Methotrexate Dose Modification for Renal Impairment

	Mild	**Moderate**	**Severe**	**Life-Threatening**
Serum creatinine	> 1.5-2 x baseline	> 2-2.5 x baseline	> 2.5-3 x baseline	> 3 x baseline or dialysis
% Methotrexate Dose reduction (Day +1, 3, 6, 11)	0-50%	50-100%	100% (no drug)	100% (no drug)

Table 5.13.3.2: Methotrexate Dose Modification for Significant Mucositis

Stomatitis, mucositis	**Painless ulcers, erythema, mild soreness or mild dysphagia**	**Painful erythema, edema, ulcers or moderate dysphagia, but can eat without narcotics**	**Cannot eat solids or requires narcotics to eat, requires parenteral or enteral support.**	**Complete obstruction or perforation**
% Methotrexate Dose reduction (Day +1, 3, 6, 11)	0%	0%	0-50%	50-100%

For significant third spacing (ascites, effusions, significant edema or weight gain > 5-10% above baseline) consider dose reductions of 50% and leucovorin rescue.

5.13.4 Guidelines for Leucovorin Rescue

Dose: Patients at risk for methotrexate toxicity should receive leucovorin at a dose of 5-10 mg/m^2 IV Q6H x 4 doses beginning 24 hours after administration of methotrexate. While most patients will need only 4 doses of leucovorin, if methotrexate levels are elevated due to renal dysfunction or other problems, leucovorin doses should be continued until serum methotrexate concentration is < 1x10^{-7}M. If serum methotrexate concentration is > 5x10^{-6}M, increase dose to 100 mg/m^2/dose IV Q3H until the serum methotrexate level is < 1x10^{-8}M.

5.13.5 Mycophenylate Mofetil (MMF)

MMF can cause decreased counts, nausea, vomiting, diarrhea, hypertension, dizziness, insomnia, hyperglycemia, electrolyte imbalances, rash, leg cramps, and bone pain. For significant diarrhea or low counts (neutropenia, etc.), a decrease of MMF by approximately 20% is usually sufficient to decrease the toxicity. Further dose medications for significant toxicity likely caused by MMF are allowed.

5.13.6 Adjustment of TBI/chemotherapy During the Preparative Regimen.

The full dose of preparative regimen TBI and chemotherapy agents will be administered unless patients have a life threatening reaction thought likely to occur again with continued administration and an appropriate substitution cannot be made (i.e. etopophos for etoposide).

5.13.7 Dose Adjustment of Chemotherapy for Patients Whose Weight Exceeds > 125% Ideal Body Weight (IBW)

Chemotherapy given during the preparative regimen (thiotepa, cyclophosphamide, and etoposide) will be dosed based on actual weight for patients ≤ 125% IBW. Those > 125% IBW will be dosed based upon adjusted ideal body weight as follows:

Adjusted ideal body weight = IBW + 0.25 (Actual weight – IBW).

The following formulas for pediatric and adult IBW calculations are recommended, but IBW may be calculated according to institutional standard operating procedures (SOPs).

<u>Recommended Ideal Body Weight Calculation for Children Age 1- 17 years</u>

$$\text{IBW} = \frac{\text{Height (cm)}^2 \times 1.65}{1000}$$

<u>Recommended Ideal Body Weight Calculation for Adults (Height > 5 feet/60 inches)</u>

IBW (females) = (cm ÷ 2.54 – 60) x 2.3 kg + 45.5 kg

IBW (males) = (cm ÷ 2.54 – 60) x 2.3 kg + 50 kg

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

7.1 Required Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated. **Obtain other studies prior to start of phase unless otherwise indicated.**

7.1a HR/IR Patients

STUDIES TO BE OBTAINED	Baseline	Block 1	Block 2	Block 3	Blinatumomab Blocks
Hx/PE with VS/Wt (BSA)	X		start of phase	start of phase	start of phase*
CBC/diff/plts	X	weekly	weekly	weekly	weekly
Bilirubin, ALT, creatinine, BUN	X	weekly	weekly	weekly	weekly
Local Bone Marrow (BM) Evaluation	X[1]	end of phase	end of phase	end of phase	end of phase
Bone Marrow (BM) for central flow MRD[2]		end of phase+	end of phase++	end of phase+++	end of Cycle 1++, end of Cycle 2+++
Bone Marrow (BM) for Immunophenotyping	X[2,7]				
CSF cell count and cytospin	X	with each IT	with each IT	with each IT	with each IT
Pharmacokinetics (PK)					Cycle 1: Day 2 and Day 14[6]
Immunogenicity					•Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1) •End of Cycle 2[$]
Echocardiogram	X				
Pregnancy test[3]	X				
Testicular exam	X	end of phase	end of phase	end of phase	end of phase
Testicular biopsy	X[4]	X[5]			

1 BM evaluation to confirm relapse and/or detect marrow disease in presumed isolated extramedullary relapse patients should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively by the COG Cytogenetics Committee. See Section 13.2 for details.

2 See Section 13.3 for details on shipping and handling

3 Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.

4 Patients with suspected testicular involvement at relapse (either isolated or with concurrent BM/CNS relapse) must have biopsy performed at baseline.

5 Patients with definite or equivocal residual testiculomegaly at end of Block 1 must have a biopsy to determine whether TRT is to be given during designated blocks of therapy (see Experimental Design Schema).

6 See lab manual on protocol webpage for sample collection and shipping details

7 Includes optional sample for CRLF2 expression for consenting patients (see Section 7.2 and Section 13.4).

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

$ In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1.

+ Evaluation 1 ++ Evaluation 2 +++pre-HSCT evaluation

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.1b **LR Patients**

STUDIES TO BE OBTAINED	Baseline	Block 1	Block 2	Block 3, Blinatumomab blocks, Continuation	Maintenance and post-therapy
Hx/PE with VS/Wt (BSA)	X		start of phase	start of phase*	every 28 days
CBC/diff/plts	X	weekly	weekly	weekly	every 28 days
Bilirubin, ALT, creatinine, BUN	X	weekly	weekly	weekly	every 28 days
Local Bone Marrow (BM) Evaluation	X[1]	end of phase	end of phase		
Bone Marrow (BM) for central flow MRD[2]		end of phase+	end of phase++		
Bone Marrow (BM) for Immunophenotyping	X[2,7]				
CSF cell count and cytospin	X	with each IT	with each IT	with each IT	with each IT
Absolute lymphocyte count with T and B subset quantification					At end of each 12 week maintenance cycle, and every 3 months after completion of therapy for 1 year
Pharmacokinetics (PK)				Blinatumomab Cycle 1:Day 2 and Day 14[6]	
Immunogenicity				•Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1) •End of Cycle 2[$]	Prior to start of Maintenance Cycle 1 therapy
Echocardiogram	X				
Pregnancy Test[3]	X				
Testicular Biopsy	X[4]	X[5]			

[1] BM evaluation to confirm relapse and/or detect marrow disease in presumed isolated extramedullary relapse patients should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively by the COG Cytogenetics Committee. See Section 13.2 for details.

[2] See Section 13.3 for details on shipping and handling

[3] Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.

[4] Patients with suspected testicular involvement at relapse (either isolated or with concurrent BM/CNS relapse) must have biopsy performed at baseline.

[5] Patients with definite or equivocal residual testiculomegaly at end of Block 1 must have a biopsy to determine whether TRT is to be given during designated blocks of therapy (see Experimental Design Schema).

[6] See lab manual on protocol webpage for sample collection and shipping details

[7] Includes optional sample for CRLF2 expression for consenting patients (see Section 7.2 and Section 13.4).

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

[$] In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1.

+ Evaluation 1 ++ Evaluation 2

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.1c **HSCT**

Observation	Prior to transplant (Tx)	1-2 weeks after ANC> 500/µL	3 mo Post-Tx	6 mo Post-Tx	9 mo Post-Tx	1 yr. Post-Tx	2 yrs. Post-Tx	3 yrs. Post-Tx	4 yrs. Post-Tx	5 yrs. Post-Tx	At subsequent relapse
Bone Marrow (BM) for central MRD[1]	X+++	X*	X**								
CSF cell count and cytospin	X										X
CBC, differential, platelets	X	X	X	X	X	X	X				X
BUN, Creatinine	X										
LFT	X	X	X	X	X	X	X				
Pulmonary function test		X									
Performance score	X	X	X	X	X	X	X	X	X	X	X

[1] See Section 13.3 for details on shipping and handling; (see Section 7.2)
+++pre-HSCT evaluation
*Day 30 (25-30)
**Day100 (+/- 3 weeks)

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.1d **Blinatumomab Salvage Therapy**

STUDIES TO BE OBTAINED	Blinatumomab Blocks
Hx/PE with VS/Wt (BSA)	Start of phase*
CBC/diff/plts	weekly
Bilirubin, ALT, creatinine, BUN	weekly
Local Bone Marrow (BM) Evaluation	end of phase
Bone Marrow (BM) for central flow MRD[2]	pre-HSCT
CSF cell count and cytospin	with each IT
Pharmacokinetics (PK)	Cycle 1: Day 2 and Day 14**
Immunogenicity	•Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1) •End of Cycle 2[$]

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e
**See lab manual on protocol webpage for sample collection and shipping details
[$] In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1.

7.1e **Recommended Observations: Blinatumomab Blocks**

The investigator is recommended to monitor the patient's vital signs (body temperature, heart rate and blood pressure) approximately every 4 hours during the first 12 hours after the start of a cycle, and upon resumption after suspension for adverse event. On Day 2 and 3 vital signs should be measured once daily."

7.2 Research Studies

The following are correlative biology studies for which patient participation is optional. Please see Section 13.0 for details on volumes of specimen collection and shipping information. **Note: Patient consent is required.**

Study (see section for details)	**Summary of Sample and Timing**
Banking for Future Research * (Section 13.1)	**Peripheral blood:** • Baseline • End Block 1 • End Block 2 • Relapse **Bone marrow:** • Baseline • End Block 1 • Relapse **NOTE:** This also includes the optional banking of residual material from required bone marrow for central flow MRD
CRLF2 expression (Section 13.4)	No separate specimen required – cell pellet from required baseline central flow bone marrow will be used

Protein Cell Stress (Section 13.6)	**Peripheral blood:**
	• Day 1 of Block 1
	  o Before chemotherapy (Hour 0)
	  o After Chemotherapy (Hour 6 and Hour 24)

Blinatumomab Pharmacodynamics (Section 13.5)	**Bone marrow:** • Prior to (Hour 0) start of first blinatumomab infusion **Peripheral blood:** • Prior to (Hour 0) start of first blinatumomab infusion During (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion

* For cases with a limited amount of tissue available for analysis, please prioritize specimen for tissue banking.

7.3 At Relapse

Patients who relapse and have consented to cell banking at time of enrollment should have samples of bone marrow sent to the Molecular Reference Laboratory for cell banking (see Section 13.1.)

7.4 Follow-up

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Treatment failure but not eligible to receive blinatumomab salvage
b) Treatment failure that receives blinatumomab salvage but does not achieve CR after 2 cycles of blinatumomab
c) Adverse events requiring removal from protocol therapy
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Completion of planned therapy.
f) Physician determines it is in patient's best interest.
g) Development of a second malignancy.
h) Second relapse at any site.
i) Repeat eligibility studies are outside the parameters required for eligibility (if applicable, see Section 3.2).
j) Inevaluable
k) Found to be ineligible for HSCT (See Section 4.9.1)
l) **Pre-Randomization (HR/IR or LR):** Interval development of significant central nervous system pathology that would preclude treatment with blinatumomab (see Section 3.2.5.13 for definition).

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

8.2 Off Study Criteria

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

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

9.1.1 Primary Endpoint

A primary objective (HR/IR Randomization) of AALL1331 is to compare disease-free survival (DFS) of HR and IR relapse patients randomized to Block 2 and 3 chemotherapy (Control) vs. two blocks of blinatumomab (Experimental), followed by allogeneic HSCT. DFS is defined as time from start of randomization to event (treatment failure, relapse, second malignancy, death) or last follow-up for those who are event-free. DFS event date will be set at Day 1 if patients are deemed as TF after randomization.

Another primary objective (LR Randomization) of AALL1331 is to compare DFS of LR relapse patients randomized to chemotherapy alone (Control: Block 3, Continuation 1, Continuation 2 and Maintenance) vs. blinatumomab/chemotherapy (Experimental: blinatumomab, Continuation 1, blinatumomab, Continuation 2, blinatumomab, Maintenance). DFS is defined as time from start of randomization to first event (relapse, second malignant neoplasm, remission death) or last follow up for those who are event-free.

9.1.2 Secondary Endpoints

A secondary objective (HR/IR Randomization) of AALL1331 is to compare overall survival (OS) of HR and IR relapse patients randomized to Block 2 and 3 chemotherapy (Control) vs. two blocks of blinatumomab (Experimental), followed by allogeneic HSCT. OS is defined as time from start of randomization to death or last date of contact.

Another secondary objective (LR Randomization) of AALL1331 is to compare OS of LR relapse patients randomized to chemotherapy alone (Control: Block 3, Continuation 1, Continuation 2 and Maintenance) vs. blinatumomab/chemotherapy (Experimental: blinatumomab, Continuation 1, blinatumomab, Continuation 2, blinatumomab, Maintenance). DFS is defined as time from start of randomization to first event (relapse, second malignant neoplasm, remission death) or last follow up for those who are event-free.

9.1.3 Exploratory Endpoints

The exploratory endpoints associated with HR/IR Randomization are to compare the rates of MRD positivity (>0.01%) at the end of Block 2 and 3 between randomized arms for HR and IR relapse patients.

Other exploratory endpoints include estimating the morphologic CR rate, MRD negativity (< 0.01%) rate and proportion that proceed to HSCT after treatment with blinatumomab for treatment failure patients not previously receiving blinatumomab, assessing the feasibility and safety of rapid taper of immune suppression for subset of HSCT patients with MRD ≥ 0.01% pre- and/or post-HSCT with no aGVHD, and collecting biologic samples for the prospective correlative biology studies described in Section 7.0.

9.2 Patient Accrual and Expected Duration of Trial

9.2.1 Stratification to be used in the randomization

All patients are assigned to Stratum 1 at enrollment. All HR/IR relapse patients who do not meet the treatment failure criteria at the end of Block 1 will be eligible for HR/IR randomization and randomized equally between experimental (blinatumomab) and control (chemotherapy) arms. The randomization will occur upon recovery from Block 1 of therapy, and will be stratified by: 1) Risk Group (HR vs. IR); 2) For HR patients, site of relapse (marrow vs. IEM); 3) For HR-marrow patients, duration of first remission (< 18 months vs. 18-36 months from diagnosis); 3) For HR-marrow patients, MRD level end Block 1 (< 0.1% vs. ≥ 0.1%) to ensure balanced randomization within these subsets (see table below).

Stratum #	Risk-Site	CR1 mos	MRD status
2	HR-Marrow	< 18	MRD < 0.1%
3	HR-Marrow	< 18	MRD ≥ 0.1%
4	HR-Marrow	18-36	MRD < 0.1%
5	HR-Marrow	18-36	MRD ≥ 0.1%
6	HR-IEM	<18	-
7	IR	-	-

All late B-ALL marrow and late B-ALL IEM relapse patients with end Block 1 MRD < 0.1% will eligible for LR randomization and randomized equally between experimental (blinatumomab) and control (chemotherapy) arms. The randomization will occur upon recovery from Block 1 of therapy, and will be stratified by: 1) site of relapse (marrow vs. IEM); and 2) MRD level at time of randomization (< 0.01% vs. ≥ 0.01%) to ensure balanced randomization within these subsets.

Stratum #	Site	CR1 mos	MRD status
8	LR-Marrow	≥ 36	MRD < 0.01%
9	LR-Marrow	≥ 36	MRD ≥ 0.01% or MRD < 0.1% with sensitivity 1/1000
10	LR-IEM	≥ 18	MRD < 0.01%
11	LR-IEM	≥ 18	MRD ≥ 0.01% or MRD < 0.1% with sensitivity 1/1000

9.2.2 Sample size with power calculation

Sample size calculations driving this study are based on the two randomized questions HR/IR Randomization and LR Randomization.

For HR/IR Randomization, approximately 170 evaluable HR/IR B-ALL patients are to be randomized between experimental (blinatumomab) and control (chemotherapy) arms after recovery from Block 1. As described in Section 9.3.1, the test of the randomization question has a power of 80.0% at a one-sided significance level of 2.5% to detect the desired improvement in 2-year DFS rate. The 170 evaluable HR/IR B-ALL patients are expected to take 3 years to be enrolled with the total rate of accrual to HR/IR Randomization to be 56 per year after adjusting for approximate 10% refusal rate to randomization. This estimate is based on the following estimates of annual accrual and dropout rate from past studies AALL01P2, AALL02P2, AALL0433 and ADVL04P2:

	Early marrow	Early IEM	Late marrow	Late IEM
# entering study	60	5	44	28
Rate of MRD ≥ 0.1%	-	-	38%	12%
Rate of not dropping out prior to block 2 (due to toxicity and/or treatment failure)	70%	70%	90%	90%
# eligible for randomization	42	3	15	3

For LR randomization, approximately 206 evaluable LR B-ALL patients are to be randomized between experimental (blinatumomab) and control (chemotherapy) arms after recovery from Block 1. As described in Section 9.3.2, the test of the randomization question has a power of 80.4% at a one-sided significance level of 5% to detect the desired improvement in 3-year DFS rate. The 206 evaluable LR B-ALL patients are expected to accrue over 5.6 years with total rate of accrual to LR Randomization to be 37 per year after adjusting for approximate 10% refusal rate to randomization. This estimate is based on the following estimates of annual accrual and dropout rate from past studies AALL01P2, AALL02P2, AALL0433 and ADVL04P2:

	Late marrow	Late IEM
# entering study	44	28
Rate of MRD < 0.1%	62%	88%
Rate of not dropping out prior to block 2 (due to toxicity and/or treatment failure)	80%	80%
# eligible for randomization	22	20

Therefore, in order to enroll 170 and 206 evaluable patients for HR/IR and LR Randomization respectively, a total of 195 early marrow/IEM and 403 late marrow/IEM patients are expected be accrued at the beginning of the study.

9.3 Statistical Analysis Methods

9.3.1 HR/IR Randomization for HR and IR relapse patients

9.3.1.1 Primary endpoint: intent-to-treat DFS

The primary efficacy analysis for HR/IR Randomization will be an intent-to-treat comparison of the DFS curves between the randomized arms based on the Log-rank test. All HR/IR relapse patients who are not deemed as treatment failures at the end of Block 1 will be eligible for HR/IR Randomization. The randomization will occur upon recovery from Block 1 of therapy, and will be stratified as described in Section 9.2. From the past studies of AALL01P2, AALL02P2 and ADVL04P2, the overall 2-year DFS rate for HR/IR patients was approximately 45%. Although most events are projected to occur within 2 years, events continue to occur in subsequent years, and hence an exponential distribution is considered more appropriate than a cure-rate model for comparing survival curves for this cohort of patients at the time of final analysis. Assuming a minimum of 2 years of follow up, an estimate of 170 evaluable patients will need to be randomized to achieve the goal of 18% improvement in 2-year DFS rate with blinatumomab over the expected 2-year DFS rate of 45% with chemotherapy backbone alone, with 80.0% power at a one-sided significance level of 2.5%, which represents a 42.1% reduction in hazard rate. The power calculations are based on the assumption of proportional hazards and using the log rank test.

Interim analysis will be conducted to monitor for efficacy and futility. The efficacy stopping boundaries to be used will be based on the O' Brien-Fleming spending function. The futility boundaries are based on testing the alternative hypothesis at the 0.024 level.[79] This monitoring rule can be applied to any interim analysis schedule and maintains the overall significance level of 0.025. Assuming exponential distribution and the final analysis is performed at the 2 years after the completion of enrollment, the expected maximum number of events to be observed is estimated to be 109. The first interim analysis will be performed after 36 events have been observed. The cumulative power to detect the desired improvement is approximately 78%. The sample of monitoring boundaries for efficacy and futility with 3 interim analyses are given in the table below.

Looks	# of events	Information	Efficacy Boundary	Futility Boundary
1	36	33%	3.731	-0.392
2	73	67%	2.504	0.280
3	109	100%	1.994	1.994

9.3.1.2 Secondary Endpoint: Intent-to-treat OS

From the past studies of AALL01P2, AALL02P2 and ADVL04P2, the 3-year OS rate for HR/IR patients was approximately 48%, and most deaths occurred within the first 3 years. Therefore, a cure-rate model with exponential distribution assumed during the first 3 years followed by a flat curve is considered for OS analysis. An interim OS analysis will be conducted at the time of the final DFS analysis, i.e. when all the 170 randomized patients are followed up for 2 years. Assuming 17% improvement in 3-year OS rate with blinatumomab over the expected 3-year OS rate of 48% with chemotherapy backbone alone, approximate 70 deaths are to be observed by the time of the interim OS analysis. The power to detect such improvement at a one-sided significance level of 2.5% is approximate 61% based on the log-rank test.

If DFS analysis meets its target level of improvement (i.e. one-sided p-value < 0.025), the formal OS analysis will be performed at at 1 year after the interim OS analysis, by which time approximate 74 deaths are to be observed. The power to detect the above desired improvement is approximately 63%.

9.3.1.3 Secondary endpoint: MRD+ rates

MRD comparisons (using an MRD+ threshold of 0.01%) will be performed at the end of Blocks 2 and 3 for marrow relapse patients participating in HR/IR Randomization. From past experience with studies AALL01P2, ADVL04P2, AALL07P1 and AALL0433, we anticipate that over the 3 years of the study, there will be 56 patients per arm evaluable for the MRD comparison at the end of Block 2 and 50 patients per arm evaluable for the MRD comparison at the end of Block 3 (see table below for derivation).

	Early marrow	**Late marrow with MRD ≥ 0.1%**	**Total**
# randomized on HR/IR Randomization (per arm)	61	24	85
Rate of not dropping out prior to end Block 2	63%	75%	
# evaluable for end Block 2 MRD testing	38	18	56
Rate of not dropping out prior to end Block 3	89%	88%	
# evaluable for end Block 3 MRD testing	34	16	50

Further, we anticipate that the rates of MRD ≥ 0.01% in the control arm will be 67% (67% for early and 68% for late) at the end of Block 2 and 47% (43% for early and 55% for late) at the end of Block 3. A two-sample Fisher's exact test of proportions (one-sided, alpha = 5%) will be used to test the hypothesis that the proportion of patients who are MRD+ on each experimental arm (with blinatumomab) is smaller than the control arm (without blinatumomab) at the end of Block 2 and 3. The corresponding power to detect various degrees of reduction in MRD+ rates is shown in the table below:

	Expected # per arm with successful MRD determination	**% MRD+ (control arm)**	**Reduction in MRD+ rates (investigational arm)**			
			10%	15%	20%	25%
End Block 2	56	67%	22.6%	41.8%	63.2%	81.2%
End Block 3	50	47%	19.2%	37.1%	59.5%	79.8%

9.3.1.4 Safety monitoring

According to the past study ALLR3, the cumulative toxic death rate of Blocks 2 and 3 of chemotherapy was estimated to be 4% (1.6% for Block 2 and 2.7% for Block 3). The toxic death rate is expected to be lower in the experimental arm than the control arm because the myelosuppressive cytotoxic chemotherapy blocks are replaced with targeted immunotherapy. Therefore, toxic deaths will be closely monitored on all patients enrolled to each arm of HR/IR Randomization separately through blocks 2 and 3 of therapy. HR/IR Randomization will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths in either arm is greater than or equal to that specified in the table. The boundary of toxic death was computed based on Pocock-type spending function at one-sided 20% significant level.

Looks	**# evaluable patients**	**Information**	**Pocock boundary of excessive toxic death**	**Excessive toxic death rate**

1	28	33%	4	14.29%
2	57	67%	5	8.77%
3	85	100%	7	8.24%

Either arm of HR/IR Randomization will be rejected for excessive toxicity if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring an arm too toxic are approximately 95.2%, 80.8%, 47.2% and 10.1% when the true toxic death rate is 13%, 10%, 7% and 4%, respectively.

In addition, occurred during Block 2 and 3 of chemotherapy the toxic deaths and all toxicities of all grades between the two arms will be monitored/compared during the study. If the toxic death rate or the rate for any specific toxicity is significantly higher on the blinatumomab arm compared to the control arm (ALLR3 backbone), the data will be reviewed for possible suspension of the randomization and modification of therapy.

9.3.2 LR Randomization for LR relapse patients

9.3.2.1 Primary endpoint: intent-to-treat DFS from randomization

The primary efficacy analysis for LR Randomization will be an intent-to-treat comparison of the DFS curves between the randomized arms based on the Log-rank test. All late B-ALL marrow and IEM relapse patients with end Block 1 MRD < 0.1% who are not deemed to be treatment failures at the end of Block 1 or Block 2 will be eligible for LR Randomization . For IEM patients, uninterpretable MRD (due to lack of diagnostic marker) will be considered to be MRD negative. The randomization will occur upon recovery from Block 2 of therapy, and will be stratified as described in Section 9.2. Data from past studies suggest that most events are to occur within 3 years, but events continue to occur in subsequent years, and hence an exponential distribution is considered more appropriate than a cure-rate model for comparing survival curves for this cohort of patients at the time of final analysis. An estimate of 206 evaluable patients will be randomized 1:1 (103 evaluable patients per arm) between randomized experimental (blinatumomab) and control (chemotherapy) arms. Assuming a minimum of 3-years of follow up, this sample size estimate is based on a goal of achieving a 11% improvement in 3-year DFS rate with blinatumomab over the expected 3-year DFS rate of 73% with chemotherapy backbone alone, with 80.4% power at a one-sided significance level of 5%, which represents a 44.6% reduction in the hazard rate. The power calculations are based on the assumption of proportional hazards and using the log rank test.
Interim analysis will be conducted to monitor for efficacy and futility. The efficacy stopping boundaries to be used will be based on the O' Brien-Fleming spending function. The futility boundaries are based on testing the alternative hypothesis at the 0.039 level.[79] This monitoring rule can be applied to any interim analysis schedule and maintains the overall significance level of 0.05. Assuming exponential distribution and the final analysis is performed at the 3 years after the completion of enrollment, the

expected maximum number of events to be observed is estimated to be 75. The first interim analysis will be performed after 25 events have been observed. The cumulative power to detect a difference is approximately 80%. The sample of monitoring boundaries for efficacy and futility with 3 interim analyses are given in the table below.

Looks	**# of events**	**Information**	**Efficacy Boundary**	**Futility Boundary**
1	25	33%	3.202	-0.312
2	50	67%	2.140	0.288
3	75	100%	1.695	1.695

9.3.2.2 Secondary Endpoint: Intent-to-treat OS

From past studies suggest that most events for LR patients are to occur within 4 years after randomization and the 4-year OS rate is estimated to be 77%. Therefore, a cure-rate model with exponential distribution assumed during the first 4 years followed by a flat curve is considered for OS analysis for LR randomized patients. An interim OS analysis will be conducted at the time of the final DFS analysis, i.e. when all the 206 randomized patients are followed up for 3 years. Assuming 10% improvement in 4-year OS rate with blinatumomab over the expected 4-year OS rate of 77% with chemotherapy backbone alone, approximate 36 deaths are to be observed by the time of the interim OS analysis. The power to detect such improvement at a one-sided significance level of 5% is approximate 60% based on the log-rank test.
If DFS analysis meets its target level of improvement (i.e. one-sided p-value < 0.05), the formal OS analysis will be performed at 1 year after the interim OS analysis, by which time approximate 37 deaths are to be observed. The power to detect the above desired improvement is approximately 61%.

9.3.2.3 Monitoring for severe toxicities and toxic deaths

According to the past study of ALLR3, the cumulative toxic death rate of Block 3, Continuation and Maintenance chemotherapy was estimated to be 4% (2.7% for Block 3 and 1.5% for Continuation and Maintenance). The toxic death rate is expected to be lower in the experimental arm than the control arm because the myelosuppressive Block 3 is replaced with targeted immunotherapy. Therefore, toxic deaths will be closely monitored on all patients enrolled on to each arm of LR Randomization separately from the start of Block 3 of therapy to the completion of protocol therapy. LR Randomization will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths in either arm is greater than or equal to that specified in the table below. The boundary of toxic death was computed based on Pocock-type spending function at one-sided 20% significant level.

Looks	# evaluable patients	Information	Pocock boundary of excessive toxic death	Excessive toxic death rate
1	34	33%	4	11.76%
2	69	67%	6	8.70%
3	103	100%	7	6.80%

Either arm of LR Randomization will be rejected for excessive toxicity if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring an arm too toxic are approximately 98.7%, 90.9%, 61.5% and 14.4% when the true toxic death rate is 13%, 10%, 7% and 4%, respectively.
In addition, occurred during Block 3, Continuation 2 (Week 1-5) and Maintenance (Week 6-10) the toxic deaths and all toxicities of all grades between the two arms will also be monitored/compared during the study. If the toxic death rate or the rate for any specific toxicity is significantly higher on the blinatumomab arm compared to the control arm, the data will be reviewed for possible suspension of the randomization and modification of therapy.

The potential for late adverse effects due to long term depletion of $CD19^+$ normal lymphocytes following blinatumomab treatment is unknown. We will monitor for lymphocyte recovery and late events related to delayed recovery. Since HR/IR/TF patients go to HSCT soon after blinatumomab, it would be difficult to make sense of lymphocyte recovery/late events after blinatumomab for them. However, the LR patients that are randomized to +/- blinatumomab and do not proceed to HSCT serve as an excellent population to monitor for these delayed adverse effects. For all LR patients, we will collect absolute lymphocyte counts (ALC)/lymphocyte subset counts (total T and B cells) and data regarding late infections and progressive multifocal leukoencephalopathy (PML) after each 12-week maintenance cycle and every 3 months after completion of therapy for 1 year. The peripheral B-cell recovery rates and rates of late events by randomized arms will be monitored and compared descriptively between the two randomized arms every 6 months in the biannual study progress report and DSMC report.

9.3.3 Pilot intervention for very high risk subset of HSCT recipients based on MRD and aGVHD

9.3.3.1 Primary endpoint

The primary endpoint of this non-randomized exploratory pilot intervention (accelerated taper of immune suppression) is feasibility and safety, with "success" defined as < 25% rate of Grade III-IV aGVHD and < 5% rate of treatment-related mortality (TRM) associated with the accelerated taper. We anticipate that 36 patients will meet the criteria to receive the intervention. We will calculate the observed rates of Grade III-

IV aGVHD and TRM among this subset with 95% confidence intervals and compare descriptively to our target rates.

9.3.3.2 Exploratory endpoint

As secondary endpoints, we will calculate the percent of patients able to wean off immunosuppression without significant aGVHD (future intervention group), DFS of intervention group (vs. similar pts in ASCT0431 historical controls), rate of conversion from MRD+ to MRD- among preMRD-/postMRD+ subset (correlated with DFS), aGVHD rates post-intervention (correlated with DFS). These data will be analyzed descriptively.

9.3.3.3 Safety monitoring

The toxic death and Grade 3+ GVHD rates will be closely monitored for the subset of HSCT patients with MRD ≥ 0.01% pre- and/or post-HSCT with no acute graft versus host disease (aGVHD) who undergo accelerated taper of immune suppression during the study. According to past studies, the cumulative toxic death rate was estimated to be 5% and the cumulative incidence rate of Grade 3+ GVDH was approximately 25%.
The safety stopping boundaries to be used for toxic death and Grade 3+ GVHD, respectively, will be based on the Pocock-type spending function at one-sided 20% significance level. Assuming 85% of evaluable HR/IR patients will proceed to HSCT study and approximately 25% of them will have MRD ≥ 0.01% pre- and/or post-HSCT with no evidence of aGVHD, an estimate of 36 patients will be monitored in this subset. The intervention (accelerated taper of immune suppression) will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths or the number of Grade 3+ GVHD is greater than or equal to that specified in the corresponding table below,

Table for toxic death monitoring boundary:

Looks	**# evaluable patients**	**Information**	**Pocock boundary of excessive toxic deaths**	**Excessive toxic death rate**
1	12	33%	3	25.00%
2	24	67%	4	16.67%
3	36	100%	4	11.110%

The intervention will be rejected for excessive toxicity death if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring the intervention too toxic are approximately 88.5%, 71.1%, 41.6% and 10.9% when the true toxic death rate is 17%, 13%, 9% and 5%, respectively.

Table for Grade 3+ GVHD monitoring boundary:

Looks	# evaluable patients	Information	Pocock boundary of excessive toxicity	Excessive toxicity rate
1	12	33%	6	50.00%
2	24	67%	10	41.67%
3	36	100%	13	36.11%

The intervention will be rejected for excessive Grade 3+ GVHD if the number of observed Grade 3+ GVHD is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring the intervention too toxic are approximately 96.4%, 80.5%, 45.9% and 13.2% when the true rate of Grade 3+ GVHD is 49%, 41%, 33% and 25%, respectively.

See Appendix XII for guidelines for establishing organ stage and overall grade of acute GVHD.

9.3.4 Treatment Failure (TF) patients who are non-randomly assigned to blinatumomab

Point estimate and the corresponding exact 95% confidence interval based on Clopper-Pearson's method will be provided to estimate the hematologic CR , the rate of MRD < 0.01%, and the proportion treatment failure patients able to proceed to hematopoietic stem cell transplant (HSCT).

The toxic death will be closely monitored for TF patients who are non-randomly assigned to blinatumomab. According to past studies, an approximate 60 (10%) of enrolled patients will be deemed as TF, and the cumulative toxic death rate is estimated to be 6%. The safety stopping boundaries to be used for toxic death will be based on the Pocock-type spending function at one-sided 20% significance level. The intervention for TF patients will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths is greater than or equal to that specified in the corresponding table below,

Table for toxic death monitoring boundary:

Looks	# evaluable patients	Information	Pocock boundary of excessive toxicities	Excessive toxic death rate
1	12	33%	3	25.00%
2	24	67%	4	16.67%
3	36	100%	5	13.89%
4	48	33%	6	12.50%
5	60	67%	7	11.67%

The intervention will be rejected for excessive toxicity death if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring the intervention too toxic are approximately 85.9%, 67.1%, 39.1% and 12.9% when the true toxic death rate is 15%, 12%, 9% and 6%, respectively.

9.3.5 Blinatumomab related reportable adverse event (RAE)

A reportable adverse event (RAE) with respect to blinatumomab is defined in Section 5.2. The reporting period case report form (CRF) for each blinatumomab course will specifically collect data regarding blinatumomab RAEs. Due to limited experience with blinatumomab, very little information is available estimate the expected incidence of blinatumomab RAEs. We will prospectively monitor the blinatumomab RAE rate on monthly study committee calls, and will report the blinatumomab RAE rate every 6 months in the biannual study progress report and DSMC report. RAE rates ≥ 10% will be of particular concern and will prompt discussion with the DSMC.

9.4 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	85	79	164
Not Hispanic or Latino	225	209	434
Ethnic Category: Total of AllParticipants	310	288	598
Racial Category			
American Indian/Alaska Native	5	3	8
Asian	12	14	26
Black or African American	35	22	57
Native Hawaiian or Other Pacific Island	2	1	3
White	256	248	504
Racial Categories: Total of All Subjects	310	288	598

* These totals must agree

This distribution was derived from past studies on AALL01P2, AALL02P2, ADVL04P2 and AALL0433.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (i.e., v4.02 and all subsequent iterations prior to version 5.0).

10.2 Response Criteria

See definitions in Section 3.3.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

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

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

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

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

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

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

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the NCI's CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: 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 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"*** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

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

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

11.4.5 Pregnancy, Fetal Death, 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.

11.4.5.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy*)"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, **pregnancy in partners of men on study needs be reported and followed in the same manner as a patient pregnancy**.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.5.2 **Fetal Death**

Fetal death, defined in CTCAE as "*A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation*", needs to be reported expeditiously, as **Grade 4 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)*"**. Do NOT report a fetal death as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.5.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"A disorder characterized by cessation of life occurring during the first 28 days of life*" needs to be reported expeditiously, as **Grade 4 "*General disorders and administration - Other (neonatal loss)*" when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

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

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://webapps.ctep.nci.nih.gov/openapps/plsql/gader_accept$.startup.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.
In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via

CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (e.g., H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **301-230-0159** (back-up: 301-897-7404).

Also: Fax or email to COG for **all** IND studies (fax # 626-303-1768; email: COGCTEP-AERS@childrensoncologygroup.org; Attention: COG CTEP-AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

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: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[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

11.10 Protocol Specific Additional Instructions and Reporting Exceptions

- **Grades 1-4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.**
- **Any blinatumomab-related AE that results in interruption of dosing as described in Section 5.2 requires expedited reporting.**

11.11 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 that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

11.12 **Routine Adverse Event Reporting**

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting is split into three categories:

1. During all blinatumomab cycles as well as parallel control arm cycles, routine reporting will include **all toxicities of all grades (see table)**.
2. HSCT routine reporting will include All toxicities reported via CTEP-AERS and all Grade 4 and higher non-hematological Adverse Events
3. During all other blocks of therapy, routine reporting will include **all toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events (see table).**

ADVERSE EVENT REPORTING BY TREATMENT PHASE		
ALL PATIENTS		**REPORTING REQUIREMENT**
Block 1		All toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events
HR/IR		
Arm A (Control)	**Arm B (Experimental)**	
Block 2	Blinatumomab: Cycle 1	All toxicities of all grades
Block 3	Blinatumomab: Cycle 2	All toxicities of all grades
Bridging Therapy		All toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events
HSCT	HSCT	All toxicities reported via CTEP-AERS and all Grade 4 and higher non-hematological Adverse Events

<table>
<tr><th colspan="2">LR</th><th></th></tr>
<tr><th>Arm C
(control)</th><th>Arm D
(Experimental)</th><th></th></tr>
<tr><td>Block 2</td><td>Block 2</td><td>All toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events</td></tr>
<tr><td>Block 3</td><td>Blinatumomab cycle 1</td><td>All toxicities of all grades</td></tr>
<tr><td>Continuation 1</td><td>Continuation 1</td><td>All toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events</td></tr>
<tr><td>Continuation 2
(first 5 weeks – days 1-35)</td><td>Blinatumomab cycle 2</td><td>All toxicities of all grades</td></tr>
<tr><td>Continuation 2
(last 3 weeks – days 36-53)</td><td rowspan="2">Continuation 2</td><td rowspan="2">All toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events</td></tr>
<tr><td>Maintenance
(first 5 weeks – days 1-35)</td></tr>
<tr><td>Maintenance
(second 5 weeks – days 36-70)</td><td>Blinatumomab cycle 3</td><td>All toxicities of all grades</td></tr>
<tr><td>Maintenance
(remainder)</td><td>Maintenance (all)</td><td>All toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events</td></tr>
<tr><th colspan="2">TF-Salvage Therapy</th><th></th></tr>
<tr><td colspan="2">Blinatumomab-S 1</td><td rowspan="2">All toxicities of all grades</td></tr>
<tr><td colspan="2">Blinatumomab-S 2</td></tr>
</table>

12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

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

12.2 CTA/CRADA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

12.2.1 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.

12.2.2 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.

12.2.3 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.

12.2.4 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.

12.2.5 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.

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

Email: ncicteppubs@mail.nih.gov

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

13.0 SPECIAL STUDIES AND SPECIMEN REQUIREMENTS

Enrollment on companion protocol AALL05B1 (Cell Banking for Relapsed ALL) is ENCOURAGED, but NOT REQUIRED. Patients who do enroll on AALL05B1 only require a single cell bank specimen (i.e. not separate AALL1331 and AALL05B1 specimens).

13.1 Banking for Future Research (optional)

NOTE: Enrollment on companion protocol AALL05B1 (Cell Banking for Relapsed ALL) or APEC14B1 (Project: Every Child) is ENCOURAGED, but NOT REQUIRED. Patients who do enroll on AALL05B1 or APEC14B1 only require a single cell bank specimen (i.e. not separate AALL1331 and AALL05B1 or APEC14B1 specimens).

For cases with a limited amount of tissue available for analysis, please prioritize specimen for tissue banking.

This study is designed to provide material for banking for the purpose of performing retrospective studies to refine risk stratification, identify new targets for therapy, identify biomarkers to predict response, and to link host polymorphisms with various disease characteristics and toxicities. See Appendix VI for details.

Sample Collection Procedures
A Specimen Transmittal Form should accompany every shipment of specimen(s) to the COG Reference Laboratory. Please complete one form per patient per shipment.

Please note: The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Shipping Media (SM)
Samples for the Reference Laboratories are to be collected in shipping media (SM) in special 15 mL conical tubes. The SM contains RPMI with EDTA as the anticoagulant. These tubes will be prepared in the Molecular Reference Laboratory and shipped in batches to each participating institution, where they can be stored frozen at -20°C until use. Tubes are stable for 3 months if refrigerated and stable for 1 year if frozen. To request prepared and pre-packaged sample shipping tubes, order tubes through the Biopathology Center kit management system (use the link provided on the CRA Web page).

Please Note: The receiving institutions are strongly encouraged to make requests for sample tubes well in advance of their first patient registration on AALL1331; it will not be possible to expedite shipping because of prohibitive costs.

Bone Marrow/Peripheral Blood Collection Procedures for Reference Laboratories:

a. Collect BM/PB into a syringe and transfer the specimen immediately into the SM tube with RPMI/EDTA.
b. Mix well. At least 2 mL and up to 5 mL of BM/PB can be placed in 1 SM tube. If you don't have SM tubes, you can place the BM into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is greatly enhanced in the SM tubes.

c. For BM, use multiple syringes and tubes as necessary. Reposition the BM aspirate needle at least once during the diagnostic procedure to ensure the maximum quality of BM. DO NOT SHIP SYRINGES.

d. Label each tube with COG registration number/Biopathology number, patient name and date of birth, date, institution and type of specimen (bone marrow).

e. Samples are to be shipped at room temperature except for international samples that are expected to be delayed for more than 48 hours – place a cold pack (not ice pack) in shipment.

NOTE: For patients who are not having a diagnostic BM for medical reasons, and who have an absolute blast count of at least 1,000/µL, 2 mL of PB at diagnosis may be submitted for each 1 mL of required marrow and submitted to the Reference Laboratories instead of diagnostic BM.

Reference Laboratory – Shipping Address (including Saturday delivery):

Molecular Laboratory
Julie Gastier-Foster, PhD
COG ALL Reference Laboratory
Nationwide Children's Hospital
700 Children's Drive, C1961
Columbus, OH 43205
Contact Person: Yvonne Moyer
Phone: (614) 722-2866
Fax: (614) 722-2887
Email: Julie.Gastier-Foster@nationwidechildrens.org

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.
Notify Laboratory of each Saturday delivery

13.2 Local Bone Marrow: Central review of cytogenetics/FISH

Bone marrow aspiration to confirm relapse (and/or to detect potential marrow disease in presumed isolated extramedullary relapse patients) is required for **study entry**. Morphologic, immunophenotypic, & cytogenetic/FISH analysis should be performed by the local institution. Cytogenetic analysis should include FISH for any cytogenetic abnormalities known from the patient's original leukemia if applicable. All FISH should be performed on uncultured directly harvested cells or unstimulated overnight cultured cells if the former is not possible. FISH for abnormalities shown by cytogenetics to be unique to the relapse specimen should also be done on directly harvested cells or unstimulated overnight cultured cells if the former is not possible. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively by the COG Cytogenetics Committee.
Please see the following link for a list of COG approved cytogenetics labs:
https://members.childrensoncologygroup.org/Disc/cytogen/default.asp

Required Material:

a) Two **original** karyotypes of different cells from each abnormal clone or of two normal cells when no abnormalities are found; full-size metaphase images of the karyotypes cells.

b) A completed COG Cytogenetics Reporting Form and FISH Form (if done). These reporting forms are available on the AALL1331 protocol web page. Electronic submission of the karyotypes/FISH images is required.

Shipping: The review materials on each case should be sent to the COG ALL Cytogenetic Coordinators within 4 weeks of study entry. If the institution is west of the Mississippi River, send these materials to Dr. Andrew Carroll (University of Alabama). If the institution is east of Mississippi River (except Minnesota and Wisconsin, which go to Dr. Carroll), send all materials to Dr. Nyla Heerema (The Ohio State University).

Western Laboratory – Shipping Address:
Dr. Andrew Carroll, Ph.D.
Ph.D. Department of Genetics
University of Alabama at Birmingham
720 20th St. So. Kaul Bldg. Room 314B
Birmingham, AL 35294
Phone: 205-934-0665
Fax: 205-934-1078
Email: acarroll@ uab.edu

Eastern Laboratory – Shipping Address:
Dr. Nyla Heerema, Ph.D.
Professor and Director of Cytogenetics
The Ohio State University
Division of Clinical Pathology
Hamilton Hall, Room 167
1645 Neil Ave. Columbus, OH 43210
Phone: 614-292-7815
Fax: 614-292-7072
Email: Nyla.Heerema@osumc.edu

13.3 **Bone Marrow for Central Flow-Immunophenotping and MRD (required)**

Immunophenotyping will be done on fresh bone marrow specimens collected **at study entry** (see Section 7.1). Minimal residual disease will be detected using 6 color flow cytometry (Dr. Michael Borowitz, Johns Hopkins University) on fresh bone marrow specimens collected **during therapy at various designated time points** (see Section 7.1). For patients who have consented to specimen banking, residual material should be sent for banking. See section Section 13.1 for details.

Sample Collection Procedures

A Specimen Transmittal Form should accompany every shipment of specimen(s) to the COG Reference Laboratory. Please complete one form per patient per shipment.

Please note: The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Shipping Media (SM)

Samples for the Reference Laboratories are to be collected in shipping media (SM) in special 15 mL conical tubes. The SM contains RPMI with EDTA as the anticoagulant. These tubes will be prepared in the Molecular Reference Laboratory and shipped in batches to each participating institution, where they can be stored frozen at -20°C until use. Tubes are stable for 3 months if refrigerated and stable for 1 year if frozen. To request prepared and pre-packaged sample shipping tubes, order tubes through the Biopathology Center kit management system (use the link provided on the CRA Web page).

Please note: The receiving institutions are strongly encouraged to make requests for sample tubes well in advance of their first patient registration on AALL1331; it will NOT be possible to expedite shipping because of prohibitive costs.

Bone Marrow Collection Procedures for Reference Laboratories:

a. Collect BM into a syringe and transfer the specimen immediately into the SM tube with RPMI/EDTA.

b. Mix well. At least 2 mL and up to 5 mL of BM can be placed in 1 SM tube. If you don't have SM tubes, you can place the BM into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is greatly enhanced in the SM tubes.

c. Use multiple syringes and tubes as necessary. Reposition the BM aspirate needle at least once during the diagnostic procedure to ensure the maximum quality of BM. DO NOT SHIP SYRINGES.

d. Label each tube with COG registration number/Biopathology number, patient name and date of birth, date, institution and type of specimen (bone marrow).

e. Samples are to be shipped at room temperature except for international samples that are expected to be delayed for more than 48 hours – place a cold pack (not ice pack) in shipment.

NOTE: For patients who are not having a diagnostic BM for medical reasons, and who have an absolute blast count of at least 1,000/µL, 2 mL of PB at diagnosis may be submitted for each 1 mL of required marrow and submitted to the Reference Laboratories instead of diagnostic BM.

Please note: Specimens will be shipped to the COG Reference Laboratory at Johns Hopkins (Eastern) ONLY.

Reference Laboratory – Shipping Address (including Saturday delivery):

Michael Borowitz, MD, PhD
Flow Cytometry Laboratory, Johns Hopkins Medical Institutions
Weinberg Building – Room 2300
401 N. Broadway
Baltimore, MD 21287
Phone: 410-614-2968
Fax: 410-502-1493
Email: mborowit@jhmi.edu

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf. **Notify Laboratory of each Saturday delivery at 410-614-2968 or via email at kbowles3@jhmi.edu**

13.4 **Bone Marrow for CRLF2 expression (optional)**

We will quantify surface CRLF2 expression by flow cytometry and correlate with outcome. This assay will be done in conjunction with the immunophenotyping performed at study entry in Dr. Mike Borowitz's lab at Johns Hopkins University (see Section 13.3). For details, refer to Appendix IX.

Sample Collection Procedures

NOTE: A separate specimen is NOT REQUIRED. Please note on the specimen transmittal forms that accompany the required immunophenotyping specimen whether the patient has consented for the optional CRLF2 expression assay.

13.5 **Blinatumomab Pharmacodynamics (optional)**

Immunopharmacologic testing will be performed using blood and bone marrow specimens in consenting patients treated with blinatumomab during the first exposure to blinatumomab in an effort to identify biomarkers of blinatumomab response. For details, refer to Appendix X.

Sample Collection Procedures

A Specimen Transmittal Form should accompany every shipment of specimen(s) to the Brown Laboratory. Please complete one form per patient per shipment.

Please note: The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Blood and marrow collection schedule during first blinatumomab cycle (see Section 7.2)

- Blood (7 samples, 3mL each in sodium heparin tubes)
  - Day 1
    - 0 hr (just prior to start of blinatumomab infusion)
    - 6 hr
    - 12 hr
  - Day 2
  - Day 7
  - Day 14
  - Day 21
- Marrow (1 samples, 5-10mL in sodium heparin tube)
  - No more than 72 hours prior to start of blinatumomab

Samples should be shipped at room temperature.

Brown Laboratory – Shipping Address (including Saturday delivery):

Dr. Patrick Brown
Johns Hopkins Oncology
Cancer Research Building I, Room 262
1650 Orleans Street
Baltimore, MD 21231
Laboratory phone: 410-955-8688
Pager no: 410-434-0732
E-mail: pbrown2@jhmi.edu

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.

Saturday deliveries are permissible. If a Saturday delivery is required, please notify Dr. Brown of the planned shipment via email (pbrown2@jhmi.edu) PRIOR to the time of shipment and clearly mark the package "For Saturday Delivery".

13.6 Protein Cell Stress Pathways (optional)

This study is designed to analyze two specific aims: 1) To determine if specific protein expression profiles, as determined by reverse-phase protein lysate array (RPPA) analysis and phospho-flow analysis, correlate with therapy response and 2) To determine if alterations in specific cell stress proteins (such as the UPR) during chemotherapy can identify low risk patients with "high risk" protein signatures. For details, refer to Appendix XI.

Consenting patients will have peripheral blood samples (5mL for those ≥ 10kg, 3 mL for those < 10 kg) collected at 0h (prior to start of Block 1 systemic chemotherapy), and at 2 time points after the initiation of therapy (6 hours (h) and 24h after the first dose of Block 1 systemic chemotherapy) to examine for changes in protein expression patterns. Blood samples for RPPA using sucrose centrifugation and (if necessary) the lymphoblast population will be isolated by either bead technology or flow cytometry. Sample collected for phospho-flow will be analyzed directly from whole blood. Sorted lymphoblasts will be made into lysates for RPPA analysis prior to freezing. Remaining samples will be frozen as pellets for protein analysis.

Eligible samples:

Sample should be sent to the Horton lab only if the patient has an initial absolute blast count of **at least 1000 lymphoblasts/μL**. To calculate the absolute blast percentage, multiply the total WBC by the % peripheral blasts:

$$(\text{WBC})(\%\ \text{blast})(1000) = \text{absolute blast count}/\mu\text{L}$$

Example: If the patient has a WBC of 10 and 50% blasts, the absolute blast count is:

$$(10)(.5)(1000) = 5000/\mu\text{L}$$

If the initial % blasts is unknown, send samples only if the total WBC is more than 10,000 and notify the Horton lab of the % blast as soon as available (contact info provided below).

Sample Collection Procedures

A Specimen Transmittal Form should accompany every shipment of specimen(s) to the Horton Laboratory. Please complete one form per patient per shipment. **Please note:** The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Sample collection time points:

	Day 1, Hour 0 (before start of systemic chemotherapy)	**Day 1, Hour 6-8**	**Day 1, Hour 24**
Peripheral Blood (Block 1 only)	• 3mL in CellSave Preservative Tube* • 3mL in heparin tube	• 3mL in CellSave Preservative Tube* • 3mL in heparin tube	• 3mL in CellSave Preservative Tube* • 3mL in heparin tube

*CellSave tubes will be provided by the Horton lab to each institution upon IRB approval. To obtain more CellSave tubes, contact the Horton lab at the numbers provided below. If the CellSave tubes are not available, submit entire 6 mL sample in 2 heparin tubes. Note that the **sample integrity is greatly enhanced by the use of CellSave tubes.**

Store samples in refrigerator until shipment, and use Thermosafe with ice pack (or similar Styrofoam shipping containers with sufficient ice packs if these are not available at your site.) These containers maintain biology samples at a constant temperature and are strongly recommended for biology sample shipment, particularly in warm weather months.

Horton Laboratory – Shipping Address (including Saturday delivery):

Dr. Terzah Horton c/o Gaye Jenkins
Feigin Center, Room 760.01
1102 Bates St.
Baylor College of Medicine
Houston, TX 77030
Phone: (832) 824-4676 or (832) 824-4269
email tmhorton@txccc.org.

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.

The Horton lab can accept Saturday shipments if we are contacted ahead of time. Please contact Gaye Jenkins or Dr. Horton (832-824-4676 or 832-824-4269) for alternative address and shipping information for Saturday delivery.

13.7 Blinatumomab Immunogenicity Assessment (Required)

(See lab manual on protocol webpage for sample collection and shipping details)

Blinatumomab is a novel protein therapeutic under clinical development. As outlined in the Draft Guidance: Immunogenicity Assessment for Therapeutic Protein Products (Feb 2013) pre-specified immunogenicity sampling will be performed to evaluate and mitigate risk (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf).

Blood samples for the assessment of blinatumomab immunogenicity will be collected to determine whether anti-idiotype antibodies directed against blinatumomab have been developed. Screening for these antibodies will be done by ELISA assay on ECL Basis (electrochemiluminescence), and binding will be confirmed with a Biacore assay to measure protein-protein interaction and binding affinity.

In a tiered approach patient samples are initially tested in a screening assay. Samples that produce signals above a certain screening cut point (classified as “positive”) may be subjected to a confirmatory assay. The screening assay is designed to minimize false negatives, so positive screening assays need to be confirmed as positive. These are performed using the same format as the screening assay. A comparison of patient serum in the presence and absence of excess blinatumomab is used to confirm or deny the existence of anti blinatumomab antibodies. The screening and confirmation assay in the context of blinatumomab clinical studies will be performed according to an internal standardized protocol using a validated assay.

Immunoassay-positive samples will be analyzed in a third step using a cell based blinatumomab-mediated cytotoxicity assay to determine if the detected antibodies have neutralizing properties. Detection of neutralizing anti-blinatumomab antibodies relies on a validated bioassay measuring changes in the biologic activity of blinatumomab triggered by the presence of the antibody.

Blood Serum samples for antibody testing are being collected on all patients randomized to receiving blinatumomab for the measurement screening of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. The ‘cell-based assay’ for neutralizing antibody detection tests patient sera in a model cell based system. This does not require patient cells or additional serum to be collected. Both the screening and the neutralizing assays are well-established at the Amgen Research Munich laboratory.

COG will be notified of any positive neutralizing antibody results to blinatumomab. If results are not provided, no neutralizing antibodies to blinatumomab have been detected.
Patients who test positive for neutralizing antibodies to blinatumomab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every three months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least one year (± 4 weeks) post administration of blinatumomab. All follow-up results, both positive and negative will be communicated to COG. More frequent testing (e.g. every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab. Patients who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab antibody response may also be asked to return for additional follow-up testing.

13.8 Blinatumomab PK (required)

Please see the Lab Manual posted on the protocol web page for sample collection and shipping details

14.0 RADIATION THERAPY GUIDELINES FOR ALL PATIENTS

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

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

14.1 General Guidelines

The objective of this protocol is to compare the benefits and risks of Blinatumomab in the treatment of first relapse B-ALL. Patients eligible for this study will undergo risk classification after an initial block of chemotherapy (Block 1). Risk classification and the indications for irradiation will be based on site of first relapse, time to first relapse, MRD status following Block1 chemotherapy and clinical response to chemotherapy (when testicular leukemia is present at protocol entry).

Patients determined to be low risk (LR) after Block 1, will receive additional chemotherapy (Block 2) post randomization to a control arm or an experimental arm. The experimental arm includes blinatumomab. Both the control and experimental arms include maintenance chemotherapy to complete the respective regimens. LR patients with testicular leukemia at protocol entry will receive testicular irradiation (2400cGy) during Block2 if they do not have a clinical complete response after Block1. LR patients with CNS leukemia at protocol entry will receive cranial irradiation (1800cGy) during maintenance chemotherapy.

Intermediate Risk (IR) and High Risk (HR) patients will be randomized to a control arm or an experimental arm. The experimental arm includes blinatumomab. Both arms will proceed to protocol-specified hematopoietic stem cell transplant (HSCT). Selected patients that do not respond to Block1 and HR and IR patients that do not respond to the control arm will receive blinatumomab in a separate treatment arm and may proceed to HSCT depending on their response to Blinatumomab provided they do not have a history of CNS leukemia (CNS3) at or after protocol entry. IR/HR patients with testicular leukemia at protocol entry will receive testicular irradiation (2400cGy) during Block 2 (control arm) or the first cycle of Blinatumomab (experimental arm) if they do not have a complete response after Block1. IR/HR patients with testicular leukemia who have a complete clinical response to Block 1 will receive *supplemental* testicular irradiation (600cGy) sequentially with total body irradiation (TBI). IR/HR patients with CNS leukemia at protocol entry will receive *supplemental* cranial irradiation (600cGy) sequentially with TBI. <u>*Supplemental* irradiation refers to irradiation of any site performed sequentially with TBI.</u>

Treatment failure (TF) patients are select patients that do not respond to block1 and HR and IR patients that do not respond to the control arm. They will receive Blinatumomab in a separate treatment arm and may proceed to HSCT depending on their response to Blinatumomab provided they do not have a history of CNS leukemia (CNS3) at or after protocol entry. They may also receive testicular or cranial irradiation therapy when indicated. TF patients after block1 will receive testicular irradiation (2400cGy) during their first course of Blinatumomab. TF patients with testicular leukemia who have a complete clinical response to Block1 will receive supplemental testicular irradiation (600cGy) sequentially with total body irradiation (TBI). TF patients after block2 with CNS leukemia at protocol entry will receive supplemental cranial irradiation (600cGy) sequentially with TBI.

Because there is no consensus on fractionated TBI or supplemental irradiation regimens, the radiation therapy guidelines for this study were designed to promote protocol participation and match guidelines used at the majority of approved transplant institutions and evolved from guidelines developed for other COG protocols. Questions about these guidelines should be directed to the radiation therapy coordinator or principal investigator. *Complete clinical response* refers only to the testes. *Supplemental irradiation* refers to irradiation of any site performed sequentially with TBI.

14.1.1 Required Benchmark and Questionnaires

Radiation therapy will be administered using photons or electrons according to treatment site. All centers participating in this protocol must have completed the the TBI benchmark available at IROC RI (QARC) website: www.IROCRI.QARC.org. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center (www.qarc.org) and must be submitted before a patient treated on this protocol can be evaluated. The calibration of therapy units used in this protocol must be verified by IROC Houston (RPC) (http://irochouston.mdanderson.org).

14.2 Indications for Radiation Therapy

14.2.1 Total Body Irradiation

TBI is indicated as part of the preparative regimen for IR/HR patients undergoing HSCT.

14.2.1.1 Supplemental cranial irradiation is indicated for HSCT patients with a history of CNS leukemia at protocol entry and shall be given sequentially.

14.2.1.2 Supplemental testicular irradiation is indicated for HSCT patients with the diagnosis of testicular leukemia and complete response after Block1 and shall be given sequentially. Those with testicular leukemia and without complete response after Block1 will not require supplemental testicular irradiation because they will have already received 2400cGy earlier in the regimen.

14.2.1.3 Patients who require irradiation to extra-medullary sites other than brain and testes should contact the Study Chair.

14.2.2 Cranial Irradiation

LR patients with a history of CNS leukemia at protocol entry should receive cranial irradiation. Cranial irradiation will be given between the first and second 12 week blocks of Maintenance chemotherapy. This corresponds to Week 40 for LR patients treated on the control arm and Week 54 for LR patients treated on the experimental arm. IR/HR patients will receive supplemental cranial irradiation sequentially with TBI prior to HSCT. Exceptions to the use of cranial irradiation include concerns about additional effects due to patient age, history of prior cranial irradiation and history or imaging evidence of CNS toxicity including leukoencephalopathy, stroke and necrosis.

14.2.3 Testicular Irradiation

Patients with persistent testicular leukemia at the end of Block 1 will receive 2400 cGy of testicular radiation during either Block 2 chemotherapy (for LR patients and HR/IR patients randomized to the control arm) or during blinatumomab (for HR/IR patients randomized to the experimental arm and TF patients after Block 1). Prior testicular irradiation will not be a contraindication to supplemental testicular irradiation on this protocol.

14.3 Timing

14.3.1 All patients who might require irradiation should be seen in consultation by a radiation oncologist in advance of treatment. The purpose of the consultation is to participate in planning the sequence of treatment and to determine the need for extra medullary (cranial, testicular and other) and supplemental irradiation in conjunction with HSCT.

14.3.2 The timing of TBI and supplemental irradiation will be determined in part by the TBI fractionation regimen. Supplemental irradiation should precede TBI and be performed during weekdays.

14.4 Emergency Irradiation

There may be instances when radiation therapy has been administered prior to enrollment on this protocol because of potentially life-threatening or function-threatening extramedullary involvement. Although it is not expected that prior treatment would make total body irradiation contraindicated, it should be considered when describing to the patient or parent the potential complications of treatment on this protocol.

14.5 Equipment and Methods of Delivery

Treatment Site	Photons	Electrons
TBI	Any Energy	
Cranial Irradiation	4 or 6MV	
Testicular Irradiation	Any Energy	Any Energy

Any energy for photons or electrons can be used as long as the skin and target dose requirements are met.

14.6 Treatment Volumes

14.6.1 Total Body Irradiation

The entire body will be treated including the head and feet in one field. Care should be taken to insure that the patient is entirely within the 90% isodose line of the beam and not in the penumbra region.

14.6.2 Cranial Irradiation

The treatment site consists of the entire brain and intracranial subarachnoid volume as well as the optic nerves and the posterior halves of the optic globes. The caudal border shall be the C2/3 vertebral interspace.

14.6.3 Testicular Irradiation

The treatment site consists of the testes in the scrotal sac.

14.7 Target Dose

14.7.1 Dose Definition

Photon and electron dose is to be specified in centigray (cGy)-to-muscle.

14.7.2 Prescribed Dose, Fractionation and Dose Rate for TBI

The preferred TBI regimens:

- 1200 cGy administered over 3 consecutive treatment days (Days -7, -6, -5) at 200cGy BID
- 1200 cGy administered over 4 consecutive treatment days (Days -8, -7, -6, -5) at 150cGy BID

Allowable but not preferred TBI regimen:

- 1320 cGy given over 4 consecutive treatment days (Days -8, -7, -6, -5) at 165cGy BID

Important considerations for TBI:

- Effort should be made to avoid interruptions in TBI administration
- The inter-fraction interval shall be no less than 5 hours between treatments (start to start)
- A mid-plane dose rate of between 6 and 15cGy per minute is required

14.7.3 Prescribed Dose and Fractionation for Cranial Irradiation

14.7.3.1 LR patients will receive 1800cGy administered in 10 daily fractions of 180cGy during Maintenance chemotherapy.

14.7.3.2 IR/HR patients will receive 600cGy administered in 3 daily fractions of 200cGy immediately before TBI

14.7.4 Prescribed Dose and Fractionation for Testicular Irradiation (testicular leukemia at protocol entry)

14.7.4.1 LR patients will not receive testicular irradiation if a complete clinical response is observed after Block1.

14.7.4.2 LR patients will receive 2400cGy testicular irradiation administered in 12 daily fractions of 200cGy during Block 2 if a complete clinical response is not observed after Block 1.

14.7.4.3 IR/HR patients will receive 600cGy administered in 3 daily fractions of 200cGy immediately before TBI if complete clinical response is observed after Block 1.

14.7.4.4 IR/HR patients will receive 2400cGy testicular irradiation administered in 12 daily fractions of 200cGy During Block 2 if a complete clinical response is not observed after Block1.

14.7.5 Prescribed dose and fractionation for testicular irradiation (testicular leukemia not present at protocol entry)

14.7.5.1 Supplemental testicular irradiation of 400cGy in 1 or 2 daily fractions prior to or during TBI may be administered according to institutional preference but is not required.

14.8 Treatment Technique

14.8.1 TBI

Supine and prone, lateral decubitus, upright seated and standing positions are allowed. Treatment will be delivered with equally weighted parallel opposed portals. Each treatment will include both fields. All treatment techniques and patient positions should meet the criteria on dose, dose rate, and dose uniformity. Beam spoilers or other equally effective devices may be used to increase skin dose to meet the dose uniformity requirements. Changes in patient positioning after the patient has started TBI must be documented. Changes in lung blocking and dose recalculation should be reported.

14.8.2 TBI - Lung Shielding

Lung shielding is encouraged but optional to restrict the lung dose (see Section 14.9.1). Lung shielding to achieve dose reduction should conform to the following guidelines:

- The lateral edges will be 1.0 – 1.5 cm inside the inner border of the ribs;
- The inferior edges will be 1.0 – 1.5 cm superior from the dome of the apex of the diaphragm;
- The superior borders will be 1.0 – 1.5 cm below the clavicles;
- The medial border 2.0 – 2.5 cm lateral to edges of the thoracic vertebral bodies.
- No contouring of the lung shields will be done around the hilum unless there is residual hilar adenopathy in which case the margins around the hilar abnormality will be 1.0 – 1.5 cm. When utilized, lung blocks should be employed for sequential treatments starting with the first treatment.
- Compensatory electron boost of the portion of the chest wall shielded by the lung blocks is not required.

14.8.3 Cranial Irradiation

Supine treatment is recommended with immobilization appropriate for the age of the child. Two opposed lateral equally weighted photon beams are preferred. The fields shall extend at least 1 cm beyond the periphery of the scalp. Customized field-shaping is required with blocks that are at least 5 HVL thick. Alternatively, a multi-leaf collimator may be used provided the leaf width is less than or equal to 5 mm.

Lens sparing techniques are encouraged with 1 of 2 techniques:

- Angling of the 2 lateral fields in the anterior direction (RAO/LAO) using the lateral canthus markers to “flatten” the beam edge. Shielding blocks are used to block the anterior halves of the eyes, the nose, and mouth.
- Set the central axes of the horizontal cranial beams so that they are aligned to the lateral canthi (half-beam blocking technique). 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.

14.8.4 Testicular Irradiation

The patient shall be treated in the supine position. Field shaping for photons and electrons will be done with either customized cerrobend blocking or multi-leaf collimation. The testes may be supported posteriorly and, if possible, extended caudally in order to minimize perineal irradiation. The penis should be excluded from the field.

14.9 Organs at Risk

14.9.1 Normal tissue sparing for TBI

Restricting the lung dose to between 900cGy and 1100cGy is encouraged on this protocol. Institutions are allowed to use their preferred method of beam attenuation to achieve the dose reduction to lungs. The lung dose shall be reported as reference point C for lateral treatments and reference point D for AP/PA treatments (see Section 14.10.1.2). It should be reported on the TBI Summary form.

14.9.2 Normal tissue sparing for cranial irradiation

- Lens sparing techniques, as outlined in Section 14.8.3, are encouraged.

14.9.3 Normal tissue sparing for testicular irradiation

- Techniques for sparing perineum and penis are outlined in Section 14.8.4.

14.10 Dose Calculation and Reporting

14.10.1 Dose calculations for TBI

14.10.1.1 Suggested Methods for Dose Calculations for TBI

The TBI percent depth dose (PDD) or Tissue Maximum Ratio (TMR) and output factors may be measured under TBI treatment conditions for a range of phantom sizes to establish the database for TBI beam-on time calculations and to validate the calculation method. Measurements of entrance and exit dose at the center of a phantom equivalent to the size of the typical patient are performed and compared to the calculated dose. If differences are found, additional correction factors should be introduced to the calculation method. The prescription point is defined as the point along the longitudinal axis of the patient at the mid-plane at the level of the umbilicus (Point E below). Tissue inhomogeneity correction is not required in the calculation of dose to the prescription point.

14.10.1.2 Dose Calculations and Measurements to Selected Anatomical Reference Points for TBI

Prescription Point:

The following reference points will be determined:

The calculated and measured doses to selected anatomical points should be submitted to IROC RI as part of the quality assurance documentation:

(Point A - Head) This reference point is defined along the longitudinal axis of the skull at the greatest mid-separation (immediately superior to the nasal bridge). The depth should be taken as midway between the entrance and exit points of the opposed radiation beams.

(Point B – Neck) This reference point is defined along the patient's longitudinal axis at the level of C3/C4 (approximate mid-neck, but chosen for the thinnest mid-separation of the neck). The point is taken to be midway between the entrance and exit point of the beam.

(Point C - Mid-mediastinum) For APPA: The point is in the center of the chest along the sagittal plane midway between the anterior and posterior surfaces (Usually at the level of the carina). For opposed laterals: this point is located midway between the entrance and exit points of the beams at the level of the carina. Calculations at this reference point should include lung shielding if present.

(Point D – Mid-Lung) APPA only: This reference point is centered in the middle of the right or left lung (both medial/lateral and cephalocaudad directions). The depth should be taken as midway between the entrance and exit points of the opposed radiation beams. Calculations at this reference point should include lung shielding if present.

(Point E – Umbilicus) This is the PRESCRIPTION POINT. This point is located along the patient's longitudinal axis at the level of the umbilicus and midway between the entrance and exit points of the opposed beams.

(Point F – Hip or Pelvis) This reference point is defined at the level approximately 1 cm superior to pubic symphysis midway between the entrance and exit points of the beam.

(Point G - Knee) This reference point is defined along the midline in the mid-plane of the knee at the level of the patella.

(Point H -Ankle) This reference point is defined along the midline at the mid-plane of the ankle at the level of the lateral malleolus.

14.10.1.3 Lung Dose Calculation

Tissue heterogeneity must be accounted for in the calculation of dose to lung. The preferred method is use of CT to enable use of CT numbers in the calculation. Alternatively, other methods as developed by the participating institution may be used. Lung density value estimates, based on methods adopted by treating institutions, may be incorporated into the dose calculation. The methodology used by each participating institution for lung dose determination will be evaluated as part of the benchmark approval process.

14.10.2 Dose Uniformity and Treatment Site Coverage

14.10.2.1 TBI Dose Uniformity and Treatment Site Coverage

The TBI fields should be set up to cover the patient's entire body without any part of the patient extending into the penumbra region. The dose difference between the prescription point and each reference point (see separate guidance for lung dose in section 14.9.1) shall be within ± 10% of the prescribed dose. The calculated dose to the lung shall be in accordance with the lung dose requirements specified in Section 14.9. Partial transmission lung blocks can be used to limit the overall total lung dose.

14.10.2.2 Cranial Irradiation Dose Uniformity and Treatment Site Coverage

The prescription point for the cranial treatment is at or near the center of the field. Regardless of the location of the central axis, the dose should be prescribed at the center of the cranial volume –midway between the points of maximum separation. The variations of dose within the treatment site shall be within +7%, -5% of the dose to the prescription point.

14.10.2.3 Testicular Irradiation Dose Uniformity and Treatment Site Coverage

The scrotum should be treated with en face electrons with the prescription depth covered by the 90% isodose. If electron beam is used for testicular irradiation, the prescription should include the beam energy and the dose coverage. Photon irradiation is allowed.

14.10.3 Tissue heterogeneity

There shall be no required correction for tissue heterogeneity for the cranial and testicular treatment.

14.10.4 Interruption of therapy

Excluding weekends and holidays, supplemental cranial irradiation, testicular irradiation and fractionated TBI should be continuous. All efforts should be made not to have treatment delay or interruption. Once patients have begun testicular treatment, they should immediately proceed to TBI for transplantation. If interruptions occur, the radiation therapy coordinator should be notified.

14.11 Quality Assurance Documentation and Review

There are no on-treatment review or image submission requirements for this study. A post-treatment review will be conducted by IROC RI. Questions regarding the dose calculations or documentation should be directed to the COG Protocol Dosimetrist at the IROC RI address noted below:

Within 1 week of the completion of radiotherapy, the following data shall be submitted:

- TBI Summary Form for Total Body Irradiation.
- Measured and/or calculated doses for the TBI reference points.
- A copy of the radiotherapy record including the prescription, and daily and cumulative doses for all treated sites including TBI and supplemental sites (cranial, testicular).
- The "RT-2 Radiotherapy Total Dose Record" forms must be completed for cranial and testicular irradiation.

- If the treatment technique differs from an approved benchmark, a new benchmark must be completed and approved.

Data should be sent to:
IROC Rhode Island (QARC)
640 George Washington Highway, Building B, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
E-mail: datasubmission@qarc.org

Contact for questions regarding dose calculations or documentation
COG Protocol Dosimetrist
IROC Rhode Island (QARC)
640 George Washington Highway, Building B, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

14.12 Definitions of Deviation in Protocol Performance

14.12.1 TBI

14.12.1.1 Deviations for prescription dose

Deviations for TBI Dose

Variation Acceptable:

- The dose to the prescription point and to any of the reference points (except points C and D lung dose points) differs from the protocol specified dose by >10% or <15%.

Deviation Unacceptable:

- The dose to the prescription point and to any of the reference points (except points C and D lung dose points) differs from the protocol specified dose by >15%.

14.12.1.2 Deviations for TBI Dose Rate

- A dose rate exceeding 15cGy/min will be considered as an unacceptable deviation.

14.12.1.3 Deviations for Lung Dose

- The dose to the lungs (reference points C and D) are either < 800cGy (if no chestwall boost used) or > 1250cGy will be considered an unacceptable deviation.

14.12.2 Deviations for Cranial Irradiation Dose

Variation Acceptable:

- The dose to the prescription point differs from the protocol specified dose by > 6 but ≤ 10%.

Deviation Unacceptable:

- The dose to the prescription point differs from the protocol specified dose by >10%.

14.12.3 Deviations for Testicular Irradiation Dose

Variation Acceptable:

- The dose to the prescription point differs from the protocol specified dose by > 6% but ≤ 10%.

Deviation Unacceptable:

- The dose to the prescription point differs from the protocol specified dose by > 10%.

APPENDIX I: SUPPORTIVE CARE

NOTE: For blinatumomab-specific supportive care guidelines, please refer to Section 5.2.3.

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

Blood Components

Blood products should be irradiated 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.

Infection Prophylaxis

Patients undergoing transplantation for ALL on this protocol are at high risk for infection. This risk may be increased due to infections that occur during the intensive chemotherapy most patients will receive prior to stem cell transplant on this protocol. Centers should be especially mindful of this as they choose anti-bacterial, anti-fungal, anti-viral, and PCP prophylactic regimens. Aside from well established screening approaches for CMV, centers may wish to consider routine screening for other viral pathogens such as Adenovirus or HHV-6. Any prophylaxis regimen chosen must be the same for patients on both arms of the protocol. Special considerations should be given for antifungal prophylaxis (see below).

Pneumocystis jiroveci

All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 2.5 mg/kg/dose (maximum dose 160mg/dose) by mouth twice daily on 2 or 3 sequential days per week. For patients allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone (2 mg/kg/day by mouth, maximum dose 100 mg/day), aerosolized pentamidine (300 mg/q month ≥ 5 years of age), or atovaquone (4-24 month: 45 mg/kg/day; >24 months: 30mg/kg/day) by mouth may be considered. For children in whom TMP/SMX, dapsone, atovaquone, and inhaled pentamidine cannot be administered, IV pentamidine (4 mg/kg/dose IV every 2 to 4 weeks) should be given. (REF: Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR 2000; 49(No. RR-10):1-125. Available at http://www.cdc.gov/mmwr/PDF/rr/rr4910.pdf. Accessed November 24, 2010.) Please also see https://members.childrensoncologygroup.org/prot/reference_materials.asp for COG Supportive Care Guidelines.

Varicella Vaccine
May be given to the siblings of patients in remission and stable at the physician's discretion. Varicella vaccination is not recommended for ALL patients during therapy.

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

Antifungals
Azole antifungal agents (i.e. fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Investigator caution is advised if azole antifungals are used. Fluconazole and other azoles are expected to increase serum tacrolimus and sirolimus levels. Therefore, dosages of sirolimus and tacrolimus should be adjusted accordingly. Due to extreme interactions with sirolimus, voriconazole is contraindicated during sirolimus. Patients on voriconazole prior to transplant should have another drug substituted for voriconazole prior to starting sirolimus therapy.

Hospitalization after High-Dose Cytarabine
Empiric hospitalization after Day 8 of Induction 3 (intensively-timed Capizzi-II) until there is evidence of marrow recovery should be considered due to the risk of neutropenic sepsis; patients not hospitalized should be monitored very closely.

Treatment of Established or Presumed Infections

Fever with Neutropenia
For patients with ANC < 500/μL and temperature between 38.0° and 38.5°C twice in 12 hours, or ≥ 38.5°C, empiric parenteral broad spectrum antibiotics should be instituted after obtaining appropriate cultures. The risk of sepsis is higher during Induction and while the peripheral neutrophil count is falling rather than rising. Duration of therapy should be determined by site of infection (if identified), culture results, and response to treatment. If fever and neutropenia persist, systemic antifungal therapy should be initiated after 3-5 days. When mucositis is present (especially following HD ARAC), alpha hemolytic streptococcal infections should be suspected. It is recommended that empiric antibiotic coverage includes vancomycin or clindamycin for coverage of potential gram-positive infections.

Use of G-CSF
G-CSF may be used for severe infections with neutropenia, but routine use is discouraged.

Filgrastim (G-CSF) at a dose of 5 micrograms/kg/day given IV or subcutaneously is required for recipients of cord blood starting at Day +1 and continuing until patients are fully engrafted. G-CSF is generally not necessary for BM/PBSC recipients and is not recommended, unless engraftment is delayed.

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

Empiric Management of Pulmonary Infiltrates
Pulmonary infiltrates should be evaluated with bronchoscopy and biopsy, lavage or open lung biopsy. If a procedure cannot be tolerated, begin empiric antifungal therapy given the high likelihood of fungal disease during Induction, Re-induction and periods of intensive chemotherapy (HDAraC). Empiric coverage should include treatment for gram-negative and positive bacteria, Legionella (erythromycin), Pneumocystis

(TMP/SMX), and fungi (amphotericin) pending culture results. If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis and brain are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician. Azole antifungal agents (i.e. fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Investigator caution is advised if azole antifungals are used.

Management of Mucositis/Perirectal Cellulitis

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

Constipation

As vincristine may cause severe constipation, prophylactic stool softeners/laxatives (per investigator's discretion) are recommended during all phases in which VCR is given.

Guidelines During Induction

Patients may experience profound myelosuppression and immune suppression during this time. Since steroids may mask fever as well as other components of the inflammatory response, sepsis during Induction 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 may have an intestinal component. Patients with subtle GI symptoms should be monitored very closely.

Tumor Lysis Syndrome

In this population with ALL, rapidly assess patients clinically and by appropriate laboratory parameters for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Suggested studies to be obtained prior to initiating antileukemia therapy include complete blood count (CBC), prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes, including creatinine, BUN, uric acid, phosphorous, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated. Begin allopurinol at a dose of 300 mg/m^2/day in 3 divided doses and continue until peripheral blasts and extramedullary disease are reduced. In some situations it may be appropriate to use rasburicase instead of allopurinol. Hydrate at 2400-3000 mL/m^2/day to maintain urine output > 100 mL/m^2/hour until peripheral blasts and extramedullary disease are reduced. Alkalinize urine with NaHCO3 20-40 mEq/L IV fluid to maintain urine pH between 6.5 and 7.5. Alkalinization is not recommended when treating with rasburicase.

APPENDIX II: THERAPY DELIVERY MAPS

APPENDIX II-A **Block 1 (All patients)** Block 1 therapy is common to all patients on study	Patient COG ID number DOB

Block 1 lasts 4 weeks (28 days). Please see Section 4.2 for treatment details. This therapy delivery map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥9 15 mg	1, 8	**CNS1/2 ONLY** ***For CNS2: Continue weekly until 2 clear csf samples are obtained i.e. CNS1** Note age-based dosing	a. Hx, PE [VS/Wt (BSA)] b. CBC/diff/platelets c. Local BM evaluation% d. BM forImmunophenotyping e. CSF cell count, cytospin[1] f. Bilirubin, ALT & creatinine, BUN g. Echocardiogram h. Pregnancy test i. Testicular Exam & Testicular biopsy, if indicated® [1] Obtain with each IT/ITT See Section 7.0 for details. **Optional studies** j Banking for future research k Protein cell stress pathways l. CRLF2 expression See Section 7.2 for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Triple Therapy (ITT): Methotrexate (MTX)/ Hydrocortisone (HC)/Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	1, 8, 15, 22	**CNS3 ONLY** Note age-based dosing	
MitoXANTRONE (MITOX)	IV over 15-30 minutes	10 mg/m²/dose	1, 2	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Dexamethasone (DEX)	PO	10 mg/m²/dose	1-5, 15-19	Total Daily Dose 20 mg/m²/day divided BID **Cap dose at 40 mg per day**.	
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²	1, 8, 15, 22	+Or infusion via minibag as per institutional policy. **Maximum dose: 2mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	3, 17	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

APPENDIX II-A **Block 1 (All patients)** Block 1 therapy is common to all patients on study	Patient COG ID number DOB

Ht ________cm Wt ________kg BSA ________m²

Date Due	Date Given	Day	IT MTX **CNS1/2 ONLY*** ____mg	ITT **CNS3 ONLY** ____mg	MITOX ____mg	DEX ___mg	VCR ____mg	PEG-ASP ____IU	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below						a-i, l[$],j[+]	
		1	_____mg	_____mg	____mg	____mg	_____mg		k[¥]	
		2			____mg	↓				
		3						____IU		
		4								
		5								
		--								
		8	_____mg	_____mg			_____mg		b, e, f	
		--								
		15	_____mg*	_____mg		____mg	_____mg		b, e*, f	
		--								
		17				↓		____IU		

		19								
		22	_____mg*	_____mg			_____mg		b, e*, f	
		--								
		29							b, c[%], d, f, i[®],j[+],	
			Begin next course based on Day 29 risk assignment and treatment randomization. IR/HR patients randomized to **Arm A** receive Block 2 therapy (Section 4.3, APPENDIX II-B), IR/HR patients randomized to **Arm B** receive Blinatumomab Block-Cycle 1 therapy (Section 4.5, APPENDIX II-D). **LR patients** will be randomized to Arm C (control arm) or Arm D (experimental arm). All LR patients (**Arm C and Arm D**) receive Block 2 therapy (Section 4.3, APPENDIX II-B). Treatment failures post-Block 1 with M3 marrow without residual CNS disease (CNS1) are eligible for treatment with at least 2 blocks of Blinatumomab-S (Section 4.7, APPENDIX II-I); treatment failures with residual CNS disease (CNS2/3), irrespective of marrow status will be off protocol therapy. See Section 4.3 for further details on time frame for end-Block 1 evaluations and criteria to fulfill prior to subsequent therapy.								

***For CNS2 patients, continue weekly until 2 clear CSF (CNS1) samples are obtained; can be a max of 4 (Weeks 1, 8, 15 and 22). If still unclear, patients are treatment failures and will be off protocol therapy regardless of marrow status.**

[#] Day 29 MRD specimen should be shipped to the COG ALL Molecular Reference Laboratory for all patients that consented. ***This specimen is very important***.

[®] Testicular biopsy is only done in the setting of persistent testicular enlargement. Patients with persistent testicular leukemia at the end of Block 1 who are deemed treatment failure (TF) will receive 2400 cGy of testicular radiation during Blinatumomab.

[$] No separate specimen needed-cell pellet from required central flow MRD assays will be used (see Section 13.4 for complete details)..

[¥] PB before and after chemotherapy on Day 1 of Block 1 (see Section 13.6) for complete details).

[%] BM evaluation to confirm relapse and/or detect marrow disease in presumed isolated extramedullary relapse patients should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively

+**Bone marrow:** at Baseline and End Block 1. **Peripheral blood:** At Baseline and End Block 1. (See Section 13.1 for complete details)

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-B **Block 2** Block 2 therapy is for all LR patients post Block-1 (**Arm C and Arm D**) and HR/IR patients randomized to the control arm (**Arm A**)	Patient COG ID number DOB

Block 2 lasts 4 weeks (28 days). Block 2 should begin after receipt of risk assignment according to timing outlined in Section 4.2. Patients can proceed with Block 2 without awaiting count recovery (must be no later than 5 days after callback). Please see Section 4.3 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	3 mg/m²/dose	1-5	Total Daily Dose: 6 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Local BM evaluation d BM for MRD evaluation e CSF cell count, cytospin[1] f Bilirubin, ALT & creatinine, BUN g Testicular Exam **Optional studies** h Banking for future research [1] Obtain with each IT/ITT See Section 7.0 for details. See Section 7.2 for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
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	8	**CNS 1/2 ONLY** 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).	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) / Dose 1-1.99: MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99: MTX: 10mg, HC: 10 mg, ARAC: 20 mg 3-8.99: MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥9: MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	8, 22	**CNS3 ONLY.** Note age-based dosing.	
Intermediate Dose Methotrexate (ID MTX)	IV over 36 hours	1000 mg/m²/dose	8	See Section 5.8 & Appendix IV for admin guidelines.	
Leucovorin (LCV)	PO/IV	15 mg/m²/dose	9, 10	48 hours after the start of ID MTX infusion. See Section 5.8 & Appendix IV for admin guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	9 or 10*	*Administer 4 hours after completion of Day 8 IV MTX.	
Cyclophosphamide (CPM)	IV over 15-30 mins.	440 mg/m²/dose	15-19		
Etoposide (ETOP)	IV over 60-120 mins.	100 mg/m²/dose	15-19		
Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation during Block 2 therapy. See Section 14.2 for details of TRT.					

APPENDIX II-B **Block 2** Block 2 therapy is for all LR patients post Block-1 (**Arm C and Arm D**) and HR/IR patients randomized to the control arm (**Arm A**)	Patient COG ID number DOB

Ht ________cm **Wt ________kg** **BSA ________m^2**

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	IT MTX **CNS1/2 ONLY** ____mg	ITT **CNS3 ONLY** ____mg	ID MTX ____mg	LCV ____mg	PEG-ASP ____IU	CPM ____mg	ETOP ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below										
		1	____mg	____mg								a, b, f	
		5											
		8			____mg	____mg	____mg^					b, e, f	
		9						____mg	____IU*				
		10						____mg					
		15								____mg	____mg	b, f	
		19											
		22				____mg						b, e#, f	
		29										b,c,d,f,g,h+	
			Following count recovery, **HR/IR patients on Arm A** receive Block 3 therapy (Section 4.4, APPENDIX II-C). **HR/IR Treatment Failures** post-Block 2 have the opt of receiving 2 blocks of blinatumomab salvage therapy –Blinatumomab-S (Sections 4.7, 4.8, APPENDIX II-F, II-G). **LR patients randomized to Arm C** receive Bloc 3 therapy (Section 4.4., APPENDIX II-C), and **LR patients randomized to Arm D** receive Blinatumomab Block 1: Cycle 1 therapy (Section 4.15, APPENDIX II-D).										

^ All patients with M1 marrow must have ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 8 ID MTX. Day 8 treatment must begin no later than 14 days after risk assignment for patient to continue to receive protocol therapy.

\+ **Peripheral blood:** End Block 2 (See Section 13.1 for complete details)

*Administer 4 hours after completion of Day 8 IT MTX. (Day 9 or 10)

\# CNS3 ONLY

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-C **Block 3** Block 3 therapy is for all HR/IR patients randomized to the control arm (**Arm A**), and LR patients randomized to the control arm (**Arm C**).	Patient COG ID number DOB

Block 3 lasts 4 weeks (28 days) and starts when ANC ≥ 500/μL and platelets ≥ 50,000/μL. See Section 4.4 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	**ROUTE**	**DOSAGE**	**DAYS**	**IMPORTANT NOTES**	**OBSERVATIONS**
Dexamethasone (DEX)	PO (May be given IV)	3 mg/m^2/dose BID	1-5	Total Daily Dose: 6 mg/m^2/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Local BM evaluation d BM for MRD evaluation e CSF cell count, cytospin[1] f Bilirubin, ALT & creatinine, BUN [1] Obtain with each IT/ITT See Section 7.0 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	1	[+] Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Cytarabine (ARAC)	IV over 3 hours	3000 mg/m^2/dose Q12H	1, 2, 8, 9		
Erwinia L-asparaginase (ERWINAZE)	IM	25, 000 International units/m^2/dose	2, 4, 9, 11, 23	See Section 4.4 for administration guidelines. • On Days 2 and 9, Erwinia should be given 4 hours after last cytarabine infusions. • On Day 23, Erwinia is to be given 4 hours after the completion of the Day 22 MTX infusion.	
Intermediate Dose Methotrexate (ID MTX)	IV over 36 hours	1000 mg/m^2/dose	22	See Section 5.8 & Appendix IV for admin guidelines.	
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose	23, 24	48 hours after the start of ID MTX infusion. See Section 5.8 and Appendix IV 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	1 **All Patients** 22 **CNS 1/2 ONLY**	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). Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) — Dose 1-1.99 — MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 — MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 — MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 — MTX: 15 mg HC: 15 mg ARAC: 30 mg	22	**CNS3 ONLY** When ITT therapy and ID MTX are scheduled for the same day, deliver the ITT 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). Note age-based dosing	

APPENDIX II-C **Block 3** Block 3 therapy is for all HR/IR patients randomized to the control arm (**Arm A**), and LR patients randomized to the control arm (**Arm C**).	Patient COG ID number DOB

Ht ________cm Wt ________kg BSA ________m²

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	ERWINAZE ____IU	ID MTX ___mg	LCV ____mg	ARAC ______mg	IT MTX **All Patients** ______mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below										
		1	____mg	____mg				____mg	____mg			a, b, e, f	
		2			____IU			____mg					
		3											
		4			____IU								
		5											

		8						____mg				b, f	
		9			____IU			____mg					

		11			____IU								

		15										b, f	

		22				____mg^				____mg	____mg&	b, e, f	
		23			____IU		____mg						
		24					____mg						

		29										b, (c, d)* f	
		Following count recovery ANC ≥ 500/µL and platelets ≥ 50,000/µL, **HR/IR patients on Arm A** proceed to HSCT as soon as possible (Section 4.9); see Section 4.10, Appendix II-H for suggested bridging therapy in the event that HSCT is delayed. **HR/IR Treatment Failures** post-Block 3 have the option of receiving 2 blocks of blinatumomab salvage therapy – Blinatumomab-S (Sections 4.7, 4.8, APPENDIX II-F, II-G). **LR patients randomized to Arm C** receive Continuation 1 therapy (Section 4.11, Appendix II-H).											

^ Hold until ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 22 ID MTX.

***HR/IR Patients ONLY.**

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-D **Blinatumomab Block - Cycle 1** (HR/IR Patients in **Arm B**) This therapy is the 1st cycle of therapy with blinatumomab for the HR/IR patients randomized to the experimental arm (Arm B)	Patient COG ID number DOB

Blinatumomab Block-Cycle 1 lasts 5 weeks (35 Days). For patients with M1 marrow, treatment begins when ANC ≥ 500/µL and platelets ≥ 50,000/µL and must begin no later than 14 days after risk assignment for patient to continue to receive protocol therapy. For patients with M2 marrow, treatment begins without awaiting count recovery, and must be no later than 5 days after callback. See Section 4.5 for treatment details. This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN)	IV	15 µg/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c BM (Local evaluation & MRD) d CSF cell count, cytospin[1] e Bilirubin, ALT & creatinine, BUN f Peripheral blood for PK g Peripheral blood for Immunogenicity
Dexamethasone (DEX)	PO or IV	10 mg/m²/dose , 6-12 hours prior to blinatumomab infusion, THEN 5 mg/m² within 30 minutes of starting Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	
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	15, 29	**CNS1/2 ONLY** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg, HC: 10 mg, ARAC: 20 mg 3-8.99 MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥9 MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	15, 29	**CNS3 ONLY** Note age-based dosing	**Optional studies** h Blinatumomab PD [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation during Blinatumomab Block – Cycle 1. See Section 14.2 for details of TRT.					

APPENDIX II-D **Blinatumomab Block - Cycle 1** (HR/IR Patients in **Arm B**) This therapy is the 1st cycle of therapy with blinatumomab for the HR/IR patients randomized to the experimental arm (Arm B)	Patient COG ID number DOB

Ht _________cm Wt _________kg BSA _________m^2

Date Due	Date Given	Day	BLIN ____mg	DEX ____mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg			a*, b, e, h+,g$	
		2	↓				f&,g+	

		7					g+	
		8					b, e,	

		14					f&, g+	
		15			____mg	____mg	b, d, e	

		21					g+	
		22					b, e,	

		28						
		29			____mg	____mg	b, c, d, e	
		30-35	**Rest Period**					
			Following count recovery, start next cycle, Blinatumomab Block Cycle 2 (Section 4.6, APPENDIX II-E). Treatment failures will be taken off protocol therapy.					

\+ **Bone marrow:** Prior to start of first blinatumomab infusion and **Peripheral blood:** Prior to (Hour 0) and during (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion (see Section 13.5 for complete details).

$ Prior to (Hour 0) first blinatumomab infusion (see Section 13.7 & lab manual for details)

& See lab manual for collection and shipping details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-E **Blinatumomab Block - Cycle 2** (HR/IR Patients in **Arm B**)

This therapy is the 2nd cycle of therapy with blinatumomab for the HR/IR patients randomized to the experimental arm (Arm B)

Patient COG ID number DOB

Blinatumomab Block-Cycle 2 lasts 5 weeks (35 Days) and begins when ANC ≥ 500/µL and platelets ≥ 50,000/µL. See Section 4.6 for treatment details. This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN)	IV	15 µg/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c BM (Local evaluation & MRD) d CSF cell count, cytospin[1] e Bilirubin, ALT & creatinine, BUN f Peripheral blood for Immunogenicity [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO or IV	10 mg/m²/dose , 6-12 hours prior to blinatumomab infusion, THEN 5 mg/m² within 30 minutes of starting Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	
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	8, 29	**CNS1/2 ONLY** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg, HC: 10 mg, ARAC: 20 mg 3-8.99 MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥9 MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	8, 29	**CNS3 ONLY** Note age-based dosing	

Ht _________**cm** **Wt** _________**kg** **BSA** _________**m²**

Date Due	Date Given	Day	BLIN ____mg	DEX ____mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	____mg ↓	____mg			a*, b, e	
		8			____mg	____mg	b, d, e	
		15						
		22					b, e	
		28	↓					
		29			____mg	____mg	b, c, d, e,f$	
		30-35	**Rest Period**					
			Following count recovery, patients will proceed to HSCT (Section 4.9). See Section 4.10, Appendix II-H for suggested bridging therapy in the event that HSCT is delayed. Treatment failures will be taken off protocol therapy.					

$ In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1. See Section 13.7 and lab manual for details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

& See lab manual for collection and shipping details

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-F **Blinatumomab-S:Cycle 1 (Treatment Failure)** This therapy is the 1st cycle of therapy with salvage blinatumomab therapy for the HR/IR patients classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Blinatumomab-S: Cycle 1 lasts 5 weeks (35 Days). See Section 4.7 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN)	IV	5 µg/m²/day 15 µg/m²/day	1-7 8-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & creatinine, BUN e Local BM evaluation f BM for MRD- pre HSCT g Peripheral blood for PK h Peripheral blood for Immunogenicity
Dexamethasone (DEX)	PO or IV	10 mg/m²/dose , 6-12 hours prior to blinatumomab infusion, THEN 5 mg/m² within 30 minutes of starting Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	
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	15	Note age-based dosing	**Optional studies** i Blinatumomab PD [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation during the 1st cycle of Blinatumomab-S therapy. See Section 14.2 for details of TRT.

APPENDIX II-F **Blinatumomab-S:Cycle 1 (Treatment Failure)** This therapy is the 1st cycle of therapy with salvage blinatumomab therapy for the HR/IR patients in the HR/IR randomization classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Ht ________cm **Wt ________kg** **BSA ________m²**

Date Due	Date Given	Day	BLIN ____mg	DEX ____mg	IT MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg		a*, b, d, i[+], h[$]	
		2				g[&]	

		7				i[+]	
		8				b, d	

		14				g[&], i[+]	
		15			____mg	b, c, d, i[+]	

		21				i[+]	
		22				b, d	

		28					
		29				b, d, e, f[+++]	
		30-35	**Rest Period**				
			Patients with M1 marrow proceed to HSCT on study as soon as possible after count recovery (see Section 4.9). Patients with M2/M3 marrow start 2nd cycle of salvage therapy with blinatumomab (Blinatumomab-S: Cycle 2, Section 4.8, APPENDIX II-G) without awaiting count recovery.				

[+] **Bone marrow:** Prior to start of first blinatumomab infusion and **Peripheral blood:** Prior to (Hour 0) and during (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion (see Section 13.5 for complete details).

$ Prior to (Hour 0) first blinatumomab infusion. In cases where blinatumomab treatment will not continue to Cycle 2, collect additional sample at end of Cycle 1. (see Section 13.7 and lab manual for details)

[&] See lab manual for collection and shipping details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

+++ Pre-HSCT evaluation

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-G **Blinatumomab-S: Cycle 2** (Treatment failure) This therapy is the 2nd cycle of therapy with salvage blinatumomab therapy for the HR/IR patients classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Blinatumomab-S: Cycle 2 lasts 5 weeks (35 Days) and starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL. See Section 4.8 for treatment details. This Therapy Delivery Map is on two (2) pages.
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DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN)	IV	15 µg/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Local BM evaluation d CSF cell count, cytospin[1] e Bilirubin, ALT & creatinine, BUN f BM for MRD- pre HSCT g Peripheral blood for Immunogenicity
Dexamethasone (DEX)	PO or IV	10 mg/m²/dose , 6-12 hours prior to blinatumomab infusion, THEN 5 mg/m² within 30 minutes of starting Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	
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	8, 29	Note age-based dosing	[1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

APPENDIX II-G **Blinatumomab-S: Cycle 2** (Treatment failure) This therapy is the 2nd cycle of therapy with salvage blinatumomab therapy for the HR/IR patients classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Ht ________cm **Wt ________kg** **BSA ________m^2**

Date Due	Date Given	Day	BLIN _____mg	DEX _____mg	IT MTX _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	____mg	_____mg		a*, b, e	
		---	↓				
		8	↓		____mg	b, d, e	
		---	↓				
		15	↓			b, e	
		---	↓				
		22	↓			b, e	

		29			____mg	b, c, d, e,g$, f+++	
		30-35	**Rest Period**				
			Patients with M1 marrow proceed to HSCT (Section 4.9). In the event that HSCT is delayed, see Section 4.10, Appendix II-H for suggested bridging maintenance therapy. Patients with M2/M3 marrow after Blinatumomab-S: Cycle 2 will be taken off protocol therapy.				

$ In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1. See Section 13.7 and lab manual for details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

+++ Pre-HSCT evaluation

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

Appendix II-H **Bridging Maintenance Therapy: Optional (HR/IR patients and TF patients that are eligible for HSCT)**

This therapy is only for HR/IR patients awaiting stem cell transplant therapy due to stem cell source or facility scheduling issues causing a lag time > 2 weeks after count recovery. Bridging therapy can be given for a maximum of 6 weeks, but does not need to be given the full 6 weeks if patient is ready for HSCT earlier.

Patient COG ID number DOB

This therapy lasts for a maximum of 6 weeks (42 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50 000/µL. See Section 4.10 for 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/m²/dose	1, 22	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	**a** Hx, PE [VS/Wt (BSA)] **b** CBC/diff/platelets **c** BM for MRD evaluation **d** BUN/creatinine e LFTs See Section 7.1c for Follow up observations.
Mercaptopurine (MP)	PO	75 mg/m²/dose	1-42		
Methotrexate (MTX)	PO	20 mg/m²/dose	1, 8, 15, 22, 29, 36		

Ht _________cm **Wt _________kg** **BSA _________m²**

Date Due	Date Given	Day	VCR ____mg	MP ___mg	PO MTX ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	_____mg	_____mg	_____mg	a, b, c, d,e	

		8			_____mg		

		15			_____mg		

		22	_____mg		______mg		

		29			_____mg		

		36			_____mg		

		42					
		43				c[1]	

[1] Bone marrow for MRD evaluation must be repeated prior to the start of HSCT.

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-I **Continuation1/2 (All LR patients)** This therapy is for all LR patients and is the same for Continuation 1 and Continuation 2.	Patient COG ID number DOB

Continuation lasts 8 weeks and is given twice, for a total of 16 weeks. Begin when ANC ≥ 500/µL and platelets ≥ 50,000/µL. All Patients should have ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to starting therapy on Days 22 and 42. If at Day 22 the ANC is < 500/µL and platelets < 50,000/µL, it is permissible to delay the Day 22 divided dose oral methotrexate (25 mg/m^2/dose for CNS1/2) or ID MTX (for CNS3) by one (1) week. Omit the Day 29 standard dose oral methotrexate (20 mg/m^2/dose) in this case. If counts are not recovered after one (1) week, omit the divided dose oral MTX and ID MTX for this cycle and resume with the Day 29 standard dose MTX. See Section 4.11 for treatment details. This therapy delivery map is for one cycle of Continuation and is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	3 mg/m^2/dose	1-5	Total Daily Dose: 6 mg/m^2/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & creatinine, BUN
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m^2/dose	1	[+] Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Methotrexate (MTX)	PO	20 mg/m^2/dose	8, 15, 29, 36		
Intermediate Dose Methotrexate (ID MTX)	IV over 36 hours	1000 mg/m^2/dose	22	**CNS3 ONLY**	[1] Obtain with each IT/ITT
Methotrexate (MTX)	PO	25 mg/m/dose Q6H	22	**CNS1/2 ONLY** ANC must be ≥ 500/µL and platelets must be ≥ 50 000/µL prior to Day 22 therapy.	See Section 7.0 for further details
Mercaptopurine (MP)	PO	75 mg/m^2/dose	1-42		
Leucovorin (LCV)	IV/PO	15 mg/m^2/dose Q6H	23, 24	Begin **48 hrs** after the **START** of ID MTX infusion.	
Leucovorin (LCV)	PO	10 mg/m^2/dose Q6H	22	Begin **48 hrs** after the **START** of day 22 Methotrexate	**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 30-60 minutes	300 mg/m^2/dose	42, 49		
Etoposide (ETOP)	IV over 60-120 minutes	150 mg/m^2/dose	42, 49		
Thioguanine (TG)	PO	40 mg/m^2/dose	42-48	See Section 4.11 and Appendix IV for administration guidelines.	
Cytarabine (ARAC)	IV/SQ	50 mg/m^2/dose	43-46, 50-53		
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	1, 43	**CNS1/2 ONLY** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	1, 43	**CNS3 ONLY** Note age-based dosing	

APPENDIX II-I **Continuation1/2 (All LR patients)** This therapy is for all LR patients and is the same for Continuation 1 and Continuation 2.	Patient COG ID number DOB

Enter Cycle #: _____ Ht _________cm Wt _________kg BSA _________m^2

Date Due	Date Given	Day	DEX. ___mg	MP ___mg	VCR ___mg	POMTX ___mg	PO MTX **CNS1/2 ONLY** ___mg	ID MTX **CNS3 ONLY** ____mg	LCV ____mg	ETOP ___mg	CPM ___mg	TG ___mg	ARAC ___mg	IT MTX **CNS1/2 ONLY** ___mg	ITT **CNS3 ONLY** ___mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below														
		1	__mg	__mg	__mg									__mg	__mg	a, b, c,d	
		2															
		3															
		4															
		5															

		8				___mg										b,d	

		15				___mg										b,d	

		22				___mg	____mg	____mg^								b,d	
		23							____mg								
		24							____mg								

		29				___mg										b,d	

		36				___mg										b,d	

		42								___mg^	___mg^	___mg					
		43										^	___mg	___mg	___mg	b, c,d	

		46															

		48															
		49								___mg	___mg					b,d	
		50											___mg				

		53															

		56														b,d	
			Following Continuation 1, upon count recovery, **LR patients randomized to Arm C** will receive Continuation 2 therapy (Section 4.11, APPENDIX II-I), **LR patients randomized to Arm D** will receive Blinatumomab Block: Cycle 2 therapy (Section 4.16, APPENDIX II-N), Following Continuation 2, upon count recovery, **LR patients randomized to Arm C** will receive Maintenance Cycle 1 therapy (Section 4.12, Appendix II-J), **LR patients randomized to Arm D** will receive Blinatumomab Block: Cycle 3 therapy (Section 4.16, APPENDIX II-N),														

^ Hold until ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 22 ID MTX. Also hold Day 42 therapy until ANC ≥ 500/µL and platelets ≥ 50,000/µL.

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

Appendix II-J **Maintenance Cycle 1 (All LR patients)** This Maintenance therapy is for all LR patients (**Arm C** and **Arm D**)	Patient COG ID number DOB

Maintenance Cycle 1 lasts for 12 weeks (84 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50 000/µL. See Section 4.12 for treatment details. This therapy delivery map is for Maintenance and is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	1-5, 29-33, & 57-61	Total Daily Dose: 6 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & creatinine, BUN e Absolute lymphocyte count with T and B subset quantification.[2] f Peripheral blood for Immunogenicity [1] Obtain with each IT/ITT [2] To be done at the end of each 12 week maintenance cycle and every 3 months after completion of therapy for 1 year. See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CAR**
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m²/dose	1, 29, 57	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	
Mercaptopurine (MP)	PO	75 mg/m²/dose	1-84		
Methotrexate (MTX)	PO	20 mg/m²/dose	8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78		
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	1	**CNS1/2 ONLY** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	1	**CNS3 ONLY** Note age-based dosing	

Appendix II-J **Maintenance Cycle 1 (All LR patients)** This Maintenance therapy is for all LR patients (**Arm C** and **Arm D**)	Patient COG ID number DOB

Ht ________**cm** **Wt** ________**kg** **BSA** ________**m²**

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	MP ___mg	MTX ______mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below							
		1	_____mg	_____mg	_____mg		______mg	______mg	a, b, c, d,f$	
		2								
		3								
		4								
		5								
		8				______mg				
		15				______mg				
		22				______mg				
		29	_____mg	_____mg		______mg			a, b, d	
		30								
		31								
		32								
		33								
		36				______mg				
		43				______mg				
		50				______mg				
		57	_____mg	_____mg		______mg			a, b, d	
		58								
		58								
		60								
		61								
		64				______mg				
		71				______mg				
		78				______mg				
		84							a, b, d, e	
		85	Following Maintenance Cycle 1 therapy, **CNS3 patients ONLY** will receive CNS directed therapy with chemoradiation (Section 4.13, APPENDIX II-K). All other patients on Arm C and Arm D will continue with Maintenance Post-Cycle 1 therapy (Section 4.14, APPENDIX II-L)								

$ Arm D ONLY. Prior to start of Maintenance therapy for eligible patients (see Section 13.7 and lab manual for details)

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-K **Maintenance Chemoradiation-CNS Directed Therapy (LR Patients)** This therapy is for all CNS3 patients **ONLY** and is given between 1st and 2nd cycles of Maintenance therapy.	Patient COG ID number / DOB

This CNS directed therapy lasts 3 weeks (21 days). See Section 4.13 for treatment details. This Therapy Delivery Map is on one (1) page

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	5 mg/m²/dose	1-7, 15-21	Total Daily Dose: 10 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Bilirubin, ALT & creatinine, BUN d Absolute lymphocyte count with T and B subset quantification.[2] See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1, 8, 15	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	1	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Cranial Radiotherapy: Patients with CNS3 and isolated CNS relapse will receive cranial radiation during Maintenance, between Blocks 1 and 2. See Section 14.1 for details of cXRT.					

Enter Cycle #: _____ Ht _________cm Wt _________kg BSA _________m²

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	PEG-ASP ____IU	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	________mg	________mg	_______IU	a, b, c	
		2	↓				
		3					
		4					
		5					
		6					
		7					
		8		________mg			
		...					
		15	________mg	________mg			
		16	↓				
		17					
		18					
		19					
		20					
		21				d	
		22	Following chemoradiation, patients will receive Maintenance Post-Cycle 1 therapy (Section 4.14, APPENDIX II-L) when count parameters are met.				

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-L **Maintenance Post Cycle 1 (All LR patients)** This therapy is for all LR patients (**Arm C** and **Arm D**)	Patient COG ID number DOB

Maintenance Post Cycle 1 is given in 12 week cycles based on dose modifications for low counts and platelets. See Section 4.14 and Section 5.9 for details. This therapy delivery map is on two (2) pages.

DRUG	**ROUTE**	**DOSAGE**	**DAYS**	**IMPORTANT NOTES**	**OBSERVATIONS**
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	1-5, 29-33, & 57-61	Total Daily Dose: 6 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & Creatinine, BUN e Absolute lymphocyte count with T and B subset quantification[2] [1] Obtain with each IT/ITT [2] To be done at the end of each 12 week maintenance cycle and every 3 months after completion of therapy for 1 year. See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1, 29, 57	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Methotrexate (MTX)	PO	20 mg/m²/dose	1	**CNS3 ONLY**	
Mercaptopurine (MP)	PO	75 mg/m²/dose	1-84		
Methotrexate (MTX)	PO	20 mg/m²/dose	8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78		
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	1	**CNS1/2 ONLY** Note age-based dosing	

APPENDIX II-L **Maintenance Post Cycle 1 (All LR patients)**

This therapy is for all LR patients (**Arm C** and **Arm D)**

Patient COG ID number DOB

Ht _________cm **Wt _________kg** **BSA _________m^2**

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	MTX (PO) **CNS3 ONLY** _____mg	MTX (PO) ______mg	MP ______mg	IT MTX **CNS1/2 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below							
		1	____mg	_____mg	______mg		_____mg	______mg	a, b, c, d	
		2								
		3								
		4								
		5								
		8				______mg				
		15				______mg				
		22				______mg				
		29	____mg	_____mg		______mg			a, b, d	
		30								
		31								
		32								
		33								
		36				______mg				
		43				______mg				
		50				______mg				
		57	____mg	_____mg		______mg			a, b, d	
		58								
		59								
		60								
		61								
		64				______mg				
		71				______mg				
		78				______mg				
		84							a, b, d, e	
		85	Maintenance cycles are repeated in 12 week cycles based on dose modifications for low counts or low platelets until 2 yrs from start of Block 1 therapy for both male and female patients.							

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-M **Blinatumomab Block - Cycle 1** (LR Patients in **Arm D**) This therapy is the 1st cycle of therapy with blinatumomab for the LR patients randomized to Arm D	Patient COG ID number DOB

This cycle lasts 5 weeks (35 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50 000/µL.. See Section 4.15 for treatment details. This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN)	IV	15 µg/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & creatinine, BUN e Peripheral blood for PK f Peripheral blood for Immunogenicity **Optional studies** g Blinatumomab PD [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO or IV	10 mg/m²/dose , 6-12 hours prior to blinatumomab infusion, THEN 5 mg/m² within 30 minutes of starting Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	
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	8, 29	**CNS1/2 ONLY** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg, HC: 10 mg, ARAC: 20 mg 3-8.99 MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥9 MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	8, 29	**CNS3 ONLY** Note age-based dosing	
Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation. See Section 14.2 for details of TRT.					

APPENDIX II-M **Blinatumomab Block - Cycle 1** (LR Patients in **Arm D**) This therapy is the 1st cycle of therapy with blinatumomab for the LR patients randomized to Arm D	Patient COG ID number DOB

Ht _________cm **Wt _________kg** **BSA _________m^2**

Date Due	Date Given	Day	BLIN ______mg	DEX ______mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	____mg ↓	_______mg			a*, b, d, g+,f$	
		2					e& g+	
		7					g+	
		8			____mg	____mg	b, c, d,	
		14					e& g+	
		15					b, d	
		21					g+	
		22					b, d	
		28						
		29			____mg	____mg	b, c, d	
		30-35	**Rest Period**					
		36	Following Blinatumomab Block: Cycle 1, patients receive Continuation 1 therapy (Section 4.11, APPENDIX II-I) when count parameters are met.					

+ **Bone marrow:** Prior to start of first blinatumomab infusion and **Peripheral blood:** Prior to (Hour 0) and during (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion (see Section 13.5 for complete details).

$ Prior to (Hour 0) first blinatumomab infusion (see Section 13.7 and lab manual for details)

& See lab manual for details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-N **Blinatumomab Block - Cycle 2 and 3** (LR Patients in **Arm D**) This therapy is Cycles 2 and 3 of therapy with blinatumomab for the LR patients randomized to Arm D	Patient COG ID number DOB

Blinatumomab Block: Cycles 2 & 3; each last 5 weeks (35 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL. See Section 4.16 for treatment details.
This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN)	IV	15 µg/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets[1] c Bilirubin, ALT & creatinine, BUN d Peripheral blood for Immunogenicity [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO or IV	10 mg/m²/dose , 6-12 hours prior to blinatumomab infusion, THEN 5 mg/m² within 30 minutes of starting Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	

Enter Cycle #_________ Ht _________cm Wt _________kg BSA _________m²

Date Due	Date Given	Day	BLIN ____mg	DEX ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below			
		1	____mg ↓	______mg	a*, b, c	
		8			b, c	
		15			b, c	
		22			b, c	
		28				
		29			b, c,d$	
		30-35	**Rest Period**			
		36	Following Blinatumomab Block Cycle 2: LR B-ALL patients randomized to **Arm D** will receive Continuation 2 (Section 4.11, APPENDIX II-I) when count parameters are met. Following Blinatumomab Block Cycle 3: LR B-ALL patients randomized to **Arm D** will receive Maintenance Cycle 1 therapy- (Section 4.12, Appendix II-J) when count parameters are met.			

$Obtain at End Cycle 2. In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1. See Section 13.7 and lab manual for details
*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX III: MERCAPTOPURINE DOSING GUIDELINES

MERCAPTOPURINE 75 mg/m^2

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk
2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk

2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk
2.41 – 2.45	3½ tab/ d x 5; 4 tab / d x 2	1275 mg/wk
2.46 – 2.49	3½ tab/ d x 4; 4 tab / d x 3	1300 mg/wk
2.50 – 2.54	4 tab/ d x 4; 3½ tab / d x 3	1325 mg/wk
2.55 – 2.59	4 tab/ d x 5; 3½ tab / d x 2	1350 mg/wk
2.60 – 2.64	4 tab/ d x 6; 3½ tab / d x 1	1375 mg/wk
2.65 – 2.69	4 tab/ d x 7	1400 mg/wk
2.70 – 2.73	4 tab/ d x 6; 4½ tab / d x 1	1425 mg/wk
2.74 – 2.78	4 tab/ d x 5; 4½ tab / d x 2	1450 mg/wk
2.79 – 2.83	4 tab/ d x 4; 4½ tab / d x 3	1475 mg/wk
2.84 – 2.88	4½ tab/ d x 4; 4 tab / d x 3	1500 mg/wk
2.89 – 2.92	4½ tab/ d x 5; 4 tab / d x 2	1525 mg/wk
2.93 – 2.97	4½ tab/ d x 6; 4 tab / d x 1	1550 mg/wk
2.98 – 3.00	4½ tab/ d x 7	1575 mg/wk

Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.

APPENDIX IV: THIOGUANINE DOSING GUIDELINES

THIOGUANINE 40 mg/m^2

**Patients exceeding a BSA of 3 m^2 should have their TG doses calculated on actual BSA with no maximum dose.*

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 40 mg)	Cumulative Weekly Dose
0.27 – 0.3	Use oral compounded suspension	
0.31 – 0.34	Use oral compounded suspension	
0.35 – 0.38	Use oral compounded suspension	
0.39 – 0.41	Use oral compounded suspension	
0.42 – 0.45	Use oral compounded suspension	
0.46 – 0.48	Use oral compounded suspension	
0.49 – 0.54	½ tab / d x 7	140 mg/wk
0.55 – 0.61	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.62 – 0.68	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.69 – 0.75	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.76 – 0.82	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.83 – 0.89	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.9 – 0.96	1 tab / d x 6; ½ tab / d x 1	260 mg/wk
0.97 – 1.04	1 tab / d x 7	280 mg/wk
1.05 – 1.11	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
1.12 – 1.18	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
1.19 – 1.25	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
1.26 – 1.32	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
1.33 – 1.39	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
1.4 – 1.46	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
1.47 – 1.54	1½ tab /day	420 mg/wk
1.55 – 1.61	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.62 – 1.68	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.69 – 1.75	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.76 – 1.82	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.83 – 1.89	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.9 – 1.96	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.97 – 2.04	2 tab / day	560 mg/wk
2.05 – 2.11	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
2.12 – 2.18	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
2.19 – 2.25	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
2.26 – 2.32	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
2.33 – 2.39	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
2.4 – 2.46	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
2.47 – 2.54	2½ tab / d	700 mg/wk
2.55 – 2.61	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
2.62 – 2.68	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
2.69 – 2.75	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
2.76 – 2.82	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
2.83 – 2.89	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
2.9 – 2.96	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk
2.97 – 3	3 tab / d x 7	840 mg/wk

APPENDIX V: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY
(for children from 7 through 12 years of age)

A trial to compare 2 ways to treat children with B-Lymphoblastic Leukemia (B-ALL) that has come back (relapsed) after the first treatment

1. We have been talking with you about your illness, B-ALL. You have received treatment for this B-ALL before. After doing tests, we have found that the cancer has come back in your bone marrow, brain or spinal cord, or testes. B-ALL that has come back after the first treatment is called relapse.

2. We are asking you to take part in a research study because you have B-ALL that has relapsed. A research study is when doctors work together to try out new ways to help people who are sick. In this study we are trying to learn more about how to treat B-ALL when it has come back after the first time it was treated. During this study, we want to test whether the relapsed B-ALL responds better to combination chemotherapy or a new drug called blinatumomab. The treatment that you get will depend on a process called random assignment. Random assignment is a lot like flipping a coin and you will have an equal chance of getting both treatment options.

3. Children and teens who are part of this study will be treated with either combination chemotherapy or a new drug called blinatumomab. It is possible that some children will get radiation to their brain or testes, depending on where the leukemia is found. Some children will also get a stem cell transplant.

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 having the leukemia go away for as long as possible. But we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you might experience more side effects from the combination chemotherapy or blinatumomab. Another risk is that the therapy on this study might not be as effective as other options. 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 blood. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY
(for teens from 13 through 17 years of age)

A trial to compare 2 ways to treat children with B-Lymphoblastic Leukemia (B-ALL) that has come back (relapsed) after the first treatment

1. We have been talking with you about your illness, B-ALL. You have received treatment for this B-ALL before. After doing tests, we have found that the cancer has come back in your bone marrow, brain or spinal cord, or testes. B-ALL that has come back after the first treatment is called relapse.

2. We are asking you to take part in a research study because you have B-ALL that has relapsed. A research study is when doctors work together to try out new ways to help people who are sick. In this study we are trying to learn more about how to treat B-ALL when it has come back after the first time it was treated. During this study, we want to test whether the relapsed B-ALL responds better to combination chemotherapy or a new drug called blinatumomab. The treatment that you get will depend on a process called random assignment. Random assignment is a lot like flipping a coin and you will have an equal chance of getting both treatment options.

3. Children and teens who are part of this study will be treated with either combination chemotherapy or a new drug called blinatumomab. It is possible that some children will get radiation to their brain or testes, depending on where the leukemia is found. Some children will also get a stem cell transplant.

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 having the leukemia go away for as long as possible. But we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that you might experience more side effects from the combination chemotherapy or blinatumomab. Another risk is that the therapy on this study might not be as effective as other options. 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. These samples would be taken when other standard tests are being performed, so there would be no extra procedures. You can still be treated on this study even if you don't allow us to collect the extra samples for research.

APPENDIX VI: ADDITIONAL INFORMATION FOR BANKING FOR FUTURE RESEARCH CORRELATIVE BIOLOGY STUDY

a) Rationale

The ability to collect leukemic and normal tissue samples for future research, and to link these samples to patient characteristics and outcomes, has been critical to recent seminal discoveries regarding the molecular basis of de novo ALL and relapsed ALL, and the relationship of specific molecular lesions with outcomes and response to targeted therapies. In the context of this protocol, we will seek consent from participants to provide material for banking for the purpose of performing retrospective studies to refine risk stratification, identify new targets for therapy, identify biomarkers to predict response, and to link host polymorphisms with various disease characteristics and toxicities.

b) Aims and methods

These studies will be performed as stand-alone biology studies subject to review and approval in accordance with the NCTN policies. The following are general descriptions of the types of studies planned.

- Leukemia genomic studies

  Modern genomic studies of high risk ALL have identified novel genetic alterations in ALL that are associated with treatment failure. In particular, high frequencies of mutations have been described in genes involved in B lymphocyte development (*EBF1*, *IKZF1*, *PAX5*) and signaling (*BTLA*, *CD200*, *RAS*) and in cell cycle regulation (*CDKN2A/B*, *RB*, *TP53*).[80] Limited genomic analyses of paired diagnosis and relapse ALL samples have also shed light upon the early origin and clonal nature of such leukemia-associated mutations.[81,82] Other yet-undiscovered mutations likely contribute the pathogenesis of this heterogeneous group of malignancies, and comprehensive prospective evaluation of the genetic landscape of relapsed ALL has not been performed. We hypothesize that integration of genomic profiling data will provide important insights regarding the molecular pathogenesis of relapsed ALL and may identify potential therapeutic targets or identify novel mechanisms of resistance within the context of the agents employed.[83-85]

  We hypothesize that high-throughput genome-wide profiling via multiple non-overlapping techniques provide a comprehensive genetic and epigenetic "fingerprint" and will identify key alterations that contribute to the pathogenesis and progression of relapsed ALL. We further hypothesize that integration of these approaches will allow discovery of alterations that may also be present in *de novo* ALL and could ultimately be used for initial risk stratification and new treatment approaches.

  Consenting patients will submit bone marrow and/or peripheral blood samples at study entry and, if applicable, at second relapse to the central COG Tissue Bank at Nationwide Children's Hospital for storage of viably cryopreserved cells and for isolation nucleic acids, including DNA and RNA. Nucleic acids isolated from relapse specimens will be stored for potential use for genomic profiling, which will include single nucleotide polymorphism (SNP) arrays, array-based gene expression profiles and/or quantitative RT-PCR-based gene expression analyses, methylation arrays, and/or comprehensive sequencing approaches (e.g., RNA-seq, whole exome sequencing), depending on currently available technologies and funding sources. Banked specimens subsequently will be distributed from the reference laboratories to the laboratories performing the individual correlative biology studies. Results from these correlative biology studies may ultimately facilitate (a) enhanced refinement of risk stratification for patients with relapsed ALL, (b) detection of previously-unsuspected subset specificity of blinatumomab, and (c) generation of additional hypotheses with respect to the underlying biology of relapsed ALL.
- Host polymorphism studies

  There is substantial evidence that both inherited germline constitutional and somatically-acquired ALL-specific genomic variation may contribute to variations in response.[86-95] Blood samples obtained during remission are requested specifically for the purpose of providing constitutional (germline) DNA from each patient. Several efforts are anticipated for study of how genomic variation (SNPs, copy number variations, DNA methylation and insertions/deletions) in the constitutional DNA may be associated with phenotypes in ALL. The phenotypes could include those related to probability of cure, response, adverse events or classification. Techniques for interrogation of DNA variation are constantly evolving, and thus these techniques vary but may include candidate polymorphism testing (eg, via Taqman, GoldenGate, or PCR/RFLP assays), candidate gene sequencing (eg, via next-generation technologies coupled with exon capture) or whole-genome sequencing (eg, via next-generation technologies, with or without capture).

- MRD by next generation sequencing (NGS)

  Next-generation sequencing (NGS) offers the potential for highly sensitive and standardized detection of minimal residual disease (MRD) in ALL. In comparison to current PCR methods, NGS assays do not require the laborious generation and validation of patient-specific primers, resulting in improved turn-around time and reduced cost, and may provide improved specificity by direct enumeration of leukemia-derived sequences. Current flow cytometric methods for MRD detection rely on relatively subjective assessments by trained interpreters and are about 1 log less sensitive than PCR-based methods. To determine the suitability of NGS methods for routine MRD assessment in a clinical trial setting, we will sequence the variable regions of IGH in pretreatment and post-treatment samples. Both the presence and the frequency of the MRD clone relative to the total IGH repertoire will be noted.

APPENDIX VII-A CLINICAL SITE MANAGEMENT OF OUT-PATIENT TREATMENT USING CTEP-SUPPLIED BLINATUMOMAB

- PREPARED IV INFUSION BAGS MAY NOT BE CHANGED BY THE STUDY SUBJECT
- PREPARED INFUSION BAGS OR INTACT VIALS MUST NOT BE TRANSPORTED TO ANOTHER LOCATION BY THE STUDY SUBJECT

AGENT PREPARATION AND ADMINISTRATION OPTIONS

- Prepare all out-patient infusion bags at the registering/treating NCTN Network institution. Study subjects should return to the registering/treating institution for all infusion bag changes.

- For study subjects that cannot return to the registering/treating institution every 48-hours for infusion bag exchanges, the next preference would be for **another NCTN Network institution that is participating on the trial and is closer to the subject's home take over** responsibility for the study subject's protocol participation. In such cases, transfer of the subject's protocol registration to another participating investigator and institution should be considered.

- If transferring the subject's protocol registration to another participating investigator and trial site within the NCTN Network is not feasible, use of **a local outpatient infusion center** could be considered.

    a. First preference would be for all infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2^{o} to 8^{o}C pre-qualified shipping container to the local out-patient infusion center.

    b. The prepared infusion bags are stored at the local outpatient infusion center. The infusion center would perform each infusion bag change.

    c. If the local outpatient infusion center will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the local outpatient infusion center, with infusion bags prepared and administered by the local outpatient infusion center staff.

    d. In either case, the local outpatient infusion center would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

    e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the local infusion center by registering/treating institution or local infusion center staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the local infusion center via overnight courier delivery service in a 2^{o} to 8^{o}C pre-qualified shipping container.

- If an outpatient infusion center is not an option, use of a **home health care service** provider can be considered.

    a. The first preference would be for all outpatient infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2^o to 8^oC pre-qualified shipping container to the servicing home health care agency.

    b. The prepared infusion bags are stored by the home health care agency and each individual infusion bag transported to the subject's home by the home health care service nursing staff under refrigerated storage conditions for each infusion bag change.

    c. If home health care agency will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the home health care agency, with infusion bags prepared and administered by the home health care agency staff.

    d. In either case, the home health care agency would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

    e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the home health care agency by registering/treating institution or home health care agency staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the home health care agency via overnight courier delivery service in a 2^o to 8^oC pre-qualified shipping container.

5. If all options above are not feasible, shipping the prepared infusion bags directly to patient's home via overnight courier delivery service for administration by home healthcare agency staff is acceptable.

    a. The prepared infusion bags are to be shipped in a 2^o to 8^oC pre-qualified shipping container containing one infusion bag per box. Example, if you are making 2 x 48 hour infusion bags, each infusion bag will be shipped in a separate 2^o to 8^oC pre-qualified shipping container. The number of infusion bags that may be prepared and shipped is dependent on the duration the shipping container used is qualified to maintain 2^o to 8^oC temperature.

    b. Patients should NOT open the shipping container upon arrival. Shipping containers are to be stored in a secured area away from reach of children or pets.

    c. Shipping containers must only be opened by the home health care service staff at the time of the infusion bag change. Only one shipping container should be opened at a time. If cold-chain management of the prepared infusion bag has been interrupted by opening of the shipping container or storage of the prepared infusion bag in the shipping container exceeds the duration of the qualified time the container will maintain 2^o to 8^oC temperature, the infusion bag should not be used.

The home health care service staff should immediately contact the registering/treating institution site pharmacy as indicated on the shipment form. Within 1 business day, the registering/treating institution site should send an email to the COG Industry Sponsored Trials office at istprogram@childrensoncologygroup.org with a copy to PMB/CTEP at PMBafterhours@mail.nih.gov to report all such occurrences of prepared, unusable infusion bags shipped to a patient's home.

d. Form documenting the time of packaging in the shipping container, duration of time the container will maintain 2º to 8ºC temperature and verification that cold-chain management was maintained prior to administration must be included in each shipping container and returned to registering/treating institution for documentation purposes. (See Appendix VII-B)

e. Home health care service staff is to use GCP guidelines.

EVALUATION OF POTENTIAL SATELLITE PHARMACY SITES

When the registering/treating institution is considering use of a local infusion center or home health care agency as a satellite pharmacy, the following must be assessed by the registering/treating institution in relation to the suitability of the local infusion center or home health care agency:

- Ability to appropriately store (temperature and security) the intact agent vials and/or prepared infusion bags.
- Ability to provide documentation of controlled and monitored temperature storage conditions while the IND agent is in the local infusion center or home health care agency possession.
- Availability of appropriately trained staff to prepare doses in compliance with USP <797> guidelines and the protocol, to label infusion bags according to the protocol instructions and to store agent doses under appropriate controlled temperature conditions.
- For home health care agency services, the ability to transport each prepared dose individually to the subject's home under appropriate controlled storage conditions or the ability to assess and confirm that cold-chain management of prepared infusion bags shipped to the subject's home is maintained prior to administration.
- Availability of appropriately trained staff to administer the prepared doses and perform the infusion bag changes according to the protocol.
- Methods for proper disposal of the waste, empty vials, IV bags, etc. are in place.
- Plan for return of unused intact vials to the registering/treating institution is in place.
- Source documentation to confirm agent administration must be maintained by the local infusion center or home health care agency and must be provided to the registering/treating institution for incorporation into the patient's medical/research records and for audit purposes.
- Plan for handling missed doses is in place.

- Agent accountability must be maintained via use of the NCI Drug Accountability Record Form (DARF). The originating site must keep a Control DARF and the local infusion center or home health care agency would be required to maintain a Satellite DARF if receiving and storing supplies of intact vials or receiving and storing infusion bags prepared by the registering/treating institution. Maintenance of a Satellite DARF is not required by home health care agency staff for prepared infusions bags shipped to the subject’s home.
- The DARF must be provided to the registering/treating institution for record keeping purposes and audits.
- Documentation of IRB coverage for the protocol must be maintained. The IRB of record for the site must be informed that the study subject may receive therapy administered by a non-research site (i.e., the local infusion center or home health care agency).

TRAINING FOR ALL PARTICIPATING SITES

The Lead Network Group for the trial must work with participating sites to:

a. Implement a training process for participating NCTN Network sites regarding blinatumomab preparation and administration. Documentation of participating site training must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial

b. Develop a plan for participating NCTN Network sites to assess and train local outpatient infusion centers or home health care agency for patient treatment if required and document training of such sites

c. Have a training manual available for local outpatient infusion centers or home health care agencies on the clinical trial, appropriate agent preparation, handling and administration requirements and appropriate record keeping requirements

d. Create a definitive written communication plan for use between registering/treating institution and the local outpatient infusion centers or home health care agency on an ongoing basis during subject’s treatment regimen, including emergency contact information for the registering/treating institution and investigator

APPENDIX VII-B SHIPMENT OF BLINATUMOMAB IV BAG FROM SITE/PHARMACY TO PATIENT'S HOME

To be completed by Site/Pharmacy:

From: (Investigator Name, Address)	**To Patient:** (Patient Initials, Study ID No) _____________ ; ___________ __ __ __ Patient Initials Study ID Number	**Protocol No.:**

Prepare shipment of IV bag at 2°C to 8°C in validated/pre-qualified insulated shipper as per manufacturer instructions (see shipping container instructions). Please take care to use the applicable instructions for summer or winter package preparation, respectively.

IV Bag number	Date of packaging [DD/MMM/YYYY]	Time of packaging [hh:mm]	packed by (initials)

Please tick the boxes and fill in the information below when preparing the IV bag shipment!

- ☐ Validated/pre-qualified shipping container duration of time 2°C to 8°C temperature is maintained: ____________________________ hours
- ☐ Cooling elements for provided box used according to manufacturer's instruction

Confirmed by: ____ ____________________
(print name, signature) (date)

To be completed by Ambulant/Home Care Service Provider:

Shipment box unopened and content intact? **YES** ☐

NO ☐

IF NO, please comment_

____

Date and time shipment box opened:____
(date) (time)

Confirmed by: ____ ____________________
(print name, signature) Amb. Care Service (date)

Note: **If content is not intact, please do not use IV bag and inform site immediately!**
If time box opened minus time of packaging exceeds the time duration the shipping container maintains 2°C to 8°C, please do not use IV bag and inform site immediately!

APPENDIX VIII: ADDITIONAL INFORMATION FOR MRD CORRELATIVE BIOLOGY STUDY

a) **Rationale**

Minimal residual disease is known to be a powerful prognostic factor in childhood ALL.[1-5,12,20-22] Although the majority of work has been done in newly diagnosed ALL patients, several studies using both polymerase chain reaction methods[13,14,16-18] and flow cytometry[19,23] have shown that MRD is highly predictive of second marrow relapse.

Flow cytometric MRD results will be used for the following purposes in this study:

- For late B-ALL marrow and late B-ALL IEM patients, we will use end-Block 1 flow cytometric MRD levels of < 0.1% vs. ≥ 0.1% to define low risk group vs. intermediate risk group, respectively. The low risk group will be eligible for LR randomization. The intermediate risk group will be eligible for HR/IR Randomization.
- For the LR patients participating in LR randomization, we will use end-Block 2 MRD levels of < 0.01% vs. ≥ 0.01% as a randomization stratification criteria to ensure balanced randomization.
- For the IR and HR patients participating in HR/IR Randomization, we will use end-Block 1 MRD levels of <0.1% vs. ≥ 0.1% as a randomization stratification criteria to ensure balanced randomization.
- For HR/IR Randomization patients proceeding to HSCT, we will use the end-Block 3/pre-HSCT MRD level, the peri-engraftment MRD level and the day +100 MRD level to determine eligibility for rapid tapering of immunosuppression.
- In HR/IR Randomization, we will use flow cytometric MRD+ rates at the end of Blocks 2 and 3 as a secondary efficacy objective.

b) **Technique**

Aliquots of fresh bone marrow specimens **at study entry and during therapy at various designated time points** (see study schema and TDMs) will be adjusted to suitable cell concentrations and stained with the following combinations of monoclonal antibodies in 6-color immunofluorescence:

Tube 1: CD20-FITC/CD10-PE/CD38-PerCP-Cy5.5/CD58-APC/CD19-PE-Cy7/CD45-APC-Cy7
Tube 2: CD9-FITC/CD13-PE+CD33-PE/CD34-PerCP-Cy5.5/CD10-APC/CD19-PE-Cy7/CD45-APC-Cy7

After incubation, samples will be lysed with ammonium chloride, fixed with 0.25% ultra pure formaldehyde, and washed once before analysis. Samples will be run on a Becton Dickinson FACSCanto. A minimum of 750,000 events will be collected, and data will be analyzed by software developed by Dr. Brent Wood, University of Washington that facilitates the hierarchical gating strategy useful for identifying phenotypically aberrant cells. In cases in which the above panels are not informative for detecting abnormal cells, additional markers including but not limited to CD15 and TdT will be added to the panel to help identify MRD populations. In addition, if the administration of blinatumomab creates difficulties in identifying leukemic cells by virtue of CD19 expression, cytoplasmic CD79a and/or CD22 will be used to aid gating.

APPENDIX IX: ADDITIONAL INFORMATION FOR CRLF2 CORRELATIVE BIOLOGY STUDY

a) **Rationale**

Recent genomic studies of ALL have identified genomic alterations of CRLF2, which encodes the thymic lymphopoietin receptor (TSLPR) and which results in upregulation of CRLF2 as an important contributor to leukemic pathogenesis.[3-5,7] Upregulation may occur by gene alterations, most often fusing CRLF2 to either P2RY8 or IGH@, as well as rarely, a CRLF2 point mutation (F232C),[3-5,7] though there may also be as yet unrecognized mechanisms. In addition, patients with whose blasts show upregulated CRLF2 typically also have simultaneous activating mutations in kinase genes including IKZF1, JAK1 and JAK2, and as a result have abnormalities in signal transduction networks.[3,4,7] Our results suggested high risk children with overexpressed CRLF2 as detected by PCR have very poor outcome irrespective of whether structural rearrangements can be identified,[8] while other studies have suggested that this is only true of patients with P2RY8-CRLF2 translocations.[2,9] Moreover, in our studies CRLF2 did not appear to be prognostically significant in standard risk patients.[8] However, virtually nothing is known about CRLF2 overexpression in the relapse setting, and whether its expression has continued prognostic significance in this already poor-risk group of patients. In addition, because of the underlying kinase abnormalities in this patient population, these patients are potentially ideal candidates for treatment with novel signal transduction inhibitors. Assessing CRLF2 expression may help to identify patients who might be candidates for specific therapy in trials that may be developed as these agents mature.

b) **Technique**

In conjunction with the immunophenotyping performed at study entry as a baseline for flow cytometric MRD testing, we will also quantify surface TSLPR expression and correlate with outcome.

c) **Specific Aims**

Aims:

1) To determine if the frequency of high CRLF2 expression (which correlates with CRLF2 genomic lesions) is higher in the first marrow relapse B-ALL patient population than in the initial diagnosis B-ALL patient population.

2) To determine if first marrow relapse B-ALL patients with high CRLF2 expression have an inferior outcome to those without high CRLF2 expression.

d) **Power calculations**

Aim 1: Comparison of the frequency of CRLF2 expression among B-ALL patients in first marrow relapse to that in newly diagnosed B-ALL patients.

From past COG studies for newly diagnosed B-ALL, it is estimated that 10% of standard risk (SR) and 21% of high risk (HR) patients will relapse. Assuming there are 2/3 SR and 1/3 HR newly diagnosed patients, it is estimated that around 49% and 51% of patients in first relapse will be NCI SR and HR, respectively. Given that about 7% and 12% of the SR and HR patients have high level CRLF2 expression via flow cytometery, the overall rate of high CRLF2 expression (which correlates with genomic lesions) in newly diagnosed B-ALL patients is about 10%.

The following table provides the power to detect a difference in rates of high CRLF2 expression between newly diagnosed and 1st relapse B-ALL patients when the rate of high CRLF2 expression of the 1st relapse patients is 13%, 15%, 18% and 20% (i.e. RR=1.3, 1.5, 1.8 and 2.0), respectively. The power calculations are based on a one-sample exact test at 5% significance levels (one-sided). A total of 426 B-ALL marrow relapse ALL patients [180 early (CR1<36 months) and 246 late (CR1 ≥36 months)] were considered in this power calculation.

Significance Level	Rate of high CRLF2 expression in relapse B-ALL pts (baseline rate = 10% among newly diagnosed pts)	Power (%)
5%	13%	60.0
	15%	92.4
	18%	99.9
	20%	100.0

Aim 2: Comparison of EFS in first marrow relapse B-ALL patients with high level CRLF2 expression vs. those without high level CRLF2 expression.

It is anticipated that a total of 180 early (CR1<36 months) and 246 late (CR1 ≥36 months) marrow B-ALL patients will be enrolled to AALL1331. According to past studies, the 3-year EFS of early and late marrow relapse patients are approximately 26% and 65%, respectively, giving an overall 3-year EFS of about 48%. Assuming the above rates of high-level CRLF2 expression and minimum 2 years of follow-up, the table gives powers for comparing EFS between patient groups with and without high level CRLF2 expression. The power calculations are based on the one-sided log-rank test at the 5% significance level.

Significance Level	CRLF2 high rate for 1st relapsed pre-B pts	Sample Size		3-year EFS rates		Power
		CRLF2 +	CRLF2-	CRLF2+	CRLF2-	
0.05	0.13	55	371	0.18	0.52	100.0
	0.13	55	371	0.20	0.52	99.9
	0.13	55	371	0.23	0.52	99.8
	0.13	55	371	0.26	0.51	99.0
	0.13	55	371	0.30	0.51	96.3
	0.13	55	371	0.33	0.50	88.8
	0.13	55	371	0.36	0.50	77.7
	0.13	55	371	0.39	0.49	55.1
	0.15	64	362	0.18	0.53	100.0
	0.15	64	362	0.20	0.53	100.0
	0.15	64	362	0.23	0.52	99.9
	0.15	64	362	0.26	0.52	99.6
	0.15	64	362	0.30	0.51	97.5
	0.15	64	362	0.33	0.51	93.5
	0.15	64	362	0.36	0.50	81.2
	0.15	64	362	0.39	0.50	65.0
	0.18	77	349	0.18	0.55	100.0
	0.18	77	349	0.20	0.54	100.0
	0.18	77	349	0.23	0.53	100.0
	0.18	77	349	0.26	0.53	99.9
	0.18	77	349	0.30	0.52	99.1
	0.18	77	349	0.33	0.51	95.7
	0.18	77	349	0.36	0.51	88.8
	0.18	77	349	0.39	0.50	69.6

	0.20	85	341	0.18	0.56	100.0
	0.20	85	341	0.20	0.55	100.0
	0.20	85	341	0.23	0.54	100.0
	0.20	85	341	0.26	0.54	100.0
	0.20	85	341	0.30	0.53	99.6
	0.20	85	341	0.33	0.52	97.8
	0.20	85	341	0.36	0.51	90.6
	0.20	85	341	0.39	0.50	72.1

APPENDIX X: ADDITIONAL INFORMATION FOR BLINATUMOMAB PHARMACODYNAMICS CORRELATIVE BIOLOGY STUDY

a) Rationale

For patients with relapsed/refractory ALL, response patterns to blinatumomab are essentially binary. Some patients have a striking response, with a systemic cytokine release syndrome (CRS, most notably IL-6) accompanying clearance of leukemic blasts and culminating in an MRD-negative remission, and others do not respond.[10,11,96] For patients that have received blinatumomab in the setting of MRD positivity (i.e., with very low tumor burden), response rates are generally higher and significantly less likely to be associated with CRS.[4,5] Attempts to correlate responses with various peripheral blood parameters (such as ALC and T-cell subset quantitation) have been largely unsuccessful in either setting, although the patient numbers have been limited.[3]

The bone marrow microenvironment contains various immunologic components that have been shown to either enhance or suppress cytotoxic T-cell effector response to tumor antigens. The bone marrow serves as a reservoir of memory T-cells with heightened antigen specificity compared to peripheral blood memory T-cells, and the bone marrow microenvironment is capable of effectively priming naïve T-cell responses.[97-99] However, the bone marrow is also a reservoir for suppressive regulatory CD4/CD25/FOXP3+ T-cells (T regs).[100] Comparative studies of bone marrow vs. peripheral blood in patients with myeloma have shown that marrow-infiltrating lymphocytes (MILs) are more effectively activated and expanded and are more capable of tumor-specific cytotoxicity than peripheral blood lymphocytes (PBLs).[101] In addition, bone marrow contains myeloid-derived suppressor cells (MDSCs) that have been shown to preferentially capture and present tumor associated antigens to T regs, resulting in tumor tolerance, and preventing the capture and presentation of these antigens by dendritic cells to activate tumor-specific cytotoxic effector T-cells.[102] IL-6 is among the key mediators that skews the marrow T-cell repertoire from T regs to cytotoxic effector T-cells.[103]

As has been suggested by previous studies, lymphocyte populations and cytokine profiles in the peripheral blood may also provide insight into responses[3] and adverse effects[11]. Since our study will include more patients than any blinatumomab trial to date, our study may be particularly well-suited to detect these associations.

b) Hypotheses and specific aims

The overall objective of this correlative study is to generate new knowledge regarding the mechanisms that determine the observed heterogeneity of clinical responses to blinatumomab in relapsed ALL, for which there are currently no biomarkers. While this study is preliminary and will not by itself establish biomarkers of blinatumomab response, it may identify putative biomarkers that can then be evaluated for validation in future studies.

We hypothesize that the balance of enhancing vs. suppressive components of the cytotoxic T-cell effector response in the bone marrow microenvironment may be playing a particularly important role in determining the presence or absence of clinical response to blinatumomab. Specifically, we hypothesize that the bone marrow of patients that respond to blinatumomab (i.e., achieve complete continuous remission after treatment with blinatumomab) will be characterized by a relative predominance of cytotoxic memory/effector T-cells and a paucity of T regs and MDSCs, while the opposite pattern will be characteristic of the bone marrow of non-responders (i.e., those that relapse after treatment with blinatumomab).

- **Specific Aim 1**: To determine if the balance of enhancing vs. suppressive components of the cytotoxic T-cell effector response in the bone marrow microenvironment at baseline correlates with disease free survival (DFS) in relapsed ALL patients treated with blinatumomab.

We further hypothesize that lymphocyte populations and cytokine profiles in the peripheral blood at baseline and at post-treatment time points (hours 6 and 12 on day 1, and once on days 2, 7, 14 and 21) may also provide insight into adverse effects and clinical response, and so we will collect peripheral blood for flow cytometric characterization of lymphocyte subsets (including T-cell subsets as above, as well as circulating normal B-cells) and isolate plasma for multiplex cytokine profiling (including IL-6, IL-2R, IL-8, IL-10, MCP-1, MIP-1B, and INF-γ).

- **<u>Specific aim 2</u>**: To determine if peripheral blood patterns of lymphocyte subsets and cytokines, both at baseline and at post-treatment time points, correlates with incidence of blinatumomab-related reportable adverse events (see section 5.2.1), and DFS in relapsed ALL patients treated with blinatumomab.

c) Methods

- <u>Processing, cryopreservation and quality control</u>

Refer to Section 13.5 for specimen collection and shipment. All blood and marrow samples will first be centrifuged to allow isolation of plasma. Plasma will be stored in 250 uL aliquots and stored at -80 C for subsequent batched assays. Cell pellets will be diluted in HBSS and centrifuged over Lymphocyte Separation Medium (LSM) to isolate mononuclear cells, then suspended in cryoprotectant solution and viably cryopreserved in liquid nitrogen in aliquots of 10e6 cells for subsequent batched assays. Assays will be performed as cohorts of five patients have provided a complete set of samples.

The Brown laboratory routinely processes blood and marrow specimens from cooperative group clinical trials and performs a wide variety of assays using plasma and viably cryopreserved cells. Samples are generally received in the laboratory within 48 hours of collection and processed immediately. Plasma and cells are sufficiently stable in transport under these conditions for the proposed assays. The flow cytometric assays are routinely performed in the Pardoll laboratory, which is collaborating on this project and has provided the processing protocol described above.

- <u>Multiparameter flow cytometric measurement of lymphocyte subsets and MDSCs</u>

Vials of viably cryopreserved marrow and blood cells will be thawed and washed and viable cells counted by trypan blue exclusion. Cells will then be stained with isotype controls and the following antibody panels, and analyzed in triplicate by flow cytometry

- For lymphocyte subsets: CD3, CD4, CD8, CD19, CD20, CD45RO, CD45RA, HLADR, CD27, CD62L, CD25, CD28 and CD127.
- For MDSCs (marrow only): Lin, HLA-DR, CD33, CD11b, CD14, CD15

The **endpoint** for this assay will be the <u>relative percentage</u> and <u>absolute number</u> (in cells/uL) and of each of the following:

- T regs
- Naïve T-cells
- Memory T-cells (central vs. effector)
- Activated T-cells
- B-cells
- Monocytic MDSC (marrow only)
- Granulocytic MDSC (marrow only)

- <u>Cytokine profiling in marrow and blood plasma</u>

Vials of frozen plasma will be thawed and a panel of cytokines will be quantitated in triplicate using a custom cytometric bead array kit (custom BD CBA) designed to measure the following: IL-6, IL-2R, IL-8, IL-10, MCP-1, MIP-1B, and INF-γ. Isotype controls will serve as negative controls, and standard curves will be generated using control cytokine solutions.

The **endpoint** for this assay will be levels of each cytokine in pg/mL.

- Rationale for selection of methods and laboratories

  The methods described above are performed routinely in the Brown (processing and cryopreservation) and Pardoll (flow cytometric measurement of lymphocytes, MDSCs and cytokines) laboratories, and are likely to optimize the chances that the proposed studies will be successful.

d) Analysis and Statistical Considerations

- **Specific Aim 1:**

We will calculate ratio (R) of enhancing to suppressive components in bone marrow microenvironment for each patient as follows:

R = (# Memory T-cells + # Activated T-cells) / (# T regs + # MDSC)

We will use logistic regression to model outcome (no relapse vs. relapse) as a function of R. The Benjamin-Hochberg procedure will be used to control for multiple comparisons.

The anticipated result is that R is negatively correlated with risk of relapse (i.e., a higher ratio of enhancing to suppressive components will reduce risk of relapse). If this anticipated result is seen, multivariate analysis that includes known associations with relapse (duration of first remission, MRD, etc.) will be performed to determine whether the marrow microenvironment ratio adds anything independent to known predictors of relapse in blinatumomab-treated patients.

This analysis will be performed on the entire cohort of patients treated with blinatumomab, and also separately on the HR/IR cohort and on the LR cohort.

We anticipate that a total of 156 evaluable patients will be treated with blinatumomab on this study (Section 9.2), of which 72 will be HR/IR and 84 will be LR. We assume that we will have 90% compliance with submission of the marrow sample. We assume that about 10% of submitted samples will fail analysis for technical reasons. Thus, we expect that our sample size for R will be 127 (59 HR/IR and 68 LR).

Since we are proposing to use standard assays (flow cytometric quantification of marrow cell subsets) in a novel way (calculation of enhancing vs. suppressive components), we do not have *a priori* knowledge of the expected range of observed ratios. As such, these studies are exploratory and definitive power calculations are not possible. However, if we assume the log(R) follows a Gaussian distribution with a mean of 0 and standard deviation of 1 (i.e., a standard normal distribution), and assuming an overall relapse rate of 50% for the trial, a sample size of 127 will have 80% power to detect an effect size of 0.5, using a 2-sided significance level of 0.05. For example, if we assume patients who eventually relapse have a mean R of 1 (log(R)=0), then we would be able to detect that patients who do not eventually relapse have a mean R of >3.16 (log(R)=0.5) or a mean R of <0.316 (log(R)=-

0.5). This effect size is not unreasonable to expect. These calculations are based on methods from Hsieh, et al. Statist. Med. 17, 1623-1634 (1998).

The relationships between the ratios and rates of relapse will be described, and subsequent studies will be designed to validate these findings prospectively in the context of future clinical trials.

- **Specific Aim 2:**

There are 12 variables to be determined for each blood sample (7 samples per patient):
1) Total T-cell number
2) CD4 count
3) CD8 count
4) Memory T-cell count
5) Activated T-cell count
6-12) Level of each of 7 individual cytokines

For each of the 12 variables, we will determine the baseline value (BV; hour 0) and the maximal change value (MCV; value at the post-treatment timepoint for which the variable has increased or decreased to the greatest degree). For the MCV, a landmark approach will be used in which all cases are followed for 21 days, and the maximal change observed up to that point will be used to predict outcome *from that point forward* for all patients who are still observable up to that landmark time point.

There are 2 outcomes of interest:
1) Presence or absence of blinatumomab-related reportable adverse event
2) No relapse vs. relapse

As a first level analysis, we will use logistic regression to model each of the 2 outcomes as a function of each of the 12 variable's BV, and each of the 12 variable's MCV. The Benjamin-Hochberg procedure will be used to control for multiple comparisons.

The anticipated results are:

1) BV of some subsets of T-cell counts (memory T-cells, e.g.) are positively correlated with the risk of blinatumomab-related reportable adverse events, and negatively correlated with risk of relapse.
2) MCV of a subset of cytokines (IL-6 and INF-γ, e.g.) is positively correlated with the risk of blinatumomab-related reportable adverse events, and negatively correlated with risk of relapse.

Subsequent levels of analysis will attempt to characterize combinations of T-cell subset counts and cytokine levels that may perform better than individual variables in modeling the outcomes of interest.

If any of the anticipated results are seen with respect to the relapse outcomes, multivariate analysis that includes known associations with relapse (duration of first remission, MRD, etc.) will be performed to determine whether any of the T-cell subset/cytokine variables adds anything independent to known predictors of relapse in blinatumomab-treated patients.

This analysis will be performed on the entire cohort of patients treated with blinatumomab, and also separately on the HR/IR cohort and on the LR cohort.

We anticipate that a total of 156 evaluable patients will be treated with blinatumomab on this study (section 9.2), of which 72 will be HR/IR and 84 will be LR. We assume that we will have at least 90%

compliance with submission of the blood samples, and that about 10% of submitted samples will fail analysis for technical reasons. Thus, we expect that our sample size will be 127 (59 HR/IR and 68 LR).

Since we are proposing to use standard assays (flow cytometric quantification of blood T-cell subsets and cytokines) in a novel way (combining variables to model risks of adverse events and relapse after treatment with blinatumomab), we do not have *a priori* knowledge of the expected ranges of values for most variables. As such, these studies are exploratory and definitive power calculations are not possible.

However, some estimates based on specific assumptions are possible. If we assume that the baseline value for memory T-cell count for the entire study population follows a Gaussian distribution with a mean of 500/uL and a standard deviation of 100/uL, and we assume an overall relapse rate of 50% for the trial, a sample size of 127 will have 80% power to detect an effect size of 50/uL, using a 2-sided significance level of 0.05. For example, if we assume patients who eventually relapse have a mean BV memory T-cell count of 500, then we would be able to detect that patients who do not eventually relapse have a mean BV T-cell count of >550/uL, or a mean BV T-cell count of <450/uL. This effect size is not unreasonable to expect. These calculations are based on methods from Hsieh, et al. Statist. Med. 17, 1623-1634 (1998).

The relationships between the variable(s) and rates of adverse events/relapse will be described, and subsequent studies will be designed to validate these finding prospectively in the context of future clinical trials.

APPENDIX XI: ADDITIONAL INFORMATION FOR PROTEIN CELL STRESS PATHWAYS CORRELATIVE BIOLOGY STUDY

a) Rationale

Many excellent studies have focused on gene expression profiles in ALL.[51,52] However, changes in protein cell stress pathways and deregulated signal transduction pathways, have been much less well studied in ALL. There is an unmet need to learn more about chemotherapy-induced proteins expression changes in order to determine if specific proteins or protein clusters can help predict response to therapy. Specific protein expression patterns are likely to correlate with disease-free survival (DFS) and will enable us to identify specific populations at risk for relapse. Since it is very difficult to salvage patients after second relapse, one of the **goals** of this study is to determine which patients classified as low risk based on timing and site of relapse (Section 9.2) would benefit from being risk stratified instead into the high risk group. This would improve DFS in all patients with relapsed ALL. Relevant protein expression profiles will be validated in future COG trial for patients with relapsed ALL and (if the increase in correct risk assignment increases to meets statistical specifications) will be used, in conjunction with molecular classification systems, as an adjunct for risk assignment.

b) Hypotheses and specific aims

We **hypothesize** that activation of cell stress pathways and signal transduction pathways deregulated in ALL will correlate with DFS, and that the expression of specific proteins or proteins clusters will identify patients classified as low risk patients that would benefit from more intensive therapy. We have two **specific aims** to address these hypotheses:

1. To determine if specific protein expression profiles, as determined by reverse-phase protein lysate array (RPPA) and phosphoflow cytometry, correlate with clinical outcome (DFS)
2. To determine if alterations in specific groups of cell stress proteins can be used to generate a "high-risk" protein expression signature that identifies patients stratified to the low-risk group (based on time and site of relapse) that would benefit from stratification into the high-risk group.

c) The contributions that the proposed study will make to the current knowledge base

Little is known about the changes in cell stress proteins during chemotherapy. This analysis will contribute greatly to our current knowledge base by 1) determining if specific proteins or protein clusters correlate with response therapy, 2) increasing our knowledge about lymphoblast response to standard relapse chemotherapy, 3) allowing a better understanding of the biology-defined ALL subgroups, aiding the development of targeted therapies, and 4) allowing for the development of protein expression risk-classifiers that could be validated and utilized, along with gene expression profiling, to aid in risk stratification in subsequent relapsed clinical trials.

d) Relevant preclinical data

1. RPPA The Kornblau lab has analyzed two cohorts of adult AML using RPPA. The first, with 539 samples from 258 patients, was probed with 51 antibodies. the second, with 747 samples from 539 patients, was probed with 194 antibodies [104,105] These samples demonstrated that there were recurrent patterns of protein expression that correlated with outcome. Recent studies have shown that the analysis of RPPA and single cell network profiling by phosphoflow to can be analyzed using recently developed computational methods to provide a combined protein expression predictor.[106]
2. Phosphoflow cytometry: Studies have demonstrated that phosphoflow analyses can be predictive of outcome in pediatric acute leukemia. As an example, Redell et al. identified that responsiveness to IL-6 in pediatric AML was associated with superior survival.[107]

e) **Relevant data from previous clinical studies**

1. RPPA: Our preliminary data shows that we can reliably assess post-chemotherapy protein activation. Using a test set of 32 validated RPPA antibodies, we assessed changes in protein expression in 27 COG pediatric leukemia patients following induction chemotherapy. We have determined that 1) CellSave tubes preserve protein expression profiles post-treatment, as shown by the relative stability of actin expression, but a decrease in p-AKT; and 2) that we can detect the heterogeneous patterns of changes in protein expression over time, including changes in AKT, m-TOR, MAPkinase and the FOXO3 pathway following treatment (Horton, Kornblau, personal communication).
2. Phosphoflow: Based upon phosphoflow studies from phase 1 COG and adult trials using these assays,[108,109] we anticipate that we can reliably identify signaling upregulation at baseline and during therapy using shipped specimens. In an institutional study of adults with AML treated with sirolimus and chemotherapy, inhibition of phosphorylated S6 correlated with clinical responses (Perl 2012).

f) **The comparability of the methods proposed to those previously used, and the likelihood that the resulting data will be able to be compared with existing data**. Analysis of RPPA is currently being performed using the same methods in AAML1031, and so these results should be directly comparable. Analysis of signal transduction networks will use identical methods to those piloted in ADVL1011 and ADVL1114, and so these should be comparable as well.

g) **The reason for selection of the assay methodology**.

1. RPPA is a technique which can quantitate protein expression from over 1000 patient samples on a single slide using validated antibodies.[110] The sample requirements are quite small; analysis of protein panels can be accomplished with as little as 200,000 cells per patient. This is the only assay able to provide detailed analysis of protein expression with this number of cells. This technique is also relatively resistant to protein degradation during shipping time. Blood is collected into CellSave preservation tubes, which we have shown can stabilize protein expression for up to 72 hours (Horton et al manuscript in review).
2. Similarly, phosphoflow cytometry is a very sensitive and reproducible technique, analyzing signal transduction abnormalities and the level of the single cell. Phosphoflow can also be used to analyze samples both at baseline and following chemotherapy treatment.[108]

h) The **stability of the samples used for analysis:**

Although no formal studies have been performed to determine stability, samples collected locally over the past 15 years from the Horton laboratory were examined by RPPA. There were no statistically significant differences in expression patterns or protein intensity based on the age of the sample (Kornblau, personal communication).

i) **Technical performance characteristics**

1. Antibody validation: RPPA antibodies have gone through extensive testing prior to inclusion on the array,[88] including both analytic validation, and assay validation with clinically relevant samples.[94] Antibodies validated for RPPA demonstrate specificity of signal and, in the case of phosphorylation or cleavage sensitive antibodies, context-specific validation performed in baseline and stimulated samples.[87] Validation steps have included: 1) antibody specificity as determined by immunoblot, 2) appropriate induction of phosphorylation/cleavage in response to known inducing agents, 3) correlation of RPPA signal with immunoblot expression (R>0.5), 4) acceptable sigmoidal curve fit of signal with sample dilution (analyzed using Super-Curve), 5) variable slope normalization[111] and, in cases of high background, 6) topographical normalization. Slides with unacceptable variances will be redone. RPPA has acceptable intra-assay and inter-assay variability, with intra-assay coefficients of variation (COV) of 6-15% and

established inter-assay reproducibility. We have established standard operating procedures (SOPs) for sample processing, cell sorting and RPPA, and laboratory staff in both the Horton and Kornblau labs are experienced with the procedure.

b. Minimizing sample variability: based on prior testing samples received within 72h of collection from the patient have very similar protein expression patterns. (Horton, manuscript in preparation). Samples for RPPA will be collected in CellSave preservation tubes and mailed by FedEx courier to maintain protein integrity.

j) **A description of the positive and negative controls**

Controls will include normal adult and pediatric bone marrow, ALL cell lines, and ALL cells stimulated with chemotherapy as described .[104,105,112]

k) **The experience that the investigators have with the assay**

1. The Horton Laboratory will be collaborating with Dr. Steve Kornblau who has extensive experience with RPPA analysis of leukemia samples.[104,105,112]
2. The Tasian laboratory has extensive experience with phosphoflow cytometry analyses of primary patient leukemia specimens and of xenografted pediatric ALL and AML specimens.[113-116]

l) The methods of scoring and plan for analysis

a. Overview: Statistical analyses will be performed in a stepwise manner. First, we will analyze dynamic changes in protein activations following chemotherapy in all patients. The purpose is to discover natural groupings based on proteomic data only and to analyze the response of different biologically relevant signal transduction pathways during treatment. Second, we will examine protein clustering stratified by risk group and genetic subtype using supervised clustering analysis. Third, once clinical outcome data become available, we will analyze differences between treatment groups as they relate to DFS. This analysis will include unsupervised clustering methods.[104,105,112] Finally, we will generate a classifier(s) that best correlates with clinical outcome for the group as whole. While the primary objective of the study is DFS, we will also examine classifiers stratified by CR and relapse after study completion.

b. Statistical analysis**:** *Supercurve* algorithms were used to generate a single value from the 5 serial dilutions.[1] Loading controls[2] and topographical normalization[3] procedures will account for protein concentration and background staining variations. Analysis using unbiased clustering, perturbation bootstrap clustering and principle component analysis was then performed as previously described.[4] We (SM Kornblau, KR Coombes (MDACC) and A. Qutub (Rice University) have developed a novel modification of the Gap statistic, named “stability Gap” for selecting the optimal number of patient clusters from the range of possible clusters[117] This will be utilized to select the optimal number of clusters for comparison in outcomes analysis. Analysis typically places samples into 3-7 clusters for further analysis.

Comparison of the protein levels between paired samples will be done by performing paired t-tests. Association between protein expression levels and categorical clinical variables will be assessed in R using standard t tests, linear regression or mixed-effects linear models. Association between continuous variable and protein levels will be assessed by using Pearson and Spearman correlation and linear regression. Bonferroni corrections were performed to account for multiple statistical parameters for calculating statistical significance. The Kaplan-Meier method was used to generate the survival curves. Univariate and multivariate Cox proportional hazard modeling will be performed to investigate association with survival with protein levels as categorized variables using Statistica version 10 software (StatSoft, Tulsa, OK).

Other methods of analysis may include: Hierarchical Clustering, Principal Component Analysis (PCA), Self-Organizing Maps (SOM) and other class discovery methods.[118] Cluster stability will be accessed using reproducibility measures, including GAP,[119] and Stability Gap (manuscript in preparation), as well as robustness and discrepancy indices.[120] Differentially expressed proteins will be found using paired t-test as well as repeated measures, mixed effect ANOVA and ANOVA with contrasts. To determine if dynamic changes in specific protein pathways predict chemoresistance, we will use different regression and classification methods: Self Organizing Maps(SOM) (when no outcome is used), class prediction methods such as logistic regression, Support Vector Machine,[121] Random Forest,[122] Binary Tree Prediction, Bayesian Compound Covariate Predictor, and Discriminant analysis (http://linus.nci.nih.gov/techreport/Manual32.pdf).

Correlation of protein data with clinical variables

For Specific Aim 1, we will determine if there is a protein classifier prognostic for clinical outcome. After assignment of each patient to a risk group (based on time and site of relapse, n=403 low-risk, n=195 high-risk), samples will be stratified based on risk group and supervised clustering analysis will be performed based on clinical outcome variables (DFS).

For Specific Aim 2, we will determine which patients classified as low-risk (based on time and site of relapse) that would benefit from the more intensive chemotherapy given to high-risk patients (*i.e.*, reassignment to the high risk group). Following the generation of a risk-based protein expression classifier from all low-risk patients, further testing of the putative classifier will be based on performance characteristics using predefined cutpoints using ROC curves. Comparisons will be made using the AUC of ROC curves between standard risk stratification (time and site of relapse), MRD response, and the putative protein expression classifiers. Model overfitting and biased assessment of model performance will be minimized using bootstrap clustering as previously described [104]ROC curves will be generated for each stratification group, as well as for combinations of groups. Since attainment of CR following subsequent relapse is suboptimal,[123,124] and DFS is guarded following subsequent relapse, protein expression classifiers that maximize specificity with adequate sensitivity will be prioritized for further characterization.

m) **The sites performing the correlative studies**.

RPPA analysis will be performed in the Kornblau laboratory (MD Anderson Cancer Center, Houston TX) in collaboration with Dr. Horton. Phosphoflow analysis will be performed in the Tasian laboratory (Children's Hospital of Philadelphia).

n) **Maintenance of quality control/assurance**

Quality control will be maintained as previously described (Section i).[104,105,112]

o) **Marker prevalence**:

Since the methods will analyze multiple proteins (RPPA) and signal transduction pathways (phosphoflow), the prevalence of each marker will vary.

p) **Estimate what proportion of patients on a therapeutic trial will have available sample for correlative study analysis; discuss possible biases**.

Based on prior samples obtained for RPPA analysis from patients enrolled on the Phase 3 COG AML trial AAML1031, we estimate 40% of enrollments will provide an evaluable sample. As the most common reasons for sample dropout include technical issues (20% sample dropout due to sample quality, 40% due to samples not being drawn at site, 10% due to delays in shipping), lack of consent (10-15%), and insufficient lymphoblasts in peripheral blood to qualify for the study (20%). The latter 20% will have a bias toward high-risk disease and early marrow relapse.

q) **Specify how any cutpoints will be determined**

Specific aim 1: Performance characteristics and cutpoints will be made by comparison of AUC for ROC curves of available classifiers including standard risk stratification (time to and site of relapse) and MRD status. Since the objective of this study is to improve DFS, and DFS are can be estimated by both the hazard ratio and probability of relapse. These numbers will become available from AALL0433, AALL01P2, AALL04P2 and AALL07P1 prior to trial completion. In order to identify patients likely to relapse, without increasing the risk of overtreating patients that require minimal therapy to achieve DFS, we will choose classifiers that maximize the true positive rate (sensitivity) while maintaining adequate specificity using statistically meaningful and clinically relevant cutpoints.

Specific aim 2: To determine if alterations in specific cell stress proteins can be used to generate a "high-risk" protein expression signature that identifies patients stratified to the low-risk (based on time and site of relapse) group that would have benefited from stratification into the high-risk group. For analysis of clinical utility, assumptions are usually made based on prior clinical trials for a similar pediatric relapsed ALL cohort. However, previous relapsed ALL COG studies have used different risk assessments, making *a priori* cutpoint determination challenging. Therefore, we will present basic principles for determining cutpoints for protein expression classifiers.
To aid in determining specific cutpoints, data from the recently completed AALL0433 clinical trial will be used to determine the prevalence of relapse and DFS in a similar LR population.

Since our aim is to improve the detection of true high risk patients misclassified into the low-risk group, we are interested in both the sensitivity and specificity of a putative protein classifier. The clinical usefulness of a protein expression classifier is dependent the proportion of low-risk patients that relapse (which can be estimated from the AALL0433 trial), as well as the proportion of low-risk patients with the "high-risk" putative classifier (determined by this study). Depending on the change in DFS for those correctly identified as having a "high-risk" protein classifier, the relative risks that can be used to identify the clinical usefulness can be estimated. Once these estimates are known, we can estimate both absolute risk reduction and decrease in relative risk of a low-risk patient with a "high-risk" classifier. Our goal would be to identify a classification signature that outperforms the current method of risk stratification (time and site of relapse) and/or allowed for an absolute risk reduction of at least 5% in the low-risk group.

r) **Specify the statistical power of the correlative study**

Sample size for basis of power calculations:

Based on power size calculations (Section 9.2.2), we anticipate that the study will enroll 598 patients, including 195 high-risk and 403 low-risk patients (based on time and site of relapse). Based on sample retrieval rate of 36% (see Section p), we will have 215 patients for protein expression analysis. For specific aim 1, all evaluable patients with usable sample would be considered for analysis (n=215). For the second aim, patients in the low-risk group (n=403) would be eligible if we receive usable sample. Based on sample recruitment in AAML1031 (36%), we expect to collect usable sample for 145 of the 403 evaluable patients. Although all sample set are required to have a 0h sample, about 82% of samples have the full data set (i.e. sufficient material for RPPA (CellSave preservation tubes) and phospho-flow (heparin tubes) at 0h, 6h, and 24h). For measures of changes over time, we anticipate that we will have 176 patient sets for SA1 and 118 patients for SA2. If the unfolded protein response is of interest, we expect that 90% of patients will have sufficient material for transcript analysis (n=193 for SA1, n=130 for SA2).
A summary of sample size data is provided in Table XI-1:

In addition to determining the effect sizes (defined as the difference in the corresponding mean outcomes over a common standard deviation) of assays between treatment groups, we will also compare protein classifiers with clinical outcome (MRD status and EFS). For the analysis of data across time (0h, 6h and 24h) we do not know *a priori* the most relevant time points to compare. Short-term differences could have returned to baseline by 24h, and may be most accurately estimated by changes between 0h and 6h. Long-term differences would be best measured by 0h-24h comparison. Complex changes, such as increase at 6h and decreases by 24h (seen with NF-κB after chemotherapy) are best measured using all three time points as descriptors. However, for simplicity we have provided the affect sizes for changes from 0h to 24h in Table XI-1.

Table XI-1: Effect-size differences based on sample size for protein cell stress pathways

1. RPPA and phospho-flow studies	**Samples size (max)**	**Effect size ***
Baseline and change at 24h by treatment arm (blinatumomab therapy vs non-blinatumomab therapy; randomized patients only)	135 (67/tx group) 110 (55/tx group)	0.488 0.539
Baseline and change at 24h by MRD response (rate of MRD >= 0.1%: 62% for high-risk, 28% for low-risk; 39% overall)	All patients: 215 (84 MRD >=0.1%/ 131 MRD < 0.1%) for baseline comparisons. 176 (69 MRD >=0.1%/107 MRD < 0.1%) for changes over time. Low-risk: 145 (41 MRD >=0.1%/ 104 MRD < 0.1%) for baseline comparisons. 118 (33 MRD >=0.1%/85 MRD < 0.1%) for changes over time.	0.393 0.435 0.520 0.579
Baseline and change at 24h by 3-year DFS for randomized patients (estimated 3-year DFS 64%)	135 (86 no event/ 49 with event) for baseline changes. 110 (70 no event/ 40 with event) For changes over time.	0.505 0.560
Assumptions: alpha = 0.05, beta = 0.2.Abbreviations: grp= group, tx = treatment * With this effect size, the study will have at least 80% power at 2-sided significance level of 0.05 to detect such difference given the corresponding sample size.		

s) **Corrections for multiple comparisons**

We will use the Benjamini-Hochberg correction to account for multiple comparisons.[125]

t) **Discuss how the results will have an impact on future studies.**

This contribution will significantly impact future studies because it will add protein cell stress markers to the armamentarium of genetic mutations currently used to assess relapse risk, increasing the power of risk stratification, and identifying patients most likely to relapse and those most likely to benefit from therapies that target deregulated cell signaling pathways in relapsed ALL.

APPENDIX XII: COG STEM CELL COMMITTEE CONSENSUS GUIDELINES FOR ESTABLISHING ORGAN STAGE AND OVERALL GRADE OF ACUTE GRAFT VERSUS HOST DISEASE (GVHD)

Reporting Requirements for Acute GVHD in COG Studies
In an attempt to standardize reporting of acute GVHD, the COG Stem Cell Transplantation Committee has adopted a modification of guidelines that were originally developed at the University of Michigan.

Table 1 outlines standard criteria for GVHD organ staging. However, confounding clinical syndromes (such as non-GVHD causes of hyperbilirubinemia) may make staging GVHD in a given organ difficult. In addition, timing of organ specific symptoms affects whether that symptom is more or less likely to be true GVHD. Please refer to ***Tables 2 and 3*** to assist you in deciding whether to attribute these clinical findings to GVHD, especially in situations where a biopsy is not possible. For additional help, please see the text which follows the tables. ***Table 4*** reviews the approach to assessing GVHD as acute, chronic, or the overlap between the two.

Finally, *engraftment syndrome* will be reported separately from the GVHD scoring presented below.

Engraftment Syndrome
A clinical syndrome of fever, rash, respiratory distress, and diarrhea has been described, just prior to engraftment in patients undergoing unrelated cord blood and mismatched transplantation. If, in the judgment of the local investigator, a patient experiences this syndrome, details of the event should be reported when requested in the study CRFs.

Modified Glucksberg Staging Criteria for Acute Graft versus Host Disease

Table 1 Organ Staging (See tables and text below for details)

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GVHD rash	< 2 mg/dL	Adult: < 500 mL/day Child: < 10 mL/kg/day
1	Maculopapular rash < 25% BSA	2-3 mg/dL	Adult: 500–999 mL/day Child: 10 -19.9 mL/kg/day ***Or persistent nausea, vomiting, or anorexia, with a positive upper GI biopsy*.**
2	Maculopapular rash 25 – 50% BSA	3.1-6 mg/dL	Adult: 1000-1500 mL/day Child: 20 – 30 mL/kg/day
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL	Adult: > 1500 mL/day Child: > 30 mL/kg/day
4	Generalized erythroderma plus bullous formation and desquamation > 5% BSA	>15 mg/dL	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

For GI staging: The "adult" stool output values should be used for patients > 50 kg in weight. Use 3 day averages for GI staging based on stool output. If stool and urine are mixed, stool output is presumed to be 50% of total stool/urine mix (see Section 3.2). For stage 4 GI: the term "severe abdominal pain" will be defined as: (a) Pain control requiring institution of opioid use, or an increase in on-going opioid use, PLUS (b) Pain that significantly impacts performance status, as determined by the treating MD. If colon or rectal biopsy is +, but stool output is < 500 mL/day (< 10 mL/kg/day), then consider as GI stage 0. There is no modification of liver staging for other causes of hyperbilirubinemia

Overall Clinical Grade (based on the highest stage obtained):
Grade 0: No stage 1-4 of any organ
Grade I: Stage 1-2 skin and no liver or gut involvement
Grade II: Stage 3 skin, or Stage 1 liver involvement, or Stage 1 GI
Grade III: Stage 0-3 skin, with Stage 2-3 liver, or Stage 2-3 GI
Grade IV: Stage 4 skin, liver or GI involvement

Table 2 Evaluating Liver GVHD in the Absence of Biopsy Confirmation (See Table 3.0 below)

Establishing liver GVHD with no skin or GI GVHD

No Skin/GI GVHD Day 0-35	**Assume no liver GVHD,** unless proven by biopsy	
No Skin/GI GVHD Day 36-100	If NO other etiology identified, NO improvement with stopping hepatotoxic medications/TPN: **Stage as liver GVHD**	If other etiology identified or improves with stopping hepatotoxic drugs/TPN: **Do not stage as liver GVHD**

Establishing liver GVHD with skin or GI GVHD and other cause of hyperbilirubinemia

Skin and/or GI GVHD present	Worsening bilirubin level (includes worsening just prior to onset of skin or GI tract GVHD) OR stable elevated bilirubin despite resolution of non-GVHD cause of increased bilirubin: **Stage as liver GVHD**	Stable or improving bilirubin after diagnosis of skin or GI GVHD, irrespective of treatment: **Do not stage as liver GVHD**

Changing liver GVHD stage with other cause of hyperbilirubinemia

Skin and GI GVHD stable, improving, or absent	Liver GVHD staging is carried forward without increase in stage until other disease process resolves (e.g., if TTP is diagnosed in the presence of stage 2 liver GVHD, the liver GVHD stage 2 is carried forward despite rising bilirubin level until TTP is resolved. If there is no liver GVHD – stage 0 – and new onset TTP, the stage 0 is carried forward until TTP is resolved).

Skin and/or GI GVHD worsening	**Liver GVHD is staged according to the Glucksberg criteria. The elevated bili is attributed to GVHD alone.** Thus, when skin or GI GVHD is worsening, there is no downgrading of liver GVHD staging for other causes of hyperbilirubinemia. (e.g., if TTP is diagnosed in the presence of stage 2 liver GVHD and worsening skin or GI GVHD, the liver is staged according to the actual bilirubin level even if some of the rise in bilirubin is attributed to TTP). Similarly, even if there is no liver GVHD at onset of a new process, (such as TPN cholestasis), but skin or GI GVHD worsen during that process, then liver GVHD is diagnosed and staged according to the height of the bilirubin. **There is one exception to this**: the diagnosis of TTP, with high LDH and **unconjugated** bilirubin precludes the diagnosis and staging of new liver GVHD in the absence of a confirmatory liver biopsy.

Table 3 Evaluating GI GVHD in the Absence of Biopsy Confirmation (See Table 4.0 below)

Establishing GI GVHD with new onset diarrhea and no skin or liver GVHD

No Skin/liver GVHD Day 0 through engraftment	Assume no GI GVHD, unless proven by biopsy	
No Skin/liver GVHD Engraftment through day 100	NO other etiology of diarrhea identified: **Stage as GI GVHD**	Any other etiology of diarrhea identified: **Do not stage as GI GVHD**

Establishing GI GVHD with pre-existing diarrhea and skin or liver GVHD

Skin and/or liver GVHD present	Worsening diarrhea (includes worsening just prior to onset of skin or liver GVHD) OR persistent diarrhea despite resolution of non-GVHD cause: **Stage as GI GVHD**	Improving diarrhea after the diagnosis of skin or liver GVHD (irrespective of treatment) OR persistent diarrhea without resolution of underlying non-GVHD cause: **Do not stage as GI GVHD**

Differentiating Acute GVHD, Chronic GVHD, and Overlap Syndrome

There is often confusion differentiating acute from chronic GVHD, especially in the setting of reduced intensity transplants, DLI and new prophylactic treatments. The NIH Working Group recently published new classifications for GVHD:

Table 4 Acute GVHD, Chronic GVHD, and Overlap Syndrome

Category	Time of Symptoms after HCT or DLI	Presence of Acute GVHD features	Presence of Chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤100 d	Yes	No
Persistent, recurrent, or late-onset acute GVHD	>100 d	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

- Scoring of acute GVHD may need to occur past day 100. In particular, patients should continue to be scored for acute GVHD when classic acute GVHD symptoms (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea - particularly if bloody and ileus) persist past day 100 or if identical symptoms previously scored as acute GVHD resolve and then recur within 30 days during immunosuppression taper but past day 100.

- Those patients being scored as having acute GVHD should NOT have diagnostic or distinctive signs of chronic GVHD.

- **Patients with both acute and chronic symptoms should be diagnosed as having Overlap Syndrome and scored according to their <u>chronic</u> GVHD score**.

Further Explanation of Criteria presented in Tables 2 and 3

1.0 <u>Assessment of Skin GVHD</u>

1.1 Presence or Absence of Skin GVHD: Skin GVHD will be considered present if a rash characteristic of acute GVHD develops after allogeneic marrow transplantation involving more than 25% of the body surface not clearly attributable to causes such as drug administration or infection. The extent of the body surface area involved can be estimated by the "Rule of Nines". In estimating the extent of skin GVHD, the area involved is calculated for individual anatomic areas, such as the arm or leg, and then the total is derived from a simple summation. Areas that are non-blanching should not be considered involved regardless of the overlying color of the rash (red, brown, etc.). Limited distribution erythema (with the exception of palms and soles) in the absence of associated rash elsewhere on the body will not be considered GVHD.

2.0 <u>Assessment of Liver GVHD</u>

2.1 Assessing for the Presence or Absence of Liver GVHD

A. Hyperbilirubinemia (total bilirubin $\geq$ 2.0 mg/dL) in the **absence** of other signs of acute GVHD in the skin or GI tract:

i) Day 0-35: If hyperbilirubinemia alone is present with no other signs of acute GVHD in other organ systems, acute GVHD will not be diagnosed based solely on laboratory abnormalities. Acute GVHD will be diagnosed if findings on histopathology studies of liver from a biopsy or autopsy are confirmatory.

ii) Day 35-100: If hyperbilirubinemia (must be conjugated bilirubin) is not improving or is exacerbated (especially if serum alkaline phosphatase is increased), in the absence of acute GVHD in other organ systems, no other etiologies are identified, and does not improve with discontinuation of hepatotoxic drugs, acute GVHD will be diagnosed. However, it is distinctly unusual to develop ascites or a coagulopathy in the early stages of acute GVHD of the liver alone. In the absence of histopathology studies of liver from a biopsy or autopsy specimen, ascites or a coagulopathy secondary to liver dysfunction will be considered to indicate the presence of another disease process (e.g. veno-occlusive disease). Recommended non-invasive studies to define an etiology for hyperbilirubinemia are:

a. Imaging of liver (CT or ultrasound)
b. Hepatitis screen (only if ALT is elevated)
c. PT
d. Blood cultures
e. Review of medication list for potentially hepatotoxic drugs
f. Review of risk factors for viral liver infection (HSV, CMV, VZV, adenovirus, EBV, HBV, and HCV)
g. Hemolysis screen

B. Pre-existing hyperbilirubinemia clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems.

i) If pre-existing non-GVHD liver disease (documented clinically, by lab assessment, or by imaging studies) is stable or improving at the onset of signs of acute GVHD in other organs, then acute GVHD of the liver will not be considered to be present unless proven by liver biopsy or autopsy.

ii) If hyperbilirubinemia worsens several days before or at the time of onset of signs of acute GVHD in other organ systems, GVHD will be considered to be present unless histopathology studies of liver are available and negative on a biopsy during that time interval or autopsy results exclude GVHD.

iii) If hyperbilirubinemia persists and is not improving after resolution of a pre-existing non-GVHD liver disease process (e.g. localized infection of liver, systemic sepsis, biliary tract obstruction) when signs of acute GVHD are present in other organ systems or no other intervening cause has been diagnosed, then acute GVHD will be considered to be present in the absence of a new, clearly identifiable cause of non-GVHD liver disease or unless a liver biopsy or autopsy specimen is negative.

C. Prior acute GVHD in liver with new onset of a disease process that exacerbates pre-existing or recently resolved hyperbilirubinemia:

i) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia and acute liver GVHD has been diagnosed and has been stable, improving, or resolved, then the liver will not be restaged for acute GVHD until the resolution or stabilizing of the concurrent disease process (i.e., the liver stage prior to the onset of the new disease process will be carried forward until the new disease process resolves). Example: Acute GVHD of the liver and gut is diagnosed on day 20. Treatment of acute GVHD results in falling bilirubin levels to liver stage 1. Sepsis or TTP develops with transient worsening of the hyperbilirubinemia. The liver stage is not increased, despite a higher bilirubin level, because the cause of worsening hyperbilirubinemia is attributed to sepsis or TTP.

ii) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia in the presence of already worsening acute liver GVHD **or** GVHD of the skin or GI tract is simultaneously worsening, then the liver GVHD will be staged according to the actual bilirubin level, even though another cause of hyperbilirubinemia is present.

3.0 Assessment of GVHD of the Gastrointestinal Tract

3.1 Assessing for the Presence or Absence of GVHD of the Gastrointestinal Tract

A. Diarrhea (≥ 500 mL/day in adults or > 10 mL/kg in pediatric patients) in the absence of other signs of acute GVHD in other organ systems

i) Day 0-engraftment: If diarrhea alone is present without other signs of acute GVHD in other organ systems, acute GVHD will not be considered present. Diarrhea will be attributed to acute GVHD if histopathology studies of gastrointestinal tract from a biopsy or autopsy are diagnostic.

ii) Engraftment-day 100: If diarrhea persists and is not improving, is exacerbated, or develops de novo in the absence of acute GVHD in other organ systems, histopathology studies of gut biopsies or from autopsy specimens are not available, and no other etiologies are clearly identified, acute GVHD will be considered to be the cause. A stool specimen should be examined to rule out infectious causes (e.g. rotavirus, adenovirus, and C. difficile toxin). It is recommended, if at all possible, that biopsies be obtained for diagnostic purposes.

B. Pre-existing diarrhea clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems:

i) If pre-existing diarrhea caused by a process other than GVHD has been documented clinically or by lab assessment and is stable or improving at the onset of signs of acute GVHD in the skin or liver, then acute GVHD of the intestine will not be considered to be present in the absence of biopsy confirmation or autopsy report.

ii) If diarrhea or gastrointestinal symptoms are already present, but worsen significantly at the time of onset of signs of acute GVHD in the skin or liver, GVHD will be considered present, unless biopsy or autopsy are negative.

iii) If diarrhea persists after resolution of a pre-existing disease process with signs of acute GVHD present in other organ systems, GVHD will be considered present, unless biopsy or autopsy are negative.

C. Prior or present acute GVHD in other organ systems with new onset of diarrhea:

If diarrhea is **clearly** attributable to an etiology other than acute GVHD (e.g., infection) and a history of acute GVHD exists or acute GVHD is present in other organ systems and is stable, then the gastrointestinal tract will not be evaluable for acute GVHD until the resolution or stabilizing of the other disease process (e.g., infection) in the absence of biopsy or autopsy confirmation.

D. Persistent anorexia, nausea or vomiting in the absence of signs of acute GVHD in other organ systems:

Persistent anorexia, nausea or vomiting in the absence of other known causes of these symptoms will be considered stage 1 acute GVHD if confirmed by endoscopic biopsy.

If a biopsy is not possible (e.g. secondary to thrombocytopenia) but the clinical findings are compatible with acute GVHD, then the patient will be treated and recorded as having acute GVHD.

3.2 Staging of the Gastrointestinal Tract for the Severity of Acute GVHD

The severity of gastrointestinal tract GVHD will be staged according to modified Glucksberg criteria. To minimize errors caused by large day-to-day variation, diarrhea volume is measured as an average over 3 days and reported as the volume in milliliters per day. When urinary mixing is noted the stool volume will be considered half of the total volume unless nursing staff is able to give a better estimate from direct observation. Abdominal cramps are considered significant for staging if the severity results in a clinical intervention (e.g. analgesia, fasting, etc.). Blood in the stools is considered significant if the blood is visible or hematochezia/ melena is present and not clearly attributed to a cause other than GVHD (e.g. epistaxis/ hemorrhoids).

APPENDIX XIII: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for AALL1331 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

APPENDIX XIV: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

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.*

Cyclosporine

Drugs that may interact with cyclosporine

• Antibiotics
    • Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
    • Citalopram, clozapine, escitalopram, fluoxetine, fluvoxamine, lurasidone, nefazodone, paliperidone, quetiapine, thioridazine, ziprasidone
• Antifungals
    • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, amphotericin
• Anti-inflammatory, arthritis, or pain medications
    • Aspirin, celecoxib, hydroxychloroquine, ibuprofen, indomethacin, ketorolac, leflunomide, naproxen, meloxicam, oxaprozin, sulindac, tofacitinib, tolmetin
• Anti-rejection medications
    • Mycophenolate, sirolimus, tacrolimus
• Antiretrovirals and antivirals

- Atazanavir, boceprevir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
- Anti-seizure medications
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Cholesterol medications
  - Atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, ezetimibe, fenofibrate, gemfibrozil, colesevelam
- Heart medications
  - Aliskiren, amiodarone, dronedarone, carvedilol, digoxin, diltiazem, eplerenone, verapamil, captopril, enalapril, lisinopril, ramipril
- Kidney medications
  - Acetazolamide, amiloride, spironolactone, triamterene
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Ambrisentan, bosentan, sitaxentan, aprepitant, allopurinol, colchicine, danazol, dexamethasone, fluoxymesterone, methyltestosterone, oxandrolone, mifepristone, natalizumab, pimozide, butabarbital, secobarbital, ivacaftor, octreotide

Food and supplements that may interact with cyclosporine*
• Alfalfa • Black cohosh • Echinacea • Grapefruit, grapefruit juice, Seville oranges, star fruit • Red Yeast Rice • St. John's Wort

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

<u>Cytarabine (by vein)</u>

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.*

Dexamethasone

Drugs that may interact with dexamethasone

• Antibiotics
  • Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine
• Antifungals
  • Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tofacitinib
• Anti-rejection medications
  • Cyclosporine, sirolimus, tacrolimus
• Antiretrovirals and antivirals
  • Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  • Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, amlodipine, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Some oral contraceptives or birth control medications
• Many other drugs, including the following:
  • Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**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.*

<u>Fludarabine</u>

Drugs that may interact with fludarabine
• Clozapine, leflunomide, natalizumab, pentostatin, tofacitinib

Food and supplements that may interact with fludarabine*
• Echinacea

**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.*

Methotrexate (by mouth or by vein)

Drugs that may interact with methotrexate
• Some antibiotics (amoxicillin, Bactrim, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline) • Some anti-inflammatory drugs (aspirin, acetaminophen, ibuprofen, naproxen, ketorolac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, retinoids, theophylline, warfain

Food and supplements that may interact with methotrexate*
• Alcohol • Echinacea • Some vitamins, including those that contain folic acid or high doses of vitamin C

**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.*

Mitoxantrone

Drugs that may interact with mitoxantrone
• Aripiprazole • Clozapine • Cyclosporine • Dofetilide • Leflunomide • Natalizumab • Pimozide • Tofacitinib

Food and supplements that may interact with mitoxantrone*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Mycophenolate mofetil

Drugs that may interact with mycophenolate mofetil
• Antacids such as aluminum hydroxide, magnesium hydroxide • Arthritis medications such as leflunomide, tofacitinib • Some antibiotics and antiviral medications (be sure to talk to your doctor about this) • Some heartburn medications including esomeprazole, lansoprazole, omeprazole, pantoprazole • Other medications such as cholestyramine, natalizumab, oral contraceptives ("birth control"), probenecid, rifabutin, rifampin, rifapentine, sevelamer

Food and supplements that may interact with mycophenolate mofetil*
• Echinacea • Vitamins and supplements containing magnesium

**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.*

<u>**Tacrolimus**</u>

Drugs that may interact with tacrolimus

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, paliperidone, quetiapine, thioridizine, ziprasidone
• Antifungals
  • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Anti-inflammatory, arthritis, or pain medications
  • Leflunomide, tofacitinib
• Anti-rejection medications
  • Cyclosporine, sirolimus
• 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, disopyramide, procainamide, sotalol, verapamil
• Kidney medications
  • Amiloride, spironolactone, triamterene
• Stomach and reflux medications
  • Dexlansoprazole, esomeprazole, lansoprazole, omeprazole
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  • Ambrisentan, bosentan, sitaxentan, aprepitant, colchicine, dexamethasone, mifepristone, natalizumab, pimozide

Food and supplements that may interact with tacrolimus*
• 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.*

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
  • Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Aripiprazole, nefazodone, trazodone
• Antifungals
  • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tocilizumab, tofacitinib
• Anti-rejection medications
  • Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  • Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir
• Anti-seizure medications
  • Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, digoxin, dronedenarone, propranolol, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  • Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vincristine*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

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AALL1331: Brief Summary of Amendments

Amendment #1A (03/23/15): This study was primarily amended to mandate that lung shielding with total body irradiation limit the lung dose to less than 800 cGy. It was also amended to include changes from the blinatumomab Rapid Request for an Amendment issued on 03/09/2015, and to address CTEP recommendations, update callback instructions for patients continuing to Salvage Therapy, update specimen requirements for blinatumomab pharmacodynamics optional study, to include an aim and statistical analysis plan for the required pharmacokinetics study, and to make other administrative edits for consistency and clarity.

Amendment #1B (04/27/15): This study was amended to correct errors regarding days of drug administration.

Amendment #2 (12/28/15): This study was amended to provide protocol updates and clarification in several places. Of note, this amendment incorporates the allowance of a 96 hour infusion time for Blinatumomab. Eligibility criteria has also been updated to clarify that the diagnosis of extramedullary disease is limited to the CNS and testicles. Additionally, revisions have been incorporated to clarify that intrathecal chemotherapy administered at the time of required diagnostic lumbar puncture to establish baseline CNS status is allowed. This amendment also provided clarification regarding Evaluation 1 timing and details. Instructions for blinatumomab infusion interruptions for technical reasons as well as a recommendation for hospitalization during Block I have also been incorporated.

Amendment #3 (02/29/16): This amendment is being implemented in order to provide administrative updates and clarification in several places. Of note, text was inserted to require reporting of Grade 3 or higher infections. The volume calculations table in the blinatumomab drug monograph was updated to include a 72 hours' bag change option. Additionally, Appendix II-A has been updated to reflect that Day 1 IT MTX is required for all patients in place of Day 1 ITT for CNS 3 patients.

Amendment #4 (05/31/16): This amendment is being submitted in response to a request for amendment from Dr. Ravie Kem dated March 28, 2016. With this amendment, the NCI is replacing the current vial 30.3 mcg/vial with new vial strength, 38.5 mcg/vial of blinatumomab. This will result in a different vial concentration following reconstitution, currently 9.87 mcg/mL changing to 12.5 mcg/mL.

Amendment #5 (01/17/17): This study has been amended in response to a request for Rapid Amendment (RRA) from Elad Sharon, MD, MPH (sharone@mail.nih.gov) dated November 18th, 2016 for Blinatumomab (NSC 765986). Please review the action letter for Blinatumomab. In this amendment the revised CAEPR for Blinatumomab (NSC 765986) has been inserted in the protocol and the associated risk information in the informed consent documents has been revised accordingly. Specific changes to the protocol and informed consents are detailed in COG website. There are not any amendment-related changes to the CRFs other than revision of the amendment date. The NCI approval notice includes one recommendation which the study committee has considered and plans to address at the time of the next amendment.

Amendment #6a (09/25/17): This amendment modifies the consent to indicate there is no published data on the safety of the protocol regimen in patients greater than 18 years of age at the time of study entry and enhances supportive care criteria in the protocol for these patients. The toxicity stopping rule has been updated to better reflect current data. In addition, the dosing of dexamethasone as a pre-med has been updated to reflect the pediatric label for blinatumomab. In addition, several changes were made to clarify blinatumomab preparation, administration and ordering procedures.

Amendment #7 (07/23/18): This amendment updates consent forms to indicate that blinatumomab is now approved by the FDA for the treatment of children with relapsed or refractory B-ALL and also for the treatment of children in first or second complete remission with MRD greater than or equal to 0.1%.

Amendment #8 (12/03/18):This amendment updates the statistical plan to increase the accrual goals for both the standard and high risk arms. In addition, the seven-day blinatumomab infusion schedule has been added. Updates have been made to the dose modifications. In the consents, the potential side effects for drugs used in the study have been updated to match the current template.

In addition, the home health care manual, preparation and administration training module,and general training module have been updated to reflect this amendment and are posted on the protocol web page. Sites are strongly encouraged to review the updated training modules as they become available, and are expected to remain current on study training. Please note, submission of the Blinatumomab Preparation and Administration training attestation to CTSU is only required for initial site activation.

Amendment #9 (03/11/19): This amendment modifies the protocol and consent forms to update new and/or modified risk information associated with Blinatumomab. The CAEPR list for Blinatumomab is revised from version 2.3 to version 2.4 along with the associated risk information in the ICDs.

Amendment #10A (02/24/20): This amendment modifies the protocol and consent forms to update new and/or modified risk information associated with Blinatumomab. The CAPER list for Blinatumomab is revised from version 2.4 to version 2.5 along with the associated risk information in the ICDs. This amendment also describes the closure of the HR/IR randomization that occurred on September 18, 2019.

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Memo

To: Principal Investigators and Clinical Research Associates

From: Catherine Shannon, Protocol Contact

Re: **AALL1331**, *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: May 11, 2015

ENROLLMENT IS BLOCKED PENDING IRB APPROVAL OF THIS SAFETY AMENDMENT

X	**AMENDMENT #1B**	**X**	**STATUS CHANGE**
___	Change of Participants/Coordinator(s)	___	Closure
X	Editorial or Administrative Changes	___	Partial Closure
X	Scientific Changes*	___	Temporary Closure
X	Therapy Changes*	**X**	Reactivation
X	Eligibility Changes*		
X	Informed Consent Changes*		

***FOR THE PURPOSE OF INSTITUTIONAL PERFORMANCE ASSESSMENT, THIS AMENDMENT WILL REQUIRE SUBMISSION TO AND APPROVAL BY IRBS WITHIN 90 DAYS.**

AALL1331 will reopen to patient enrollment on Monday, May 11, 2015. However, sites will be blocked from enrollment of new patients pending IRB approval of Amendment #1B.

The study has been amended in response to a Rapid Request for Amendment (RRA) from Dr. Sharon Elad (sharone@mail.nih.gov) dated 3/9/15 for blinatumomab. Note: the action letter for blinatumomab was posted on 4/3/15. Please review the action letter.

Additional changes implemented in this amendment include:

- Mandate lung shielding with total body irradiation to limit the lung dose to less than 800 cGy. This is based on a recent review of data from the ACST0431 study which showed that lung irradiation doses above 800 cGy were significantly associated with an increased risk of treatment-related mortality and relapse, largely due to toxicity (Pulsipher and Lu, unpublished data November 2014).
- Address a CTEP recommendation and a Pediatric CIRB stipulation.
- Update callback instructions for patients continuing to Salvage Therapy.

- Update specimen requirements for the optional blinatumomab pharmacodynamics study.
- Addition of an aim and statistical analysis plan for the required pharmacokinetics study.
- Correction of errors regarding days of drug administration.

In addition, this amendment provides administrative updates, corrections and clarifications within the protocol.

Please note: This is a combined amendment, multiple submissions were made to CTEP following the initial CTEP review of Amendment #1. All changes made to the protocol since activation are detailed in the list of changes below, and are indicated in the tracked version of Amendment #1B. Changes as a result of the RRA are listed first and followed by a list of other changes.

TRAINING

Required Training: Blinatumomab Preparation and Administration Training Module

Documentation of the completion of site training with regard to the preparation and administration of blinatumomab must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial. The Blinatumomab Preparation and Administration training slides can be found on the protocol web page. This training module has not been revised as a result of the amendment and so it is not required to be repeated as a result of the amendment. However, administrative updates were made to update the Protocol Coordinator details and to clarify the attestation text.

Recommended Training: AALL1331 General Training Module

The study general training module has been updated to reflect this amendment and is posted on the protocol web page. The completion of this training is recommended/not required. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training.

RRA Changes: Protocol

#	Section	Page(s)	Change

1.	Protocol Section 6.1	103-108	Inserted the revised CAEPR (Version 2.2, February 11, 2015) for blinatumomab. A detailed description of the changes are below:
			
			• Added New Risk:
			    • Less Likely: Alkaline phosphatase increased; Insomnia
			    • Rare but Serious: Dysarthria; Facial nerve disorder; Gastric hemorrhage; Pancreatitis; Personality change; Pneumonitis; Reversible posterior leukoencephalopathy syndrome; Transient ischemic attacks
			    • Also Reported on Blinatumomab Trials But With the Relationship to Blinatumomab Still Undetermined: Bronchospasm; Cardiac arrest; General disorders and administration site conditions - Other (thrombosis in device); Genital edema; Metabolism and nutrition disorders - Other (fluid overload); Pericardial effusion; Somnolence; Syncope
			
			• Increase in Risk Attribution:
			    • Changed to Likely from Less Likely: Fever; Headache; Tremor
			    • Changed to Less Likely from Rare but Serious: Chills
			    • Changed to Likely from Reported But Undetermined: Diarrhea; Hypokalemia; Nausea; White blood cell decreased
			    • Changed to Less Likely from Reported But Undetermined: Abdominal pain; Acute kidney injury; Anemia; Back pain; Bone pain; Constipation; Cough; Dyspnea; Edema limbs; Hyperglycemia; Hypertension; Hypomagnesemia; Hypophosphatemia; Investigations- Other (C-reactive protein increased); Pain in extremity; Respiratory failure; Skin and subcutaneous tissue disorders - Other (rash); Vomiting; Weight gain
			    • Changed to Rare but Serious from Reported But Undetermined: Activated partial thromboplastin time prolonged; Allergic reaction; Creatinine increased; Blood and lymphatic system disorders - Other (lymphadenitis); Blood and lymphatic system disorders - Other (pancytopenia); Gastrointestinal disorders - Other (pneumoperitoneum); Hypoxia;

			Intracranial hemorrhage; Investigations - Other (blood fibrinogen increased); Investigations - Other (fibrin D dimer increased); Non-cardiac chest pain; Oral hemorrhage; Pleural effusion; Psychosis ◦ Changed to Likely from Rare but Serious: Fatigue • *Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:* ◦ Added: Abdominal pain; Alkaline phosphatase increased; Anemia; Back pain; Blood bilirubin increased; Chills; Constipation; Cough; Diarrhea; Edema limbs; Fatigue; Febrile neutropenia; Hyperglycemia; Hypertension; Hypokalemia; Immune system disorders - Other (immunodeficiency [immunoglobin decreased]); Insomnia; Investigations- Other (C-reactive protein increased); Nausea; Pain in extremity; Skin and subcutaneous tissue disorders - Other (rash); Vomiting; Weight gain; White blood cell decreased • Deleted Risk: ◦ Also Reported on Blinatumomab Trials But With the Relationship to Blinatumomab Still Undetermined: Abdominal distension; Adult respiratory distress syndrome; Allergic rhinitis; Ascites; Blood and lymphatic system disorders - Other (basophilia); Blood and lymphatic system disorders - Other (eosinophilia); Blood and lymphatic system disorders - Other (hypoglobinemia); Blurred vision; Cardiac disorders - Other (cardiovascular insufficiency); Chest wall pain; Conjunctivitis; Dry eye; Dry mouth; Dry skin; Erythema multiforme; Eye disorders - Other (blepharitis); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (eyelid irritation); Eye disorders - Other (Sicca syndrome); Fall; Fecal incontinence; Flank pain; Flatulence; Flu like symptoms; Hematoma; Hot flashes; Hypocalcemia; Hyponatremia; Immune system disorders - Other (graft versus host disease); Injection site reaction; Injury, poisoning and procedural complications - Other (tongue injury); Investigations - Other (blood alkaline phosphatase decreased); Investigations - Other (blood chloride increased); Investigations - Other (blood immunoglobulin G increased); Investigations - Other (blood urea increased); Investigations - Other

			(erythroblast count decreased); Investigations - Other (granulocyte count increased); Investigations Other (hypogammaglobulinemia); Investigations - Other (leukocyturia); Investigations - Other (mean cell hemoglobin concentration increased); Investigations - Other (monocyte count increased); Investigations - Other (monocytosis); Investigations - Other (pH urine decreased); Investigations - Other (reticulocyte count increased); Investigations - Other (vital capacity abnormal); Localized edema; Lymphedema; Lymphocyte count increased; Metabolism and nutrition disorders - Other (glucose urine present); Mucositis oral; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (leukemic infiltration extramedullary); Nervous system disorders - Other (balance disorder); Pain; Pelvic pain; Phlebitis; Productive cough; Purpura; Renal and urinary disorders - Other (crystalluria); Renal calculi; Serum amylase increased; Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration; Sneezing; Urinary retention; Urinary tract pain; Vaginal discharge; Vascular disorders - Other (circulatory collapse); Watering eyes

RRA Changes: Consent Forms

#	Section	Page(s)	Change

1.	ICDs 2-4: Risks of Study	**ICD2:** 10-11
		ICD3: 12-13
		ICD4: 8-9
			Updated the consent risk insert for blinatumomab per the RRA.
			• Added New Risk:
			  ◦ Occasional: Difficulty sleeping; Pain; Change in personality; Swelling of the body which may cause shortness of breath
			  ◦ Rare and Serious: Damage to the brain or nerves which may result in confusion, restlessness, worry, or sensing things that are not there; Internal bleeding which may cause black tarry stool, blood in vomit; Brain damage, which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome); Mini stroke

			• Increase in Risk Attribution:
			    • Changed to Common from Occasional: Fever; Headache; Abnormal body movement, difficulty talking; Infection, especially when white blood cell count is low
			    • Changed to Occasional from Rare and Serious: Chills
			    • Changed to Common from Reported But Undetermined: Diarrhea; Nausea
			    • Changed to Occasional from Reported But Undetermined: Pain; Kidney damage which may require dialysis; Anemia which may require blood transfusion; Constipation; Cough; Shortness of breath; Swelling of the body which may cause shortness of breath; High blood pressure which may cause blurred vision; Damage to organs which may cause shortness of breath; Rash; Vomiting; Weight gain; Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
			    • Changed to Rare and Serious from Reported But Undetermined: Air trapped in internal organs that may cause discomfort or pain; Bleeding in the brain; Bleeding of the mouth; State of mind that involves a "loss of contact with reality"
			    • Changed to Common from Rare and Serious: Tiredness
			
			Note: All changes made as compared to the original risk insert used for the AALL1331 study consent forms are visible in the tracked amendment document.

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

Section	Page	Comments
Throughout		The version date has been updated throughout.
Title Page	1	Version date and Amendment number have been updated along with the Study Chair's email address.
Table of Contents	3-6	The TOC has been updated accordingly.
Experimental Design Schema, 3.1.5, 3.1.6, 3.1.7, 3.1.10, 4.1.1, 4.1.1.3, 4.2.7, 4.3.1, 4.3.5, 4.3.6, 4.7	11, 25-27, 35-36, 39, 41, 43.-44, 53-55	These sections have been updated to reflect updated callback procedures for patients continuing to Salvage Therapy and modified for clarification.
1.3.4, 9.1.3	12, 163	PK aim and corresponding statistical analysis plan have been added per Amgen request.
2.2.3	17	Table 3 has been updated to include treatment failures for clarification.
3.1.5	24	Removed "LR and IR" for consistency and clarification.
3.1.7	26	Added "Callback is performed using the Oncology Patient Enrollment Network (OPEN)" for clarification.
3.2.3	28	An additional Prior Therapy inclusion criterion has been added for clarification.
3.3	32, 33	1) "Post Block 1" has been changed to "End Block 1" for clarification. 2) The definition of Complete Remission has been added to correct an error.
3.1.10, 4.2.7, 4.3.1	27, 39-41	Edits to clarify that End-Block 1 Callback must occur within 5 days of risk group/stratum assignment and Block 2 treatment must occur within 5 days of End-Block 1 Callback.
4.1	34-35	1) Added "CR" for clarification. 2) Modified the table content for clarification. 3) Under "HSCT", replaced "remission" with "CR" and changed "blinatumomab salvage" to "Salvage Therapy (Blinatumomab-S)" for clarification.
2.2.8, 4.1, 4.3.6, 4.7, 4.9.1, 9.1.3	21, 34, 44, 53, 60, 163	"morphological" was removed for consistency and clarification.
4.3.4	42	Leucovorin (LCV) is to begin 48 hours after the start of the Day 8 ID MTX infusion; therefore, the days of LCV administration were changed from Days 9, 10 to Days 10, 11.

4.3.4, 5.8.1	42, 93	ID MTX suggested hydration guidelines have been updated per current COG templates.
4.4.3	46	1) Added "(may be given IV)" to the Erwinia route of administration. This change was made to address the following PedCIRB stipulation: "Block 3 (HR/IR Patients on Arm A; LR Patients on Arm C) - 4 weeks (page 4), Section 4.4, Block 3: Per the Dose Modification Guidelines, Erwinia can be given IV, but the route of administration stated in section 4.4 block 3 only lists IM. The CIRB determined that the IV route of administration should be added as an option." 2) To reflect 48 hours between MTX and LCV, the days of LCV administration were changed from Days 23, 24 to Days 24, 25.
4.4.4, 4.6.4, 4.7.6, 4.8.5	47, 52, 55, 57	"CR" has been changed to "M1" for clarification.
4.5.4, 4.6.3, 4.7.4, 4.8.3, 4.15.3, 4.16.3	49, 51, 54, 56, 80, 82	For clarification, the blinatumomab dosing unit, micrograms, was written in full.
4.7.2	53	Changed "salvage blinatumomab" to "Salvage Therapy (Blinatumomab-S: Cycle 1)" for clarification.
4.7.6, 4.8.5, 4.9.1.1, Appendix II (F, G)	54-55, 57, 60, 219, 221	The criteria for continuing treatment have been updated for clarification.
4.8	56, 57	1) Changed "Treatment Failure" to "Salvage Therapy" for consistency. 2) Under Methotrexate Intrathecal (IT), Day 15 has been changed to Day 8 and 29 to correct an error.
4.9.1	59	Changed "salvage blinatumomab therapy" to "Salvage Therapy (Blinatumomab-S)" for clarification.
4.9.1, 14.1.1, 14.7-14.12	59-60, 197, 199--204	Lung shielding guidelines have been updated based on recent review of ASCT0431 data.
4.10.3, 4.11.3, 4.12.4, 4.14.4	69, 71, 75, 79	Mercaptopurine administration guidelines have been updated according to current COG templates.
4.11.1	70	Day 42 was changed to Day 43 to match a change made in Section 4.11.3
4.11.3	72-73	1) LCV is to begin 48 hours after the start of the ID MTX infusion; therefore, the days of LCV administration were changed from Days 23, 24 to Days 24, 25. 2) Etoposide and Cyclophosphamide should be given on day 1 of the 7th and 8th week of the course; therefore, the days of administration were changed from Days 42, 49 to Days 43, 50.

		3) Thioguanine should be given for 7 days; therefore, the days of administration were changed from Days 42-48 to Days 43-49. 4) Cytarabine should begin on day 2 of the 7th and 8th week of the course; therefore, the days of administration were changed from Days 43-46 to 44-47, and from Days 50-53 to 51-54.
4.12.4	75	The heading was revised for clarification.
4.14.4	79	Mercaptopurine administration days have been updated for consistency and to correct an error.
5.1, 6.2	84-85, 113-115	Asparaginase dose modification guidelines and the drug monograph have been updatd per current COG templates.
7.1a, b, d	158-160	“Peripheral blood for” has been added to PK and Immunogenicity observations for clarification.
7.1d	160	“(Blinatumomab-S)” has been added to title of Salvage Therapy for clarification.
7.2, 13.5, Appendix II (A, B, D, F, M)	161, 191, 209-210, 211-212, 216, 219, 231	Timing of the pre-blinatumomab bone marrow sample has been changed to correspond with required bone marrow samples.
13.5	191	A note has been added to provide clarification for the sampling. Blood samples will not be collected from all patients, only from those patients randomized or assigned to treatment with blinatumomab (Arm B, Arm D, or Salvage Therapy).
13.6	192	A note that isolated extramedullary relapse patients are not eligible for this sub-study has been added for clarification.
14.1.1, 14.7.2, 14.8.2	197, 199-200	Revisions were made for clarification.
14.9.1, 4.10.2.1	201, 203	Revisions were made to restrict the lung dose to < 800 cGy.
4.12	204	The text regarding deviations for lung dose were revised.
Appendix II (A, B, C, F, G)	210, 212, 214, 218-221	“blinatumomab-S” or “salvage blinatumomab therapy” has been changed to “Salvage Therapy (Blinatumomab-S)” for clarification.
Appendix II-A	210	1) Footnote # has been removed to correct an error. 2) Footnote ^ added for clarification.
Appendix II-B	211-212	1) Midcourse count recovery notes have been added for clarification. 2) HD has been changed to ID to correct an error. 3) The days of LCV administration were revised to match updated Section 4.3.4. 4) “IT” has been changed to “IV” to correct an error.
Appendix II-C	213-214	1) Count recovery note added for clarification and footnote ^ edited for consistency. 2) The days of LCV administration were revised to match updated Section 4.4.3.

		3) Cytarabine is to be administered every 12 hours; therefore, the lower table of the therapy delivery map was revised to reflect 2 doses per day. 4) Super script “&” has been removed to correct an error.
Appendix II-D	216	On several rows of the lower table, changed study “g” to “h” to correct an error.
Appendix II (D, E, F, G, M, N)	215-221, 230-232	1) For clarification, the blinatumomab dosing unit, micrograms, was written in full in the top table table of the relevant TDMs. 2) The lower table of several TDMs incorrectly indicated that the blinatumomab dose is to be recorded in milligrams. All relevant TDM tables were revised to reflect the dose recorded should be in micrograms (as detailed throughout Section 4, Treatment Plan, and in the top table of relevant TDMs).
Appendix II-I	223-224	1) This Continuation 1/2 TDM was revised to reflect the changes outlined above regarding Section 4.11.3. 2) The day of the PO LCV dose that follows Day 22 PO MTX for all patients was revised from Day 22 to Day 24. This is for consistency with Section 4.11.3. 3) In the lower table of the TDM, the PO MTX indicated for all patients on Day 22 was removed. This had been included in error. 4) Studies b and d were moved from Day 49 to Day 50 to coincide with the revised administration day of Etoposide and Cyclophosphamide. 5) Footnote ^ was modified to refer to Day 43 rather than Day 42. 6) Midcourse count recovery notes have been edited for clarification.
Appendix VII-A	241	Agent Preparation and Administration Option, in the fourth bullet added: **Note: If a home health care agency is being considered to prepare and change the blinatumomab infusion bag, the drug company that provides blinatumomab will cover the costs associated with a home health care agency providing these services.** This addition was recommended by CTEP in the Approval Notice for the trial.
Appendix XIV	276	Drug interactions for thiotepa have been added to correct an error.

SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENTS

Consent Form #1 (Block 1)

Section	Page	Comments
Throughout		The version date has been updated.
Required Study Tests	3	MRD information has been updated to correct an error.
Treatment Plan Tables	5	“HR” has been removed to correct an error.
Protein Cell Stress Study	6	Clarified that isolated extramedullary relapse patients are not eligible for this sub-study.
Optional Biology Research Studies and Cell Banking; Specimens for optional research tests and cell banking	6, 12	Information regarding the optional research study test ‘Blinatumomab Pharmacodynamics’ has been added to these sections.
How Many People Will Take Part In This Study	9	Total number of participants has been changed from 438 to 598 to correct an error.
Attachment II	15	Erwinia Asparaginase risk table has been added to correct an error.

Consent Form #2 (HR/IR)

Section	Page	Comments
Throughout		The version date has been updated.
Summary of Study Treatments	3	“Block 1 or” has been removed for clarification.
Treatment plan for HR/IR Subjects	4	Schema has been updated to correct an error.
Treatment that is Research	6	1) In the tables for Block 2 and Block 3 of therapy, the days of leucovorin administration were corrected. 2) The administration method was clarified for dexamethasone in Block 2 and vincristine in Blocks 2 and 3. 3) The cyclophosphamide infusion time was corrected in Block 2.

		4) Per PedCIRB recommendation, added IV administration as an option for Erwinia in Block 3. 5) The methotrexate infusion time was corrected in Block 3.
Treatment that is Research; Signature	8, 15	Information regarding the optional research study test 'Blinatumomab Pharmacodynamic study' has been removed from this consent and moved to the Block 1 consent.
How Many People Will Take Part In This Study	12	Total number of participants has been changed from 438 to 598 to correct an error.
Attachment I	19-20	Text and treatment tables have been revised for clarification.
Attachment II	31, 37	Risk tables for Mercaptopurine and Thiotepa have been added to correct an error.

Consent Form #3 (LR)

Section	Page	Comments
Throughout		The version date has been updated.
Treatment that is Research	5-9	1) Treatment tables have been updated to correct administration timing errors, to reflect changes made in the protocol and to provide clarification. Changes of note include: a) The days of leucovorin administration were corrected. b) Details of the administration of cyclophosphamide, etoposide, methotrexate, thioguanine and vincristine were revised. 2) Per PedCIRB recommendation, added the IV route of administration as an option for Erwinia.
Treatment that is Research; Signature	9, 17	Information regarding the optional research study test 'Blinatumomab Pharmacodynamic study' has been removed from this consent and moved to the Block 1 consent.
How Many People Will Take Part In This Study	14	Total number of participants has been changed from 438 to 598 to correct an error.

Consent Form #4 (Salvage Therapy)

Section	Page	Comments
Throughout		The version date has been updated.
Title Page	1	Consent form title has been updated for clarification.
Treatment that is	4	Text was revised to correct an error.

Research		
Treatment with blinatumomab	5	1) The days of IT methotrexate in Cycle 2 were updated to reflect Section 4.8. 2) The text “for CNS1/2 ONLY” was removed as this is not applicable.
Required Study Tests	5	The text regarding MRD was revised for clarification.
How Many People Will Take Part In This Study	10	Total number of participants has been changed from 438 to 598 to correct an error.
Attachment I	17-18	Text and treatment tables have been revised for clarification.
Attachment II	20, 26, 28, 31, 32	Risk tables for Cyclophosphamide, Mercaptopurine, Methotrexate by mouth or vein, Thiotepa and Vincristine have been added to correct an error.

Consent Form #5

The version date was updated.

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Memo

To: Principal Investigators and Clinical Research Associates

From: Teni Karimian, MS, Protocol Coordinator

Re: **AALL1331**, *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: December 28, 2015

X	**AMENDMENT #2**	___	**STATUS CHANGE**
X	Change of Participants/Coordinator(s)	___	Closure
X	Editorial or Administrative Changes	___	Partial Closure
___	Scientific Changes*	___	Temporary Closure
X	Therapy Changes*	___	Reactivation
X	Eligibility Changes*		
X	Informed Consent Changes*		

***FOR THE PURPOSE OF INSTITUTIONAL PERFORMANCE ASSESSMENT, THIS AMENDMENT WILL REQUIRE SUBMISSION TO AND APPROVAL BY IRBs WITHIN 90 DAYS.**

This amendment is being implemented in order to provide protocol updates and clarification in several places. Of note:

- This amendment incorporates the allowance of a 96 hour infusion time for Blinatumomab.
- Eligibility criteria has been revised to clarify that the diagnosis of extramedullary disease is limited to the CNS and testicles.
- Additionally, revisions have been incorporated to clarify that intrathecal chemotherapy (methotrexate strongly preferred) administered at the time of required diagnostic lumbar puncture to establish baseline CNS status is allowed.
- More details have been provided to clarify Evaluation #1 and all steps involved in the callback procedure
- Instructions incorporated for blinatumomab infusion interruptions for technical reasons.

Please note, the following new data entry requirements:

- A new CRF has been added (Consent Documentation) for the required capturing and uploading of Informed Consent Forms.

- In the relapse CRF a new data element has been added to allow the upload of source documentation for 1st on-protocol therapy relapse

Further details are provided below under “Changes to the Case Report Forms (CRFs)”.

Several other administrative changes have been made; specific changes are detailed below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked in the protocol but not specified below.

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

#	Section	Page(s)	Change
1.	Title Page	1	Protocol version date and amendment number have been updated
2.	Table of Contents	3-10	Table of contents has been updated to account for repagination.
3.	Study Committee Roster	11-13	1. Study committee contact information has been updated. 2. Brooke Bernhardt has replaced Alix Dabb as the study pharmacist.
4.	Study Agents List	13	The list of study agents has been re-organized to be in alphabetical order.
5.	Experimental Design Schema	15	1. Text box expanded to show footnote denoted by '+'that was cut off due to formatting. 2. The footnote denoted by '+' has been linked to the appropriate time point ('Relapse') in the schema.
6.	3.1.4 3.1.5 3.2.3.3 3.2.3.7	28 28 33 33	Text revised to clarify that intrathecal chemotherapy (methotrexate strongly preferred) administered at the time of required diagnostic lumbar puncture to establish baseline CNS status is allowed.
7.	3.1.6	29	1. Diagram inserted to provide visual overview of Evaluation 1. 2. Text inserted to clarify Evaluation 1 timing and details.
8.	3.1.8 6.1	31 120	Blinatumomab preparation text revised to account for Canadian regulations.
9.	3.1.10	32	Repetitive text deleted, as it more appropriately appears in Section 4.1.1.
10.	3.2.2 3.3	32 35	1. Text revised to clarify that the eligible diagnosis for this study is restricted to extramedullary disease limited to the CNS and testicles. First relapse of B-ALL with or without extramedullary disease. **Extramedullary sites are limited to the CNS and testicles.** Please refer to Section 3.3 for definitions of relapse and criteria for risk classification. 2. Definition of relapse in Section 3.3 updated for consistency.
11.	4.1	38	1. Repetitive text deleted: ~~Hospitalization:~~ ~~Hospitalization is STRONGLY recommended during the first 3 days of the first blinatumomab Cycle and the first 2 days of subsequent blinatumomab cycles in case of a cytokine reaction.~~ This text appears at the start of the relevant treatment sections. 2. Text inserted to clarify timing of IT MTX and ITT doses.

12.	4.1.1.1 4.1.1.2 4.1.1.3 4.2.7	39-40 40 40 44	Section reference inserted for details of Evaluation 1.
13.	4.2	41	The following recommendation was inserted: ***NOTE: The risks of significant morbidity and mortality, including sudden death in patients with relapsed leukemia, are sufficient to strongly recommend hospitalization during remission Induction, until patients show consistent neutrophil recovery and transfusion needs that are deemed to be manageable in the outpatient setting. Please see Appendix I for additional details.***
14.	4.2.3 4.3.4 4.4.3 4.10.3 4.11.3 4.12.4 4.13.4 4.14.4	42 47 51 77 79-80 85 87-88 89-90	Text inserted to clarify vincristine administration details: **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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.**
15.	4.2.3 4.3.4 4.13.4	42 47-50 87-88	Pegasparagase precautions moved to the proper treatment details sections.
16.	4.2.3	42-43	Text revised to require IT MTX on Day 1 for all patients. Subsequent text regarding IT MTX and ITT revised to remove Day 1 requirement.
17.	4.2.4	43-44	Text inserted for clarity: **The evaluation includes a bone marrow aspirate for all patients, a diagnostic lumbar puncture for patients who were CNS2 or CNS3 at study entry, and a testicular biopsy for patients with definite or equivocal residual testiculomegaly at end of Block 1.**
18.	4.2.7	44-45	Text revised for clarity: Post-Block 1 treatment should begin after **submission of end-Block 1 Callback and** receipt of **treatment** ~~risk~~ assignment ~~and submission of end-Block 1 Callback~~ as soon as clinically acceptable to the treating institution… …Treatment must begin no later than 14 days after **callback** ~~risk assignment~~ for patient to continue to receive protocol therapy.

19.	4.3.1 4.5.1	46 55	Criteria to begin cycle revised for consistency with changes in Section 4.2.7
20.	4.3.4 4.5.4 4.6.3 4.11.3 4.12.4 4.15.3	47-49 56-57 58-59 79-82 85-86 91-92	Age column for age based intrathecal dosing updated for clarity and consistency with corresponding TDMs.
21.	4.4.3	51-53	1. Cytarabine administration timing text revised for clarity ~~Q12H~~ **every 12 hours** 2. Erwinia L-asparaginase administration timing inserted: <u>Erwinia L-asparaginase:</u> IM (may be given IV **over 1 hour**) The corresponding TDM in Appendix II-C has been updated accordingly.
22.	4.5 4.6 4.7 4.8 4.15 4.16	55 58 61 64 91 93	Text inserted detailing instructions for Blinatumomab infusion interruptions for technical reasons.
23.	4.5.4 4.6.3 4.7.4 4.8.3 4.15.3 4.16.3	56-57 58-59 62 65 91-92 93-94	Blinatumomab administration guidelines revised to allow for 96 hour infusion time. * IV bag will be changed every 24 – **96** ~~48~~ hours
24.	4.5.4 4.6.3 4.7.4 4.8.3 4.15.3 4.16.3	56-57 58-59 62 65 91-92 93-94	1. Dexamethasone dosing details updated to include maximum dose • A single dose of 10 mg/m^2/dose **(maximum 20 mg/dose)**… • A single dose of 5 mg/m^2/dose **(maximum 10 mg/dose)**… 2. Text revised for clarity and consistency with corresponding TDMs …will be administered ~~within~~ **0 to** 30 minutes prior to the start of the blinatumomab infusion The corresponding TDMs in Appendix II-D, Appendix II-E, Appendix II-F, Appendix II-G, Appendix II-M, Appendix II-N were revised accordingly.
25.	4.6.4	59-60	Text revised for accuracy: <u>Notes regarding End-**Blinatumomab** Block ~~3~~**: Cycle 2** Disease Assessment</u>:
26.	4.9.2.3	71	1. Text revised for readability and to require the use of Mesna for consistency with COG's Chemotherapy Administration Guidelines: • Hyperhydration**,** ~~and~~ maintenance of significant urine output after administration**, and the use of Mesna** is required. ~~Mesna administration is encouraged, but not~~

			~~required.~~ 2. Administration details updated: • Recommended mesna dosing: 360 mg/m² during cyclophosphamide followed by 120 mg/m²/hour for **12** ~~24~~ hours after each dose. Institutional standards or protocols for mesna administration may also be used.
27.	4.9.6.1	74	Text inserted to provide additional details: **…Younger children (eg. < 6 years of age) may require more frequent PO tacrolimus dosing (every 8 hours) to maintain target trough concentrations…**
28.	4.9.6.4	75	Text revised to allow for laboratory methodology variations: The target serum trough concentration for cyclosporine is 200 – ~~350~~ **400** ng/mL. **Variations in dosing levels based upon laboratory methodology (e.g. tandem mass-spec analysis) allowed.**
29.	4.9.6.5	75	Text revised for accuracy: Refer to Section 5.13 for dose adjustments based ~~on serum drug levels~~ **upon clinical and laboratory findings.**
30.	4.11.1	79	Text revised for consistency and accuracy. • If at Day 22 the ANC is < 500/µL and platelets < 50,000/µL, it is permissible to delay the divided dose oral methotrexate (ddMTX) (25 mg/m²/dose for CNS1/2) or ID MTX (for CNS3) by ~~14~~ **7** days. ~~Omit the Day 29 standard dose oral methotrexate (20 mg/m²/dose) in this case.~~
31.	4.11.3	79-83	1. Text inserted for clarity: Leucovorin: PO **CNS 1 AND 2 PATIENTS ONLY** 2. Text revised for consistency with Section 5.8: Continue hydration using D 5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m²/hour throughout IDMTX infusion, and **until the last dose of leucovorin has been given** ~~for a minimum of 48 hours after its completion~~. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is < 0.**1** ~~25~~ µM. 3. Text inserted for clarity: Leucovorin: PO/IV **CNS 3 PATIENTS ONLY** 4. Timing details inserted for administering cytarabine. Cytarabine: IV **over 1 - 30 minutes or** ~~/~~SQ The corresponding TDM in Appendix II-I was revised accordingly.
32.	4.15	91	The following text was deleted as it is not applicable in this section. ~~END- BLOCK 1 CALLBACK OCCURS PRIOR TO STARTING BLINATUMOMAB BLOCK: CYCLE 1 THERAPY. PLEASE SEE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON STAGED CONSENT, AND APPROPRIATE TIMING TO OBTAIN CONSENT.~~

33.	5.1	95-97	Contradictory text deleted as it is not relevant to this study: ~~NOTE: Patients with allergy/anaphylaxis to pegaspargase may be eligible to receive IV pegcrisantaspase, a pegylated form of *Erwinia* asparaginase, on COG AALL1421 at doses prescribed on that protocol. Patients who have previously received *Erwinia* asparaginase or are receiving other investigational agents are not eligible for AALL1421.~~
34.	5.2	97-100	The following text was inadvertently omitted and has been inserted: In case of a change in finger-nose-finger or handwriting test it is recommended to start dexamethasone on the schedule above to prevent **possible deterioration of nervous system toxicity. Patients who experience nervous system toxicity in the first cycle typically do not experience it again in subsequent cycles, although it is possible.**
35.	5.8.1	104-106	1. Section heading revised: 5.8.1 ID MTX Infusion Guidelines **and dose modifications for toxicity** 2. Text revised for consistency with Section 4.11.3 3. The following text was deleted as it contradicts with the protocol specified cut-off points: ~~Myelosuppression: All chemotherapy should be held for ANC < 750/µL and platelets < 75000/µL.~~
36.	5.13.5	113	Typographical error corrected: Further dose ~~medications~~ **modifications** for significant toxicity likely caused by MMF are allowed.
37.	6.1	114-124	1. Blinatumomab drug monograph has been updated to account for allowance of 24 to 96 hour infusion time for both inpatient and outpatient administration. 2. The following text has been inserted: **Premedication with dexamethasone is required prior to each blinatumomab cycle, and for infusion interruptions longer than 4 hours.**
38.	6.2	124-127	Asparaginase Erwinia chrysanthemi monograph was updated to reflect the current template monograph.
39.	6.3 6.4 6.6 6.7 6.8 6.9 6.10 6.11 6.14 6.15 6.16 6.17	127-129 129-131 134-135 135-138 138-139 139-143 143-144 144-145 151-153 153-157 157-159 160-163	Monograph version dates inserted and minor typographical and administrative corrections made to reflect posted version of commercial agent monographs manual.

40.	6.5	131-134	Cytarabine monograph was updated to reflect the current template monograph.
41.	6.13	147-151	Monograph date inserted and repetitive text deleted.
42.	6.19	164-167	Thiotepa monograph was updated to reflect the current template monograph.
43.	6.20	167-168	Vincristine monograph updated to reflect the current template and special precautions have been moved to the appropriate treatment details sections throughout Section 4.
44.	7.1a	169	Removed requirement of testicular exam at the end of Block 3 and at the end of Blinatumomab blocks for consistency with TDMs
45.	7.1b	170	Inserted the following footnote for consistency with corresponding TDM in regards to the peripheral blood requirement for immunogenicity prior to maintenance Cycle 1 [8] **Arm D ONLY. Prior to start of Maintenance therapy for eligible patients (see Section 13.7 and lab manual for details)**
46.	7.1c	171	Requirement for pulmonary function test moved from '1-2 weeks after ANC > 500/µL' column to 'Prior to transplant (tx)' column for accuracy.
47.	7.2	172	Text deleted for clarity as no leftover specimen will be banked: ~~NOTE: This also includes the optional banking of residual material from required bone marrow for central flow MRD~~
48.	9.3.2.3	180-181	Text revised for readability: In addition, ~~occurred~~ during Block 3, Continuation 2 (Week 1 - 5) and Maintenance (Week 6 - 10) the toxic deaths and all toxicities of all grades between the two arms will also be monitored/compared ~~during the study~~.
49.	Throughout Section 11	185-194	1. Text revised throughout Section 11 to reflect current template language. 2. Section numbers updated.
50.	11.8	190-191	1. NCI CTEP-AERS link updated. 2. COG CTEP-AERS fax number and email address updated.
51.	11.12	193-194	Text revised for accuracy: Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting is split into ~~two~~ **three** categories:
47.	13.0	197	Text updated for accuracy and inclusion of APEC14B1.
48.	13.1	197-198	1. Repetitive text deleted. 2. Text inserted to clarify that peripheral blood can also be placed into large purple EDTA tubes if SM tubes are unavailable.

49.	13.3	199-200	Text deleted for accuracy, and to reflect changes made in Section 7.2, as no residual material will be banked: ~~For patients who have consented to specimen banking, residual material should be sent for banking. See section 13.1 for details.~~
50.	13.6	202-203	Sample collection details updated for consistency: **Day 1, Hour 0** (before start of systemic chemotherapy) • 3 **– 5** mL# in CellSave Preservative Tube* • 3mL in heparin tube **# 5 mL for those ≥ 10kg, 3 mL for those < 10kg**
51.	14.11	213-214	Address for IROC Rhode Island (QARC) re-organized for accuracy.
52.	Appendix I	216-218	1. For consistency with the recommendation in Section 4.2, for hospitalization during Induction, text regarding Guidelines During Induction was moved up in Appendix I and revised for consistency: 2. The associated section titled "Tumor Lysis Syndrome" was also moved up. 3. Text inserted for clarity: Begin allopurinol at a dose of 300 mg/m²/day or **10 mg/kg/day…** 4. Text inserted to specify that potassium should not be added to hydration fluids. 5. The following text regarding alkalization of urine removed: ~~Alkalinize urine with $NaHCO_3$ 20 – 40 mEq/L IV fluid to maintain urine pH between 6.5 and 7.5. Alkalinization is not recommended when treating with rasburicase.~~ 6. The following text was revised for readability, to update the reference and provide a link: Guidelines for preventing ~~opportunistic~~ infecti**ous**~~ons~~ **complications** among hematopoietic stem cell transplant recipients: ~~recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR 2000; 49(No. RR-10):1-125. Available at http://www.cdc.gov/mmwr/PDF/rr/rr4910.pdf.~~ **a global perspective. http://www.cdc.gov/vaccines/pubs/downloads/hemato-cell-transplits-508.pdf** Accessed ~~November~~ **July** 2~~4~~, 201~~0~~**5**.) 7. Text revised for clarity: …~~G-CSF~~ **filgrastim**…
53.	Appendix II-A	219-220	Footnote associated with the local bone marrow evaluation added to baseline BM evaluation and deleted from the Day 29 BM evaluation for consistency with Section 7.1a.
54.	Appendix II-B	221-222	1. For consistency with Section 4.3.4 and Section 5.8.1, the following text was revised:

			Block 2 lasts 4 weeks (28 days). Block 2 should begin after receipt of risk assignment according to timing outlined in <u>Section 4.2</u>. **All p**~~P~~atients can proceed with **Day 1 of** Block 2 without awaiting count recovery (must be no later than 5 days after callback). **Patients with M1 marrow after Block 1 should a**~~A~~wait count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning **Day 8 ID MTX; Patients with M2 marrow after Block 1 should not await recovery prior to beginning Day 8 ID MTX. All patients should await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning** Day 15 cyclophosphamide and etoposide. Please see <u>Section 4.3</u> for treatment details. This Therapy Delivery Map is on two (2) pages. 2. Incorrect appendix reference removed for accuracy.
55.	Appendix II-D Appendix II-M	225-226 240-241	Text revised for accuracy: This Therapy Delivery Map is on ~~one (1)~~ **two (2)** page**s**.
56.	Appendix II-D Appendix II-E Appendix II-F Appendix II-G Appendix II-M Appendix II-N	225-226 227 228-229 230-231 240-241 242	1. The following unit was revised for clarity: **____mc**~~µ~~g 2. The following was inserted in the dexamethasone column to clarify that the dose is divided and administered at two time points prior to the start of the Blinatumomab administration. ______mg **______mg**
57.	Appendix II-F	228-229	Blinatumomab PD observation removed from Day 15 for accuracy and consistency with Section 7.2
58.	Appendix II-G	230-231	Text revised for accuracy and consistency with Section 4.8.1: Blinatumomab-S: Cycle 2 lasts 5 weeks (35 Days) and starts **no earlier than Day 36 after the beginning of Blinatumomab-S: Cycle 1** ~~when ANC ≥ 500/µL and platelets ≥ 50,000/µL.~~
59.	Appendix II-K	237	Text inserted for accuracy and consistency with Section 4.13.1: This CNS directed therapy lasts 3 weeks (21 days) **and starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL (whichever occurs later)**.
60.	Appendix II-L	238-239	Given that this cycle is repeated, the following text was inserted: **Cycle # ______**
61.	Appendix III	243-244	The following text was inserted for clarity: **Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.**
62.	Appendix V	246-247	Youth Information Sheets updated for consistency and to indicate that both blood and bone marrow are requested for the optional correlative studies.
63.	Appendix VII-A	250-253	Agent preparation and administration options updated to account for 96 hour infusion time.

SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT

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

#	Section	Page(s)	Change
1.	ICD 1: Treatment Plan Tables	5	1. The following text was inserted for consistency with the changes made to Section 4.2 and Appendix I of the protocol: **Note: you may be hospitalized during this cycle as a precaution.** 2. Vincristine administration details updated for consistency. 3. The following footnote was inserted and linked to Pegasparagase: $ **If an allergy develops, 6 injections of a different form of Asparaginase (called Erwinia L-asparaginase) may be substituted for each dose for of pegaspargase in future cycles** 4. Block 1 Therapy table updated to reflect IT methotrexate requirement on Day 1.
2.	ICD 1: Specimen Banking	7	Text revised to more accurately reflect that specimens will be collected solely for banking and no leftover specimen will be banked.
3.	ICD 1 What are the costs?	10	1. The following text was inserted for clarity: **If you agree to take part in the optional studies, those will be done at no charge to you.** 2. The following COG template text has been inserted: **For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.**
4.	ICD1 ICD 2 What are my rights as a participant?	11 14	Text revised for consistency with COG template text: During your follow-up visits ~~after treatment~~, you may ask to be given a summary of the study results…
5.	ICD 2 Diagram of Treatment Plan	4	Diagram of treatment plan updated to more accurately reflect the treatment plan for patients with CNS disease.
6.	ICD 2: Treatment that is Research	6-8	1. The following footnote was inserted under the Block 2 therapy table and linked to Pegasparagase: * **If an allergy develops, 6 injections of a different form of Asparaginase (called Erwinia L-asparaginase) may be substituted for each dose for of pegaspargase in future cycles** 2. Erwinia asparaginase administration details updated in Block 3 therapy table for consistency.

7.	ICD 2 ICD 3 Required Study Tests	7-8 9	Text revised to clarify that the Blinatumomab Immunogenicity and Pharmacokinetics studies are required: If you are randomized to receive treatment with blinatumomab, we ~~would like your permission to~~ **will** collect extra blood to study how your body responds to blinatumomab.
8.	ICD 2: How many people will take part in this study?	12	The following text was inserted: **The number of patients taking part in HR/IR randomization is expected to be 170.**
9.	ICD 2: What are the costs?	13	The following COG template text has been inserted: **For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.**
10.	ICD 2 ICD 4: Attachment #1	16-21 14-19	1. Attachment #1 has been re-arranged for clarity and repetitive text has been deleted. 2. The following text has been inserted for clarity: Stem cells can be found in the circulating blood **(also called peripheral blood, or PB for short)**,… 3. Text inserted for accuracy and consistency: • The leukemia returned in your bone marrow 36 months or more after you were first diagnosed with ALL **plus your MRD is > 0.1% after Block 1 therapy.** 4. Vincristine administration details inserted for consistency: IV **push over 1 minute (or may be given over a longer infusion)** 5. Pre-transplant therapy table headers updated for clarity: Treatment before transplant (for patients who receive bone marrow or ~~cord~~ **peripheral** blood **stem cells** from either sibling or **an** unrelated donor) 6. The following table header was updated for accuracy: Treatment before transplant (for patients who receive ~~bone marrow or~~ cord blood from either sibling or **an** unrelated donor) 7. The following text was inserted: **Myeloid Growth Factor Support** **An additional drug referred to as the myeloid growth factor (filgrastim, G-CSF) may be given after the transplant. It helps start the production of white blood cells (infection fighting cells) and will help your body recover from transplant. Filgrastim (G-CSF) will be given on Day +1 until your body begins producing new blood cells (engraft).** 8. Drug name revised for consistency with protocol Cyclosporine ~~A~~

11.	ICD 3 Why am I being invited to take part in this study?	1	The following typographical errors have been corrected: 1. You a**re**~~nd~~ in the low risk (LR) arm because… 2. The leukemia took 36 months or more to return in your bone marrow after you were first diagnosed with ALL ~~for~~ or…
12.	ICD 3 Treatment that is Research	5-9	1. Erwinia asparaginase administration details updated in Block 3 therapy table for consistency. 2. Cytarabine administration details updated in the Standard Continuation 1 and Standard Continuation 2 tables for consistency. 3. Dexamethasone administration details updated in CNS3 and isolated CNS Relapse ONLY tables for consistency.
13.	ICD 3 Risks of Study	10-12	Text revised for clarity: …you will not get the 4-week Block 3 of chemotherapy and there **are** ~~is~~ 12 fewer weeks…
14.	ICD 3 How Many People Will Take Part in this Study?	13	The following text was inserted: **The number of patients taking part in LR randomization is expected to be 206.**
15.	ICD 3 ICD 4 How long is the study?	13 10	Repetitive text deleted: We would like to follow your health status for about ~~for about~~ 10 years…
16.	ICD 3 What are the costs?	14	Text revised to reflect the current COG template text.
17.	ICD 4 Research Study Tests and Procedures	5	Test deleted for consistency: • Before blinatumomab ~~S~~ Cycle 1
18.	ICD 4 How Many People Will Take Part in the Study?	9	The following text was added: **The number of patients deemed as treatment failure after Block 1 or Block 2 is estimated to be 60.**

Multiple risk inserts have been revised to reflect the current CTEP approved risk inserts. Specific changes to the consents are detailed below:

#	Section	Page(s)	Change
1.	ICD 1 ICD 2 ICD 3 Attachment #2: Erwinina Asparaginase	15 26 21	The following text was deleted from the Erwinia Asparaginase risk insert: • ~~Increased blood level of liver tests which may mean there has been damage to the liver~~ • ~~Increased blood sugar levels which could lead to diabetes~~

2.	ICD 1 Attachment #2: Mitoxantrone	18	1. The following text in the Mitoxantrone risk insert was moved from the "Common, Some May Be Serious" category to "Rare, and Serious" category: • **Abnormal or absence of menstrual period** 2. The following risk text was deleted: • ~~Liver damage which may cause y~~ **Yellowing…**
3.	ICD 1 ICD 2 ICD 3 ICD 4 Attachment # 2: Dexamethasone	19 25 20 22	1. The following text in the Dexamethasone risk insert was revised **In children and adolescents: d** ~~D~~ecreased height 2. The following text was deleted: • Bleeding of the eye ~~which may cause blurred vision with a chance of blindness~~ • Mood swings~~, depression, extreme feeling of happiness~~ • ~~High blood sugar which may lead to d~~ **D**iabetes 3. The following risk was deleted from the "Occasional, Some May Be Serious" category: • ~~Abnormal heartbeat~~
4.	ICD 1 ICD 2 ICD 3 ICD 4 Attachment # 2 Vincristine	20 39 30 33	The following risks were deleted from the "Rare, and Serious" category: ~~• Blurred vision with a chance of blindness~~ ~~• Difficulty with balance and hearing, hearing loss~~
5.	ICD 1 ICD 2 ICD 3 Attachment # 2 Pegaspargase	21 36 28	The following risk was deleted from the "Common, Some May Be Serious" category: • Blockage of the airway which may cause cough, wheezing, ~~shortness of breath~~ • ~~High blood sugar which may lead to diabetes~~
6.	ICD 2 ICD 4 Attachment # 2 Cyclosporine	23 21	The following risk was deleted from the "Occasional, Some May Be Serious" category: ~~High or low levels of certain salts in the body which may require you to take another medicine to correct the salt level~~
7.	ICD 2 ICD 3 Attachment # 2 Cytarabine	24 19	The following risk was added to the "Rare and Serious" category: • ~~None~~ **Coma**
8.	ICD2 ICD4 Attachment #2 Filgrastim	28 24	Filgrastim risk insert has been added.
9.	ICD 2 ICD 3 ICD 4 Attachment # 2 Methorexate (by mouth or by vein)	34 26 29	1. The following risks were added to the "Occasional, Some May Be Serious" category: • **Scarring of the lungs which may cause shortness of breath** • Nausea, vomiting**, diarrhea** • **Hair loss** 2. The following risks were deleted from the "Rare, and Serious" category:

			• ~~Diarrhea~~ • ~~Hair loss~~ • ~~Inflammation of the lungs that can affect your ability to breath and make you short of breath~~ 3. The following risk was added to the "Rare, and Serious" category: • **Damage to the brain which may cause tiredness, or changes in thinking**
10.	ICD 2 ICD 4 Attachment # 2 Mycophenolate Mofetil	35 30	The following risks were deleted from the "Common, Some May Be Serious" category: • ~~Low or high levels of certain salts in the body which may require you to take another medicine to correct the salt level~~ • ~~High blood sugar~~ • ~~Increased blood level of liver tests which may mean there has been damage to the liver, may cause yellowing of the skin~~
11.	ICD 2 ICD 4 Attachment # 2 Tacrolimus	37 31	1. The following risk was added to the "Common, Some May Be Serious" category: • **Dizziness** 2. The following text was inserted: Infection**, especially when white blood cell count is low** 3. The following risk was deleted from the "Common, Some May Be Serious" category" • ~~High or low levels of certain salts in the body which may require you to take another medicine to correct the salt level~~ 4. The following risks were added to the "Occasional, Some May Be Serious" Category: • Change in the heart rhythm**, abnormal heartbeat, or heart stops beating** • **Heart attack or failure which may cause chest pain, swelling of ankles, and tiredness** • **A tear or a hole in the stomach which may cause belly pain or that may require surgery** 5. The following text was deleted: • Brain damage, ~~Reversible Posterior Leukoencephalopathy Syndrome,~~ which may cause headache, seizure, blindness

STUDY TRAINING MODULE

Required Training: Blinatumomab Preparation and Administration Training Module

Documentation of the completion of site training with regard to the preparation and administration of blinatumomab must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial. The Blinatumomab Preparation and Administration training slides can be found on the protocol web page. This training module has been updated to reflect this amendment and is posted on the protocol web page. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training.

Recommended Training: AALL1331 General Training Module

The study general training module has been updated to reflect this amendment and is posted on the protocol web page. The completion of this training is recommended/not required. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training.

CHANGES TO THE CASE REPORT FORMS (CRFs)

All CRFs have been updated with amendment approval date and posting date. Other changes are detailed below. Of note, a new CRF has been added to capture Informed Consent forms and a new data element has been added to the relapse CRF (see details below).

Amendment-related CRF revisions are as follows:

Eligibility CRF:

1. Question related to current version of protocol updated to version 2.
2. Help text added clarifying eligible extramedullary sites of relapse and protocol reference for definitions of relapse sites.

Non-amendment-related revisions are as follows:

Adverse Event – Treatment CRF:

1. '**AE Status' question added:** In order to address the reporting of AE's that exist in one reporting period and were not required to be reported at that time (not a grade 3 or higher non-hematologic toxicity) but continued into the next reporting period that required all grades of all toxicities be reported ('residual AE'), a new question has been added (AE Status) that makes a distinction between a 'Residual AE from the previous reporting period' and one that is a 'New AE this reporting period.'
2. '**AE Grade' help text added:** Clarification regarding reporting of highest grade during reporting period for both new and residual AEs.
3. **'AE Attribution':** Ordering of permissible values revised to have 'probable' come before 'possible'.
4. '**Adverse event onset date':** Help text added to indicate that this field is to be left blank if the AE status is 'Residual AE'.

Relapse CRF:

1. **New data element added ('Attachments'):** Source documentation for 1^{st} on-protocol therapy relapse should be attached as a pdf via this element.

Consent Documentation – New CRF added

1. A new CRF has been added (Consent Documentation) for the required capturing and uploading of Informed Consent Forms. This CRF is to be submitted after enrollment (via 'Add Event' in RAVE) along with applicable consent (#1 and #5) uploads and then updated at time of subsequent consent signatures (consents #2, #3, or #4 at time of End Block 1 and/or End Block 2 Callback) along with consent upload.

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Memo

To: Principal Investigators and Clinical Research Associates

From: Teni Karimian, MS, Protocol Coordinator

Re: Amendment #3

Study: **AALL1331**, *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: February 29, 2016

AMENDMENT

____ Change of Participants/Coordinator(s)
__X__ Editorial or Administrative Changes
____ Scientific Changes*
__X__ Therapy Changes*
____ Eligibility Changes*
__X__ Informed Consent Changes*

STATUS CHANGE

____ Reactivation

*** FOR THE PURPOSE OF INSTITUTIONAL PERFORMANCE ASSESSMENT, THIS AMENDMENT WILL REQUIRE SUBMISSION TO AND APPROVAL BY IRBS WITHIN 90 DAYS.**

This amendment is being implemented in order to provide administrative updates and clarification in several places. Of note, text was inserted to require reporting of Grade 3 or higher infections. The volume calculations table in the blinatumomab drug monograph was updated to include a 72 hour bag change option. Additionally, Appendix II-A has been updated to reflect that Day 1 IT MTX is required for all patients in place of Day 1 ITT for CNS 3 patients.

Several other administrative changes have been made; specific changes are detailed below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked in the protocol but not specified below.

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.	Title Page	1	Protocol version date and amendment number have been updated
2.	Table of Contents	3-10	Table of contents has been updated to account for repagination.
3.	5.2	97-100	The following revision has been made throughout Section 5.2 for clarity: …~~µg~~ **mcg**/m^2/day
4.	6.1	114-124	1. Blinatumomab monograph date has been updated to match the current monograph and typographical errors have been corrected. 2. The volume calculation table has been revised to correct step 2 relating to the 96 hour IV bag: [2]stabilizer solution (**10** ~~5~~ mL) = 0.02 x total volume to be prepared (500 mL) 3. The following footnote has been inserted under the volume calculation table: * Approved bags include those made of polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP. 4. Option for 72 hour blinatumomab infusion bag option was added to the Volume Calculation table
5.	9.3.6	184	Details of monitoring for infection rate of 96 hour bag changes in Blinatumomab administration inserted.
6.	11.10	194	The following text was inserted to require reporting of Grade 3 or higher infections: • **Any Grade 3 or higher infection (defined as sepsis, bacteremia, device or catheter-related infection) that occurs more than 30 days after the last administration of blinatumomab and has an attribution of possible, probable, or definite must also be reported via CTEP-AERS.**
7.	Appendix II-A	220-221	Block 1 TDM updated for consistency with Section 4.2.3 and to reflect that Day 1 IT MTX is required for all patients in place of the Day 1 ITT for CNS 3 patients.
8.	Appendix VII-A	251-254	Text deleted for accuracy: For study subjects that cannot return to the registering/treating institution ~~every 96 hours~~ for infusion bag exchanges…

SUMMARY OF CHANGES: INFORMED CONSENT

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.	ICD 1 ICD 2 ICD 3 ICD 4 ICD 5	1-23 1-41 1-32 1-34 1	The version date in the consent footer has been updated.
2.	ICD 3 Treatment that is Research	5	The following text was inserted for clarity: **Attachment #1 describes standard treatment for patients with relapsed ALL.**

STUDY TRAINING MODULE

Required Training: Blinatumomab Preparation and Administration Training Module

Documentation of the completion of site training with regard to the preparation and administration of blinatumomab must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial. The Blinatumomab Preparation and Administration training slides can be found on the protocol web page. This training module has been updated to reflect this amendment and is posted on the protocol web page. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training.

Recommended Training: AALL1331 General Training Module

The study general training module has been updated to reflect the amendment number and version date and is posted on the protocol web page. The completion of this training is recommended/not required. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training.

CHANGES TO THE CASE REPORT FORMS (CRFs)

CRF revisions include updating the protocol version and posting date on all CRFs and the following individual CRF updates:

- Eligibility: Updated amendment number on question related to current version of protocol patient was consented to and enrolled on.
- Baseline Consents for Optional Studies: Revised edit checks on Blinatumomab Pharmacodynamics questions related to current version of protocol.
- Adverse Events – Treatment: Added amendment-related header directional text regarding the required reporting of any Grade 3 or higher infections that occurs more than 30 days after the last administration of Blinatumomab.
- Adverse Events – Follow-up: Added amendment-related header directional text regarding the required reporting of any Grade 3 or higher infections that occurs more than 30 days after the last administration of Blinatumomab.

CHILDREN'S ONCOLOGY GROUP

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Memo

To: Principal Investigators and Clinical Research Associates

From: Jeannette Cassar, Protocol Coordinator

Re: Amendment #4

Study: **AALL1331**, *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: May 31, 2016

ENROLLMENT IS BLOCKED PENDING IRB APPROVAL OF THIS AMENDMENT

AMENDMENT		STATUS CHANGE	
____	Change of Participants/Coordinator(s)	____	Reactivation
X	Editorial or Administrative Changes		
____	Scientific Changes		
X	Therapy Changes		
____	Eligibility Changes		
X	Informed Consent Changes		

Enclosed please find Amendment #4 to protocol **AALL1331,** *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*.

This amendment is being implemented in response to a request for amendment from Dr. Ravie Kem dated March 28, 2016. With this amendment, the NCI is replacing the current vial 30.3 mcg/vial with new vial strength, 38.5 mcg/vial of blinatumomab. This will result in a different vial concentration following reconstitution, currently 9.87 mcg/mL changing to 12.5 mcg/mL. The NCI expects that the current supply of the 30.3 mcg vials will be exhausted by June 30, 2016. **To ensure patients currently on therapy do not experience an interruption in Blinatumomab, please submit this amendment to your IRB of record immediately.**

NOTE: If a patient is started on a 28-day course of therapy prior to receiving Amendment #4 IRB approval it is strongly recommended that the site order a sufficient quantity of the original 30.3 mcg blinatumomab vials to complete that 28-day treatment. This is recommended to help prevent errors or delays associated with changing vial sizes in the middle of a single course. Subsequent courses for any patient on protocol therapy and any patient enrolled after implementation of the Amendment #4 should be prepared with the new 38.5 mcg blinatumomab vials.

Required Training: Blinatumomab Preparation and Administration Training Module

Documentation of the completion of site training with regard to the preparation and administration of blinatumomab must be submitted via RSS as a protocol specific requirement at the time of initial site activation for participation on the trial. The Blinatumomab Preparation and Administration training slides can be found on the protocol web page. This training module has been updated to reflect this amendment and is posted on the protocol web page. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training. **Review of the updated training module is particularly important for this amendment due to the change in vial strength and the resulting different vial concentration following reconstitution, currently 9.87 mcg/mL changing to 12.5 mcg/mL**.

Recommended Training: AALL1331 General Training Module
The study general training module has been updated to reflect the amendment number and version date and is posted on the protocol web page. The completion of this training is recommended/not required. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training.

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

REQUIRED ACTIONS FOR COG REGULATORY COMPLIANCE:

A. For sites utilizing a local IRB:
   - Local IRB approval is due within **90** days of the date on this memo.

B. For sites utilizing the Pediatric CIRB:
   - Sites are required to implement this study amendment within **30** days of the CIRB posting date of this amendment. New patients must be consented, enrolled **and treated with** this amended version of the protocol.

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.	Title Page	1	Protocol version date and amendment number have been updated
2.	Study Committee Roster	11-13	1. Contact information for study committee members has been updated. 2. Hui Zeng is no longer affiliated with COG and has been removed from the roster.
3.	3.1.5	29	Deleted last column in Table 8.
4.	3.1.6	29-30	Text inserted to clarify that completion of risk group assignment and submission of end-Block 1 callback form must occur within 5 calendar days.
5.	3.2.2	32	Text revised for clarity: First relapse of B-ALL**, allowable sites of disease include isolated bone marrow, combined bone marrow and CNS and/or testicular, and isolated CNS and/or testicular** ~~with or without extramedullary disease~~.

#	Section	Page(s)	Change
6.	4.2.7 4.3.1 4.5.1 Appendix II-B Appendix II-D	45-46 47 56 225-226 229	Text has been inserted for consistency with Section 3.1.6.
7.	6.1	115-126	1. The blinatumomab monograph was updated per the request for amendment from the NCI to reflect the new blinatumomab vial strength and concentration. 2. In response to a recommendation from the NCI, the following text has been updated for clarity: Note: Overfill volume **depends on the volume of the IV set used at each institution** ~~(IV infusion set volume) varies by infusion duration~~. See Volume Calculation Table below for details.
8.	7.1a 7.1b	170 171	For consistency with Section 3.2.5.2, the following footnote has been inserted: [0] **Adequate liver function as defined by direct bilirubin required for eligibility (see Section 3.2.5.2).**
9.	7.2	174	Text inserted for clarity: • End Block 2 **(Arm A, C or D) or End of Blinatumomab Cycle 1 (Arm B)**
10.	Appendix I	218-221	Supportive care guidelines have been updated to reflect the current COG supportive care guidelines.

SUMMARY OF CHANGES: INFORMED CONSENT

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.	ICD 1 ICD 2 ICD 3 ICD 4 ICD 5	1-23 1-41 1-32 1-34 1	The version date in the consent footer has been updated.
2.	ICD 4 What are the Costs?	11	The following COG template text has been inserted: **For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learning about.**

SUMMARY OF CHANGES: CASE REPORT FORMS (CRF)

CRF revisions include the update of version and date to all CRFs. Specific CRF revisions are as follows:

1. Eligibility: Protocol version number in help text updated to '4' and modification of diagnosis question and Help Text to match protocol.
2. Callback 1: Added word 'calendar' to number of days in directional text
3. STF – Banking for Future Research: Specimen time-point valid value 'End Block 2' updated to include 'Cycle 1' (End Block 2/End Cycle 1) and help text added to clarify treatment arms for this selection.

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

Memo

To: Principal Investigators and Clinical Research Associates

From: Jeannette Cassar, Protocol Coordinator

Re: Amendment #5

Study: **AALL1331,** *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: January 17, 2017

ENROLLMENT IS BLOCKED PENDING IRB APPROVAL OF THIS SAFETY AMENDMENT

AMENDMENT	**STATUS CHANGE**
____ Change of Participants/Coordinator(s)	_____ Reactivation
_X_ Editorial or Administrative Changes	
____ Scientific Changes	
____ Therapy Changes	
____ Eligibility Changes	
_X_ Informed Consent Changes	

Enclosed please find Amendment #5 to protocol **AALL1331,** *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

This study has been amended in response to a Request for Rapid Amendment (RRA) from Elad Sharon, MD, MPH (sharone@mail.nih.gov) dated November 18th, 2016 for Blinatumomab (NSC 765986). Please review the action letter for Blinatumomab.

In this amendment the revised CAEPR for Blinatumomab (NSC 765986) has been inserted in the protocol and the associated risk information in the informed consent documents has been revised accordingly.

Specific changes to the protocol and informed consents are detailed in the pages below. There are not any amendment-related changes to the CRFs other than revision of the amendment date.

The NCI approval notice includes one recommendation which the study committee has considered and plans to address at the time of the next amendment.

REQUIRED ACTIONS FOR COG REGULATORY COMPLIANCE:

A. For sites utilizing a local IRB:
Local IRB approval is due within **90** days of the date on this memo.

B. For sites utilizing the Pediatric CIRB:
Sites are required to implement this study amendment within **30** days of the CIRB posting date of this amendment. New patients must be consented, enrolled **and treated with** this amended version of the protocol.

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

Section	Page(s)	Change
Title Page	Title page	Updated the version date and amendment number.
TOC	2-5	Updated the table of contents to account for repagination.

6.1	116-121	CAEPR for Blinatumomab was revised as follows:
		
		• Added New Risk:
		  ◦ Less Likely: Abdominal distension; Hypocalcemia; Mucositis oral; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Paresthesia; Pain; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
		  ◦ Also Reported on Blinatumomab Trials But With Insufficient Evidence for Attribution: Blurred vision; Conjunctivitis; Depression; Dry skin; Dyspepsia; Fall; Hematoma; Hyperkalemia; Hyponatremia; INR increased; Metabolism and nutrition disorders - Other (hyperphosphataemia); Neck pain; Productive cough; Psychiatric disorders - Other (sleep disorder); Skin and subcutaneous tissue disorders - Other (petechiae)
		
		• Increase in Risk Attribution:
		  ◦ Changed to Likely from Less Likely: Anemia; Platelet count decreased
		  ◦ Changed to Less Likely from Rare but Serious: Anxiety; Investigations - Other (fibrin D dimer increased; Non-cardiac chest pain; Pleural effusion; Tumor lysis syndrome
		  ◦ Changed to Less Likely from Also Reported on Blinatumomab Trials But With Insufficient Evidence for Attribution: Anorexia; Arthralgia; Epistaxis; Generalized muscle weakness; Hematuria; Hyperhidrosis; Hypoalbuminemia; Investigations - Other (blood lactate dehydrogenase increased); Leukocytosis; Pruritus; Sinus tachycardia; Somnolence; Weight loss
		
		• Decrease in Risk Attribution:
		  ◦ Changed to Less Likely from Likely: Tremor; White blood cell decreased
		  ◦ Changed to Also Reported on Blinatumomab Trials But With Insufficient Evidence for Attribution from Less Likely: Acute kidney injury; Respiratory failure
		
		• Provided Further Clarification:
		  ◦ Footnotes have been renumbered.
		  ◦ Footnote #2 has been added to Thromboembolic event.
		  ◦ Footnote #9 has been added to Nervous system disorders - Other (cerebellar syndrome).
		  ◦ Footnote #5 has been added as follows, "Immunodeficiency (immunoglobulin decreased) includes immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and blood immunoglobulin A decreased."
		  ◦ Footnote #9 (previously footnote #8) has been altered to read, "Blinatumomab (AMG103) is known to cause a variety of nervous system

		disorders which may include: Ataxia, Cognitive disturbance, Concentration impairment, Depressed level of consciousness, Dizziness, Dysphagia, Dysarthria, Dysesthesia, Dysphasia, Encephalopathy, Facial nerve disorder, Headache, Memory impairment, Paresthesia, Peripheral sensory neuropathy, Seizure, Somnolence, Syncope, Transient ischemic attacks, Tremor, Voice alteration, Nervous system disorders - Other (allodynia), Nervous Systems disorders - Other (cerebellar syndrome), Nervous system disorders - Other (dysgraphia), Nervous system disorders - Other (epilepsy), Nervous system disorders - Other (facial palsy), Nervous system disorders - Other (hemiparesis), Nervous system disorders - Other (hypertonia), Nervous system disorders - Other (hypotonia), Nervous system disorders - Other (pleocytosis), and Nervous system disorders - Other (polyneuropathy). Additionally, symptoms of some nervous system disorders are adverse events under the PSYCHIATRIC DISORDERS SOC and may include: Agitation, Anxiety, Confusion, Hallucinations, Personality change, and Psychosis." • Footnote #10 (previously #9) has been altered to read, "Rash includes rash, rash maculo-papular, erythema, local erythema, erythematous rash, generalized rash, exanthema, allergic dermatitis, and palmar-plantar erythrodysesthesia syndrome." • Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements: • Added: Cytokine release syndrome

SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENTS

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.

The following changes have been made in consent #2, #3, and #4. Only the version date has been changed in consent #1 and #5

Section	Page(s)	Change

Risks of the Study	ICD2 pgs 9-10
	
	ICD3 pgs 11-12
	
	ICD4 pgs 7-8
		1. Added New Risk:
		  • Occasional: Bloating; Sores in the mouth which may cause difficulty swallowing; Muscle spasms; Feeling of "pins and needles" in arms and legs
		
		2. Increase in Risk Attribution:
		  • Changed to Common from Occasional: Anemia which may require blood transfusion; Bruising, bleeding
		  • Changed to Occasional from Rare: Fluid in the body which may cause low blood pressure, shortness of breath, swelling of ankles
		  • Changed to Occasional from Also Reported on Blinatumomab Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Loss of appetite; Nose bleed; Muscle weakness; Increased sweating; Itching; Abnormal heartbeat; Weight loss
		3. Decrease in Risk Attribution:

		• Changed to Occasional from Common: Infection, especially when white blood cell count is low; Abnormal body movement, difficulty talking 4. Provided Further Clarification: • Damage to organs which may cause shortness of breath (previously under Occasional) is now being reported as Damage to the brain which may cause changes in thinking (under Rare). • Internal bleeding, which may cause black tarry stool, blood in vomit (previously under Rare) is now being reported as Internal bleeding which may cause black tarry stool, blood in vomit, or blood in urine (under Occasional). • Confusion (under Occasional), Worry (under Occasional), Restlessness (Under Rare), and Sensing things that are not there (under Rare) are now being reported under Damage to the brain or nerves which may result in confusion, restlessness, worry, or sensing things that are not there (under Rare). • Swelling of the body which may cause shortness of breath (under Occasional) is now being reported as Swelling of the body (under Occasional) and Swelling of the lungs which may cause shortness of breath (under Rare).

CRFs

There are not any amendment-related changes to the CRFs other than revision of the amendment date.

CHILDREN'S ONCOLOGY GROUP

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

Memo

To: Principal Investigators and Clinical Research Associates

From: Jeannette Cassar, Protocol Coordinator

Re: Amendment 6a

Study: **AALL1331,** *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: September 25, 2017

AMENDMENT		**STATUS CHANGE**	
X	Change of Participants/Coordinator(s)	___	Reactivation
X	Editorial or Administrative Changes		
X	Scientific Changes		
X	Therapy Changes		
___	Eligibility Changes		
X	Informed Consent Changes		

Enclosed please find Amendment #6a to protocol AALL1331, *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*.

This amendment modifies the consent to indicate there is no published data on the safety of the protocol regimen in patients greater than 18 years of age at the time of study entry and enhances supportive care criteria in the protocol for these patients. The toxicity stopping rule has been updated to better reflect current data. In addition, the dosing of dexamethasone as a pre-med has been updated to reflect the pediatric label for blinatumomab. In addition, several changes were made to clarify blinatumomab preparation, administration and ordering procedures.

Several other administrative changes have been made; specific changes are detailed below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked in the protocol but not specified below.

All changes made to the protocol since Amendment #5 are detailed in the list of changes below, and are contained in the tracked version of Amendment #6a.

Study Training Modules: The General Training and Preparation and Administration Training modules have also been updated to reflect this amendment and are posted on the protocol web page. The completion of these trainings is required.

COG Biospecimen Lab Address: This amendment was processed before information could be updated and does not contain the current name and address of the COG Leukemia Biospecimen Bank. Samples for banking for future studies as described in Section 13.1 of the protocol should be shipped to the following address.

COG Leukemia Biospecimen Bank
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215
Phone: 614-722-2866
MGLab@nationwidechildrens.org

The NCI approval letter contained two recommendations which have been reviewed by the study committee and will be addressed in the next amendment.

REQUIRED ACTIONS FOR COG REGULATORY COMPLIANCE:

A. For sites utilizing a local IRB:
Local IRB approval is due within **90** days of the date on this memo.

B. For sites utilizing the Pediatric CIRB:
Sites are required to implement this study amendment within **30** days of the CIRB posting date of this amendment. New patients must be consented, enrolled **and treated with** this amended version of the protocol 30 days after the CIRB posting date.

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.	Title Page	1	Protocol version date and amendment number have been updated.
2.	Table of Contents	3-10	Table of contents has been updated to account for repagination.
3.	Study Committee Roster	11-13	• Updated the Study Statistician to Lingyun Ji. • Jeannette Cassar was added as the protocol coordinator.
4.	Experimental Design Schema	15	Added references to sections for details regarding staged consent and callback information.
5.	3.1.1	26	Removed reference to ACCRN07 and inserted information regarding APEC14B1.
6.	3.1.2	27	Updated the procedures to submit IRB/REB regulatory documents.
7.	3.1.5	28-29	Updated Table 8 to better describe which consents are required and at what time points.
8.	3.2.3.7	34	Clarified that intrathecal cytarabine is permissible to be given prior to study entry.
9.	4.1.2.1	43	Removed link to external resource for list of CYP3A4/5 inhibitors and inducers. Added recommendation to regularly consult updated medical references.
10.	4.1.2.2	43	Updated the link to the chemotherapy administration guidelines.
11.	4.1.3	43	Added supportive care recommendations for patients 15 years or older.
12.	4.2.3	45	Clarified that intrathecal cytarabine is permissible to be given prior to study entry in IT therapy does not need to be repeated if done within 7 days.
13.	4.2.4	46	Clarified that the lumbar puncture for disease evaluation at the end of block 1 should only be performed for CNS 2 or CNS 3 patients for whom clearance of CSF blasts has not yet been documented.
14.	4.3.4	51	Deleted the following: "To continue to receive protocol therapy, all patients must begin Day 8 IV methotrexate no later than 14 days after risk assignment." The statement was incorrect.
15.	4.4.3	55	Changed the name of Erwinia L-asparaginase to Asparaginase (Erwinia).
16.	4.5.4	59	• Modified the dosing of dexamethasone as a premedication for blinatumomab to match the new pediatric FDA label. • Changed timing of the dosing of dex to 30-60 minutes prior to blinatumomab. From Package Insert for Blinatumomab: "*For pediatric patients, premedicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first cycle, prior to a step dose (such as Cycle 1 day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle*."
17.	4.6	61	Deleted reference to dexamethasone as a pre-med during cycle 2 for a dose interruption.
18.	4.6.3	62	Deleted dexamethasone dosing as a premedication for blinatumomab to align with the new pediatric FDA label.

19.	4.7.4	64	• Modified the dosing of dexamethasone as a premedication for blinatumomab to match the new pediatric FDA label. • Changed timing of the dosing of dex to 30-60 minutes prior to blinatumomab.
20.	4.8	66	Deleted reference to dexamethasone as a pre-med during cycle 2 for a dose interruption.
21.	4.8.3	67	Deleted dexamethasone dosing as a premedication for blinatumomab to align with the new pediatric FDA label.
22.	4.9	69	Clarified that all transplants must occur at FACT-accredited HSCT programs.
23.	4.9.6.5	77	Updated the information about the FDA Risk Evaluation and Mitigation Strategy program for mycophenolate mofetil.
24.	4.10.3	80	Updated timing of dosing for mercaptopurine.
25.	4.11.3	82	Updated timing of dosing for mercaptopurine and thioguanine.
26.	4.12.4	87	Updated timing of dosing for mercaptopurine.
27.	4.15.3	94	• Modified the dosing of dexamethasone as a premedication for blinatumomab to match the new pediatric FDA label. • Changed timing of the dosing of dex to 30-60 minutes prior to blinatumomab.
28.	4.16		Deleted reference to dexamethasone as a pre-med during cycle 2/3 for a dose interruption.
29.	4.16.3	96	• Added link to the therapy delivery map in Appendix II-N. • Deleted dexamethasone dosing as a premedication for blinatumomab to align with the new pediatric FDA label.
30.	5.1	98	Deleted "*qod: every other day" under the dosing table. It does not belong in this section.
31.	5.2	99-102	Clarified dosing of dexamethasone to be used as supportive care.
32.	5.8.1	108	Clarified which drugs should not be co-prescribed with MTX.
33.	5.9	109	Deleted item a. and b. for dose modifications for continuation because they conflicted with count requirements to start the course.

34.	6.1	117-127	• Updated date of monograph.
			• Formulation and Stability:
			   ○ Updated formulation information.
			   ○ Removed dosing information for previous lot of blinatumomab.
			• Preparation:
			   ○ Deleted note regarding instructions for using a previous lot of blinatumomab.
			   ○ Removed reconstitution instructions for previous lot of blinatumomab.
			   ○ Removed concentration information for previous lot of blinatumomab.
			   ○ Added "Infusion rate 5 mL/hour" to the top of the Volume Calculation Table.
			• Administration:
			   ○ Updated the premedication guidelines with dexamethasone.
			   ○ Clarified the use of CADD pumps and cassettes for CADD pumps.
			• Obtaining the Agent:
			   ○ Added a comment that the study does not need a starter supply and that confirmation of patient enrollment is required for initial shipment.

			○ Deleted information about transitioning a patient from the previous lot of blinatumomab to the current lot. ○ Updated information regarding inventory records. • Added information about obtaining the Investigator Brochure. • Added useful links and contacts.
35.	6.2	128-130	Updated drug information for ASPARAGINASE Erwinia chrysanthemi regarding procedures for ordering drug in the US.
36.	6.7	138-141	Updated drug information for Etoposide for Injection indicating that in Canada is it available as a 20mg/mL solution.
37.	6.8	141-142	Updated drug information for Filgrastim to update information about bio-similar products.
38.	6.12	150-151	• Updated drug information for Mercaptopurine to update the toxicity information. • Updated guidelines for administration to indicate that drug should be taken at the same time each day.
39.	6.15	157-161	Updated drug information for Mycophenolate mofetil to update the toxicity information.
40.	6.16	161-163	Updated drug information for Pegaspargase regarding supplier and Canadian ordering.
41.	6.18	167-168	Updated drug information for Thioguanine regarding guidelines for administration.
42.	6.19	168-171	Updated drug information for Thiotepa regarding guidelines for Canadian sites.
43.	7.1.a 7.1b	173-175	Added optional bone marrow and peripheral blood time points to the table of observations.
44.	9.3.1.5	183-184	Added amended safety monitoring for implementation with amendment 6. **Rationale:** To date there have been 4 deaths during blocks 2 and 3, among 47 randomized patients on Arm A. Of these, three deaths occurred in 14 AYA patients (ages 17, 23, and 26 years), with a death rate of 21.4%. The death rate among the younger patients is 1/33 (3%). The published UKALLR3 clinical trial only enrolled patients up to 18 years of age at the time of first relapse. Hence the toxic death rate from that study (used as the baseline rate on this study), was based on a younger population than those enrolling on AALL1331. About 15% of enrollments on this study are currently greater than 18 years old. Based on prior studies in COG and other groups, it is known that the risk of toxic deaths may be higher in older patients relative to younger ones. Based on this, the monitoring for toxic deaths during Blocks 2 and 3, among HR/IR patients randomized to Arm A, has been modified to apply only to patients ≤ 18 years of age at enrollment. With this rule, the probability of stopping due to excessive toxic deaths is 12% if the true toxic death rate is 4%, 48% if the true rate is 7%, and 79.2% if the true rate is 10%. Since it is estimated that only about 13 patients on each arm will be >18 years of age at enrollment, separate stopping rules for this subset would not have much power (~74% at a true rate of 30%, or 13% power at a true rate of 10%). Instead of a formal monitoring rule for AYA patients, continuous monitoring will be done, such that any death occurring among the older patients, after the proposed supportive care changes are initiated, will trigger a study committee review and communication to the COG Data Safety Monitoring Committee.

45.	13.1	203-204	• Added reference to section 7.2 to see time points for optional banking. • Added link to BPC kit management system. • Modified wording regarding submitting of peripheral blood, clarifying that it may be submitted at diagnosis or other time points if the patient has an absolute blast count of at least 1000/μL. • Clarified shipping information.
46.	13.3	205-207	• Added link to BPC kit management system. • Modified wording regarding submitting of peripheral blood, clarifying that it may be submitted at diagnosis or other time points if the patient has an absolute blast count of at least 1000/μL.
47.	14.1.1	212	Updated the required benchmark and questionnaires for TBI.
48.	14.11	219	Updated the quality assurance documentation and review section.
49.	Appendix I	221-224	Added additional monitoring guidelines for patients age 15 and older.
50.	Appendix II-C	229-230	Changed the name of Erwinia L-asparaginase to Asparaginase (Erwinia).
51.	Appendix II-D	231-232	• Modified the dosing of dexamethasone as a premedication for blinatumomab to match the new pediatric FDA label. • Changed timing of the dosing of dex to 30-60 minutes prior to blinatumomab.
52.	Appendix II-E	233	Deleted dexamethasone dosing as a premedication for blinatumomab to align with the new pediatric FDA label.
53.	Appendix II-F	234-235	• Clarified that the prescribed and total dose of blinatumomab for days 1-7 is different from days 8-28 and added a place to record each time point dose. • Moved day 15 and 22 labs to day 14 and 21 to better align with correlative study blood draws. • Modified the dosing of dexamethasone as a premedication for blinatumomab to match the new pediatric FDA label. • Changed timing of the dosing of dex to 30-60 minutes prior to blinatumomab.
54.	Appendix II-G	236-237	Deleted dexamethasone dosing as a premedication for blinatumomab to align with the new pediatric FDA label.
55.	Appendix II-H	239-240	Deleted the requirement for a bone marrow evaluation for MRD on day 1 of Bridging Maintenance as it is not required and should have been done at the end of the previous cycle of therapy.
56.	Appendix II-I	237	Corrected the infusion rate for cyclophosphamide to 15-30 minutes to match section 4.11.
57.	Appendix II-M	246-247	• Modified the dosing of dexamethasone as a premedication for blinatumomab to match the new pediatric FDA label. • Changed timing of the dosing of dex to 30-60 minutes prior to blinatumomab.
58.	Appendix II-N	248	• Deleted dexamethasone dosing as a premedication for blinatumomab to align with the new pediatric FDA label. • Removed superscript [1] from observations as it was there erroneously.
59.	Appendix XIII	282-283	Updated CTSU submission of regulatory document instructions.

SUMMARY OF CHANGES: INFORMED CONSENT

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.	All	All	• The version date in the footer has been updated.
2.	Erwinia Asparaginase	ICD 2 ICD 3	All references of Erwinia L-asparaginase were changed to Asparaginase Erwinia, to be consistent with the protocol.
3.	What side effects or risks can I expect from being in the study?	ICD1-page 8	The following paragraph was added: "This treatment is based on a chemotherapy regimen that was studied in the United Kingdom and Europe. All the patients treated on this study were 18 years of age or younger. While this treatment has been given to many patients over 18 years of age, there is no published data on the safety of this treatment in patients over 18 years of age, and the risk of side effects may be increased in this older population."
4.	What side effects or risks can I expect from being in the study?	ICD2-page 8 ICD3-page 10	The following paragraph was added: "The treatment on the control arm is based on a chemotherapy regimen that was studied in the United Kingdom and Europe. All the patients treated on this study were 18 years of age or younger. While this treatment has been given to many patients over 18 years of age, there is no published data on the safety of this treatment in patients over 18 years of age, and the risk of side effects may be increased in this older population."
5.	Where can I get more information?	ICD1-page 12 ICD2-page 15 ICD3-page 16 ICD4-page 12	Updated the address for the COG Family Handbook. http://www.childrensoncologygroup.org/index.php/cog-family-handbook
6.	Possible Side Effects of Cytarabine (ara-c) by vein	ICD2-page 25 ICD3-page 20	Updated to reflect current NCI Consent Form Template for cytarabine.
7.	Possible Side Effects of Fludarabine	ICD2-page 30 ICD4- page 25	• Updated to reflect current NCI Consent Form Template for fludarabine. • Per request of the PCIRB, added information regarding potential for damage or inflammation to the optic nerve which can cause blurred vision, decreased vision, other visual disturbances or pain with eye movements.
8.	Possible Side Effects of Tacrolimus	ICD2-page 38 ICD4-page 31	Updated to reflect current NCI Consent Form Template for tacrolimus.
9.	Treatment with Blinatumomab	ICD2-page 7	Deleted dexamethasone dosing from cycle 2 of blinatumomab.
10.	Treatment with Blinatumomab	ICD3-page 8	Deleted dexamethasone dosing from cycle 2 and 3 of blinatumomab.
11.	Treatment with Blinatumomab	ICD4-page 5	Added Day 8 to the table for dexamethasone administration.

CRFs

- The protocol version/date has been updated on all CRFs.
- Help Text on the Eligibility CRF regarding the protocol version question has been updated to reflect the current protocol version.
- A blocking edit check has been added to the Eligibility CRF.

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

Memo

To: Principal Investigators and Clinical Research Associates

From: Arshi Reyaz, MS, Protocol Coordinator

Re: Amendment #7

Study: **AALL1331**, *A Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: July 23, 2018

AMENDMENT		**STATUS CHANGE**	
____	Change of Participants/Coordinator(s)	____	Reactivation
X	Editorial or Administrative Changes		
____	Scientific Changes		
____	Therapy Changes		
____	Eligibility Changes		
X	Informed Consent Changes		

REQUIRED ACTIONS FOR COG REGULATORY COMPLIANCE:

A. For sites utilizing a local IRB:

Local IRB approval is due within **90** days of the date on this memo.

B. For sites utilizing the Pediatric CIRB:

Sites are required to implement this study amendment within **30** days of the CIRB posting date of this amendment. New patients must be consented, enrolled **and treated with** this amended version of the protocol 30 days after the CIRB posting date.

Amendment #7 updates consent forms to indicate that blinatumomab is now approved by the FDA for the treatment of children with relapsed or refractory B-ALL and also for the treatment of children in first or second complete remission with MRD greater than or equal to 0.1%.

In addition, the amendment also notes the replacement of Don Sortillon for Susan Conway and Christine Petrossian for Jeanette Cassar as the research coordinator and the protocol coordinator, respectively. All changes made to the protocol since Amendment #6a are detailed in the list of changes below and are contained in the tracked version of Amendment #7.

AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

#	Section	Page(s)	Change
1.	Throughout	Throughout	Version date has been updated.
2.	Study Committee	13	• Don Sortillon has replaced Susan Conway as the research coordinator. • Christine Petrossian has replaced Jeanette Cassar as the protocol coordinator.

AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT 1 RE-INDUCTION

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	Throughout	Throughout	Version date has been updated.

AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT 2 HR/IR RANDOMIZATION

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	Throughout	Throughout	Version date has been updated.
2	What will happen on this study that is research	3	Included update that blinatumomab is now approved by the FDA for the treatment of children with relapsed or refractory B-ALL and also for the treatment of children in first or second complete remission with MRD greater than or equal to 0.1%.

AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT 3 LR RANDOMIZATION

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	Throughout	Throughout	Version date has been updated.
2	What will happen on this study that is research	2	Included update that blinatumomab is now approved by the FDA for the treatment of children with relapsed or refractory B-ALL and also for the treatment of children in first or second complete remission with MRD greater than or equal to 0.1%.

AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT 4 NON-RESPONDERS AFTER BLOCK 1 (ALL PATIENTS) OR BLOCK 2 (HR/IR PATIENTS)

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	Throughout	Throughout	Version date has been updated.
2	What will happen on this study that is research	2	Included update that blinatumomab is now approved by the FDA for the treatment of children with relapsed or refractory B-ALL and also for the treatment of children in first or second complete remission with MRD greater than or equal to 0.1%.

AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT 5 ADDITIONAL BONE MARROW

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	Throughout	Throughout	Version date has been updated.

AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: CRFs

There are no amendment-related changes to the CRFs other than updates to the version dates.

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

Memo

To: Principal Investigators and Clinical Research Associates

From: Arshi Reyaz, Protocol Coordinator

Re: Amendment #8A

Study: **AALL1331,** *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: December 3, 2018 (Revised December 3, 2018)

AMENDMENT

____ Change of Participants/Coordinator(s)
__X__ Editorial or Administrative Changes
__X__ Scientific Changes
____ Therapy Changes
____ Eligibility Changes
__X__ Informed Consent Changes

STATUS CHANGE

____ Reactivation

REQUIRED ACTIONS FOR COG REGULATORY COMPLIANCE:

A. For sites utilizing a local IRB:

Local IRB approval is due within **90** days of the date on this memo.

B. For sites utilizing the Pediatric CIRB:

Sites are required to implement this study amendment within **30** days of the CIRB posting date of this amendment. New patients must be consented, enrolled **and treated with** this amended version of the protocol 30 days after the CIRB posting date.

This amendment updates the statistical plan to increase the accrual goals for both the standard and high risk arms. In addition, the seven-day blinatumomab infusion schedule has been added. Updates have been made to the dose modifications. In the consents, the potential side effects for drugs used in the study have been updated to match the current template.

In addition, the home health care manual, preparation and administration training module, and general training module have been updated to reflect this amendment and are posted on the protocol web page. Sites are strongly encouraged to review the updated training modules as they become available, and are expected to remain current on study training. Please note, submission of the Blinatumomab Preparation and Administration training attestation to CTSU is only required for initial site activation.

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

Section	Page	Comments
Title Page	1	Protocol version date and amendment number have been updated.
Study Committee	12-13	Contact information for several members of the committee has been updated.
3.1.1	26	Patient Registration section was updated to include contact information.
3.1.2	27	Updated section for obtaining IRB Approval.
3.1.3	28	Updated section regarding Study Enrollment.
3.3	38	The High Risk assessment section was updated to read "The timing of relapse **(duration of first remission)** is measured from the date of initial diagnosis to the date of relapse."
4.2.7	47	The second bullet point for Treatment failures Post-Block 1 was revised to read "TF patients with M3 marrow disease and no residual CNS disease (CNS1) should proceed to **Blinatumomab-S Cycle 1** without awaiting count recovery …"
4.4.3	54	Clarified that Asparaginase Erwinia should be given 4 hours after completion of the last cytarabine infusion on Days 2 and 9.
4.5.4	58	Details pertaining to the Blinatumomab Block: Cycle 1 Chemotherapy for continuous IV infusion over 28 days were added to include "IV bag will be changed every 24 - 96 hours **or every 168 hours (7 days), depending on the details of the infusion preparation**".
4.6.3	61	Details pertaining to the Blinatumomab Block: Cycle 2 Administration Guidelines for continuous IV infusion over 28 days were added to include "IV bag will be changed every 24 - 96 hours **or every 168 hours (7 days), depending on the details of the infusion preparation**".
4.7.4	64	Details pertaining to the Blinatumomab-S: Cycle 1 Chemotherapy Guidelines for continuous IV infusion over 28 days were added to include "IV bag will be changed every 24 - 96 hours **or every 168 hours (7 days), depending on the details of the infusion preparation**".
4.8.3	67	Details pertaining to the Blinatumomab-S: Cycle 2 Chemotherapy Guidelines for continuous IV infusion over 28 days were added to include "IV bag will be changed every 24 - 96 hours **or every 168 hours (7 days), depending on the details of the infusion preparation**".
4.9.1.6	73	Replace the abbreviation "VP16" with the generic name "etoposide" for consistency with other sections of the protocol.
4.9.2	73	Updated section to add an infusion time of administration for cyclophosphamide, etoposide and thiotepa and route of administration (intravenously) for etoposide and fludarabine.
4.9.3	73-75	Preparative Regimen Administration Tables were updated to add infusion time information for drugs.
4.10.3, 4.11.3, 4.12.3	Multiple	Indicated that mercaptopurine is given once daily.

4.11.1	80-81	Updated section for Criteria to Begin and During Continuation Therapy for all LR patients given therapy during Continuation 1 and Continuation 2.
4.11.3	84	Indicated that cytarabine is given once daily.
4.14.4	91	Updated mercaptopurine dosing instructions.
4.15.3	93	Details pertaining to the Blinatumomab Block: Cycle 1 (Patients in Arm D) Chemotherapy for continuous IV infusion over 28 days were added to include "IV bag will be changed every 24 - 96 hours **or every 168 hours (7 days), depending on the details of the infusion preparation**".
4.16.3	94	Details pertaining to the Blinatumomab Block: Cycle 2/3: Chemotherapy Guidelines for continuous IV infusion over 28 days were added to include "IV bag will be changed every 24 - 96 hours **or every 168 hours (7 days), depending on the details of the infusion preparation**".
5.1	96-97	Updated section regarding dose modification for Asparaginase [Pegaspargase (PEG-Asparaginase) or Erwinia] toxicities.
5.2	97-101	Updated section regarding dose modification for Blinatumomab toxicities.
5.3	101	Updated section regarding dose modification for Cyclophosphamide toxicities.
5.4	102	Updated section regarding dose modification for Cytarabine (ARAC) toxicities.
5.5	102-103	Updated section regarding dose modification for Anthracycline-Mitoxantrone toxicities.
5.7	103-105	Updated section regarding dose modification for Intrathecal Methotrexate/Triple Intrathecal Therapy toxicities.
5.8.1	106-107	• Added link regarding Voraxaze product availability. • Updated link for COG Supportive care Guidelines for TMP/SMX substitutions.
5.10	111-112	Updated section regarding dose modification for Dexamethasone toxicities.
5.12	112-113	Updated link to COG extravasation reference.
6.1	117-128	The following sections were updated for Blinatumomab: • Drug Monograph • Updated guidelines for pregnancy • Formulation and Stability • Volume Calculation Table • IV infusion and infusion set details • Agent Ordering • Agent Accountability • Useful Links and Contacts
6.2	129-131	Updated Drug Monograph for Asparaginase Erwinia chrysanthemi to current template.
6.4	133-135	Updated Drug Monograph for Cyclosporin A to current template.
6.9	144-146	Updated Drug Monograph for Fludarabine to current template.

6.12	150-151	Updated Drug Monograph for Mercaptopurine to current template.
6.13	151-155	The following sections were updated for Methotrexate: • Drug Monograph • Formulation and Stability • Oral administration • For IM/IV use
6.15	157-160	Updated link for an approved medication guide for Mycophenolate Mofetil.
6.16	161-163	Updated Drug Monograph for Pegaspargase to current template.
6.17	163-166	Updated Drug Monograph for Tacrolimus to current template.
6.19	167-169	Updated Drug Monograph for Thiotepa to current template.
7.1b	173	The Required and Optional Clinical, Laboratory and Disease Evaluations table for LR Patients was updated for maintenance and post-therapy.
7.2	176	Added a footnote to provide instruction in the event that the infusion is interrupted.
9.1.1	177	Added that the primary analyses of DFS will include all randomized patients.
9.1.2	177	Updated section regarding Secondary Objective to add "**OS is defined as time from start of randomization to death or last date of contact.**"
9.2.3	180-184	Added section to discuss extension of accrual duration for both the LR and HR/IR cohort.
9.2.3.1	180-182	Added section to discuss the LR cohort accrual extension.
9.2.3.2	182-184	Added section to discuss the LR cohort accrual extension.
9.2.3.3	184	Added section to discuss accrual target and timelines.
9.3.1.1	184-186	• For HR/IR, section was updated to discuss the original protocol design and extended accrual duration/sample size. • Section amended statistical monitoring plan and power for DFS.
9.3.1.2	186-188	Paragraph added to discuss power of the analysis of OS with the extended accrual durations.
9.3.1.5	189	Paragraph added to discuss safety monitoring rule with increased accrual.
9.3.2.1	191-192	• For LR, section was updated to discuss the original protocol design and extended accrual duration/sample size. • Section amended statistical monitoring plan and power for DFS.
9.3.2.2	192	Paragraph added to discuss power of the analysis of OS with the extended accrual durations.
9.3.2.3	193	Paragraph added to discuss safety monitoring rule with increased accrual.
9.3.3.3	195	Paragraph added to discuss monitoring of toxic death and GVHD.
9.3.4	196	Table for toxic death monitoring boundary was updated.
9.3.7	196-197	Section was added to discuss monitoring for infection rate of the 7-day bag changes in blinatumomab administration.
9.4	197-198	The gender and minority table has been updated for amendment #8.

11.4	201-203	The following sections were updated for Special Situations for Expedited Reporting: • Death • ~~Fetal Death~~ was changed to "**Pregnancy Loss**" • "**Pregnancy Loss (Fetal Death)**" • Death Neonatal
11.8	205	Updated section regarding General Instructions for Expedited Reporting via CTEP-AERS.
11.12	208-209	Updated the wording of the Adverse Events Reporting by Treatment Phase table for clarity.
13.0	212	Updated text box to remove mention of AALL05B1 since that study is now closed.
13.1	213	Updated the shipping address for the COG Leukemia Biospecimen Bank.
13.2	213	Link for a list of COG approved cytogenetics labs**.**
13.5	216	Updated section for Sample Collection Procedures for Blinatumomab Pharmacodynamics.
14.1.1	221	Updated link for IROC website.
14.10.1.2	226	Updated section to indicate that calculated and measured doses to select anatomical points **must** be submitted to IROC RI as part of quality assurance documentation.
APPENDIX I	230-233	• Updated link to supportive care guidelines. • Updated link for Guidelines for preventing infectious complications among hematopoietic stem cell transplant recipients. • Updated link for COG Fever and Neutropenia Guidelines. • Updated section link for COG Endorsed guidelines on prevention and management of CINV.
APPENDIX II-A	234	Indicated that dexamethasone is given **BID**.
APPENDIX II-B	236	Indicated that dexamethasone is given **BID**. Indicated that leucovorin is given **Q6H**.
APPENDIX II-D	240	Added details to the Blinatumomab Block - Cycle 1 (HR/IR Patients in Arm B) table for Blinatumomab drug information to read "Blinatumomab (BLIN) **(IND#117467) Do not use commercial supply**"
APPENDIX II-E	242	Added details to the Blinatumomab Block - Cycle 2 (HR/IR Patients in Arm B) table for Blinatumomab drug information to read "Blinatumomab (BLIN) **(IND#117467) Do not use commercial supply**"
APPENDIX II-F	243	Added details to Blinatumomab-S: Cycle 1 (Treatment Failure) table for Blinatumomab drug information to read "Blinatumomab (BLIN) **(IND#117467) Do not use commercial supply**" and updated the days when Dexamethasone should be administered.
APPENDIX II-G	245	Added details to the Blinatumomab-S: Cycle 2 (Treatment Failure) table for Blinatumomab drug information to read "Blinatumomab (BLIN) **(IND#117467) Do not use commercial supply**"
APPENDIX II-I	248-249	• Indicated that dexamethasone is given **BID**. • Indicated that mercaptopurine is given daily.

		• Indicated that Day 22 PO methotrexate is given Q6H x 4 doses. • Indicated that leucovorin is given to patients with CNS3 disease only. • Updated methotrexate dosage to read "25 mg/m²/dose Q6H **x 4 doses**" • Added additional dose lines for PO MTX CNS1/2 ONLY on Day 22.
APPENDIX II-J	250	Indicated that mercaptopurine is given daily and that methotrexate is given weekly.
APPENDIX II-K	252	• Indicated that dexamethasone is given BID. • Deleted bullet point ~~d. Absolute lymphocyte count with T and B subset quantification~~ for: - Observations column - Studies column on day 21
APPENDIX II-L	253	Indicated that mercaptopurine is given daily and that methotrexate is given weekly.
APPENDIX II-M	255	Added details to Blinatumomab Block - Cycle 1 (LR Patients in Arm D) table for Blinatumomab drug information to read "Blinatumomab (BLIN) **(IND#117467) Do not use commercial supply**"
APPENDIX II-N	257	Added details to Blinatumomab Block - Cycle 2 and 3 (LR Patients in Arm D) table for Blinatumomab drug information to read "Blinatumomab (BLIN) **(IND#117467) Do not use commercial supply**"
APPENDIX XIII	291-294	Updated information regarding CTEP And CTSU Registration Procedures.

AALL1331 SUMMARY OF CHANGES

INFORMED CONSENT DOCUMENT 1: RE-INDUCTION (BLOCK 1) THERAPY FOR ALL SUBJECTS

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

Section	Page	Comments
All	Throughout	Protocol version date has been updated.
How many people will take part in the study	9	The total accrual has been increased from 598 to 700.
Where can I get more information?	12	Updated link to the COF Family Handbook for Children with Cancer.
Asparaginase Erwinia	15	The possible side effects for Asparaginase Erwinia have been updated to match the current template.
IT Methotrexate	16	The possible side effects for IT Methotrexate have been updated to match the current template.
Intrathecal Triples	17	The possible side effects for Intrathecal Triples have been updated to match the current template. Corrected the spelling of the word "seizures" under "Rare and Serious".
Mitoxantrone	18	The possible side effects for Mitoxantrone have been updated to match the current template.
Dexamethasone	19	The possible side effects for Dexamethasone have been updated to match the current template.

Vincristine	20	The possible side effects for Vincristine have been updated to match the current template.
Pegaspargase	21	The possible side effects for Pegaspargase have been updated to match the current template.

AALL1331 SUMMARY OF CHANGES
INFORMED CONSENT DOCUMENT 2: HIGH RISK/INTERMEDIATE RISK
In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

Section	Page	Comments
All	Throughout	Protocol version date has been updated.
How many people will take part in the study	12	The total accrual has been updated from 598 to 700. The total number on this arm has been updated from 170 to 220.
Cyclophosphamide	22	The possible side effects for Cyclophosphamide have been updated to match the current template.
Dexamethasone	25	The possible side effects for Dexamethasone have been updated to match the current template.
Asparaginase Erwinia	26	The possible side effects for Asparaginase Erwinia have been updated to match the current template.
Filgrastim	28	The possible side effects for Filgrastim have been updated to match the current template.
Intrathecal Triples	30	The possible side effects for Intrathecal Triples have been updated to match the current template.
Mercaptopurine	32	The possible side effects for Mercaptopurine have been updated to match the current template.
IT Methotrexate	33	The possible side effects for IT Methotrexate have been updated to match the current template.
IV Methotrexate	34	The possible side effects for IV Methotrexate have been updated to match the current template.
Mycophenolate Mofetil	35	The possible side effects for Mycophenolate Mofetil have been updated to match the current template.
Pegaspargase	36	The possible side effects for Pegaspargase have been updated to match the current template.
Thiotepa	38	The possible side effects for Thiotepa have been updated to match the current template.
Vincristine	39	The possible side effects for Vincristine have been updated to match the current template.

AALL1331 SUMMARY OF CHANGES
INFORMED CONSENT DOCUMENT 3: LOW RISK
In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

Section	Page	Comments
All	Throughout	Protocol version date has been updated.
Treatment Schema for LR Patients	4	Added an ^ in Block 2 to indicate that patients with persistent testicular involvement after Block 1 will receive testicular radiation.
Treatment that is research Standard Continuation	7	Clarified that Standard Continuation is 8 weeks.

Treatment that is research Standard Continuation 2	8	Clarified that Standard Continuation 2 is 8 weeks.
Research Study Tests and Procedures MRD	9	Clarified that MRD will be drawn after Block 2 of treatment.
How many people will take part in the study	12	The total accrual has been updated from 598 to 700. The total number on this arm has been updated from 206 to 236.
Risks of Chemotherapy Drugs and Radiation	18	Added a paragraph regarding drugs or supplements that may interact with the treatment plan.
Cyclophosphamide	18	The possible side effects for Cyclophosphamide have been updated to match the current template.
Dexamethasone	20	The possible side effects for Dexamethasone have been updated to match the current template.
Asparaginase Erwinia	21	The possible side effects for Asparaginase Erwinia have been updated to match the current template.
Intrathecal Triples	23	The possible side effects for Intrathecal Triples have been updated to match the current template.
IT Methotrexate	25	The possible side effects for IT Methotrexate have been updated to match the current template.
IV or PO Methotrexate	26	The possible side effects for IV or Oral Methotrexate have been updated to match the current template.
Mercaptopurine	27	The possible side effects for Mercaptopurine have been updated to match the current template.
Pegaspargase	28	The possible side effects for Pegaspargase have been updated to match the current template.
Thioguanine	29	The possible side effects for Thioguanine have been updated to match the current template.
Vincristine	30	The possible side effects for Vincristine have been updated to match the current template.

AALL1331 SUMMARY OF CHANGES

INFORMED CONSENT DOCUMENT 4: THERAPY FOR NON-RESPONDERS

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

Section	Page	Comments
All	Throughout	Protocol version date has been updated.
Treatment with Blinatumomab	5	Added an asterisk * to indicate that dexamethasone is only given during Cycle 1.
How many people will take part in the study	9	The total accrual has been increased from 598 to 700. The number of patients deemed as treatment failures after Block 1 or Block 2 has been increased from 60 to 70.
Cyclophosphamide	20	The possible side effects for Cyclophosphamide have been updated to match the current template.
Dexamethasone	22	The possible side effects for Dexamethasone have been updated to match the current template.
Filgrastim	24	The possible side effects for Filgrastim have been updated to match the current template.
Intrathecal Triples	26	Deleted the drug risk insert table for Intrathecal Triples from Attachment #2.

Mercaptopurine	26	The possible side effects for Mercaptopurine have been updated to match the current template.
IT Methotrexate	27	The possible side effects for IT Methotrexate have been updated to match the current template.
IV or PO Methotrexate	28	The possible side effects for IV or Oral Methotrexate have been updated to match the current template.
Mycophenolate Mofetil	29	The possible side effects for Mycophenolate Mofetil have been updated to match the current template.
Thiotepa	31	The possible side effects for Thiotepa have been updated to match the current template.
Vincristine	32	The possible side effects for Vincristine have been updated to match the current template.

AALL1331 SUMMARY OF CHANGES

INFORMED CONSENT DOCUMENT 5: CONSENT FOR ADDITIONAL MARROW

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

Section	Page	Comments
All	Throughout	Protocol version date has been updated.

AALL1331 SUMMARY OF CHANGES: Case Report Forms (CRFs)

Eligibility CRF

1. Was patient consented to and enrolled on the most current version of protocol?
    a. Edit Check update
    b. Help text update
2. Is patient diagnosed with first relapse of B-Lymphoblastic Leukemia (B-ALL)?
    a. Help text update

CHILDREN'S ONCOLOGY GROUP

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Memo

To: Principal Investigators and Clinical Research Associates

From: Arshi Reyaz, Protocol Coordinator

Re: Amendment #9

Study: **AALL1331,** *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: 03/11/2019

AMENDMENT

____ Change of Participants/Coordinator(s)
__X__ Editorial or Administrative Changes
__X__ Scientific Changes
____ Therapy Changes
____ Eligibility Changes
__X__ Informed Consent Changes

STATUS CHANGE

____ Reactivation

REQUIRED ACTIONS FOR COG REGULATORY COMPLIANCE:

A. For sites utilizing a local IRB:

Local IRB approval is due within **90** days of the date on this memo.

B. For sites utilizing the Pediatric CIRB:

Sites are required to implement this study amendment within **30** days of the CIRB posting date of this amendment. New patients must be consented, enrolled **and treated with** this amended version of the protocol 30 days after the CIRB posting date.

The study has been amended in response to CTEP's request for amendment (RA) from Dr. Elad Sharon (sharone@mail.nih.gov). The protocol and consent forms have been revised to update new and/or modified risk information associated with Blinatumomab. The CAEPR list for Blinatumomab is revised from version 2.3 to version 2.4 along with the associated risk information in the ICDs.

CHILDREN'S ONCOLOGY GROUP

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AALL1331 SUMMARY OF CHANGES
SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

Section	Page	Comments
All	Throughout	Version date and amendment number have been updated.

6.1	117-122	Updated Blinatumomab CAEPR from version 2.3 to version 2.4 to include the following changes:
		
		• The SPEER grades have been updated.
		• The section below utilizes CTCAE 5.0 language unless otherwise noted.
		
		• Added New Risk:
		  ◦ Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution: Injury poisoning and procedural complications - Other (overdose)
		
		• Increase in Risk Attribution:
		  ◦ Changed to Likely from Less Likely: Infection; Neutrophil count decreased
		
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
		  ◦ Added: Sinus tachycardia
		
		• Provided Further Clarification:
		  ◦ Footnote #9 has been updated and now reads: "Blinatumomab (AMG 103) is known to cause a variety of nervous system disorders which may include: Ataxia, Cognitive disturbance, Concentration impairment, Depressed level of consciousness, Dizziness, Dysphagia, Dysarthria, Dysesthesia, Dysphasia, Encephalopathy, Facial nerve disorder, Headache, Lethargy, Memory impairment, Paresthesia, Peripheral sensory neuropathy, Seizure, Somnolence, Syncope, Transient ischemic attacks, Tremor, Voice alteration, Nervous system disorders - Other (allodynia), Nervous Systems disorders - Other (cerebellar syndrome), Nervous system disorders - Other (dysgraphia), Nervous system disorders - Other (epilepsy), Nervous system disorders - Other (facial palsy), Nervous system disorders - Other (hemiparesis), Nervous system disorders - Other (hypertonia), Nervous system disorders - Other (hypotonia), Nervous system disorders - Other (pleocytosis), and Nervous system disorders - Other (polyneuropathy). Additionally, symptoms of some nervous system disorders are adverse events under the PSYCHIATRIC DISORDERS SOC and may include: Agitation, Anxiety, Confusion, Hallucinations, Personality change, and Psychosis".
		  ◦ Infusion related reaction, previously listed under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC (CTCAE 4.0 language), is now listed under the INJURY, POISONING AND PROCEDURAL COMPLICATIONS SOC.
		  ◦ Investigations - Other (blood lactate dehydrogenase increased) (CTCAE 4.0 language) is now reported as Blood lactate dehydrogenase increased.
		  ◦ Musculoskeletal and connective tissue disorder - Other (muscle spasms) (CTCAE 4.0 language) is now reported as Muscle cramp.

		• Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain) (CTCAE 4.0 language) is now reported as Oropharyngeal pain. • Conjunctivitis, previously listed under the EYE DISORDERS SOC (CTCAE 4.0 language), is now listed under the INFECTIONS AND INFESTATIONS SOC. • Metabolism and nutrition disorders - Other (fluid overload) is now reported as Metabolism and nutrition disorders - Other (fluid retention). • Metabolism and nutrition disorders - Other (hyperphosphatemia) (CTCAE 4.0 language) is now reported as Hyperphosphatemia. • Syncope is now listed as part of Nervous system disorders - Other • Periorbital edema, previously listed under the SKIN AND SUBCUTANEOUS TISSUE DISORDERS SOC (CTCAE 4.0 language), is now listed under the EYE DISORDERS SOC.
6.1	122 122 127 128	The following sections were updated for Blinatumomab: • Pregnancy and lactation • Formulation and Stability • Guidelines for administration • Agent Accountability
11.4.3	201	Updated second bullet point under Death for Special Situations for Expedited Reporting to read "**Newborn death occurring** ~~A disorder characterized by cessation of life~~ during the first 28 days **after birth** ~~of life~~.
11.4.6	202	Updated hyperlink and fax number under Pregnancy, Pregnancy Loss, and Death Neonatal for Special Situations for Expedited Reporting.
11.8	206	Updated fax number for General Instructions for Expedited Reporting via CTEP-AERS.

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: CONSENT FOR RE-INDUCTION (BLOCK 1) THERAPY FOR ALL SUBJECTS

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

Section	Page	Comments
All	Throughout	Version date has been updated.

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: CONSENT FOR ALL HIGH-RISK AND INTERMEDIATE-RISK PATIENTS ELIGIBLE TO TAKE PART IN HR/IR RANDOMIZATION

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

Section	Page	Comments
All	Throughout	Version date has been updated.

What side effects or risks can I expect from being in the study?	9-11	1. Updated section “Risks of Study” to add the following:
		• **May not be able to take part in future studies**
		• Some side effects may be **mild. Other side effects may be very** serious and may even result in death.
		
		2. Updated Blinatumomab risk insert as follows:
		
		2A) Under common some may be serious:
		• Updated heading to read “In 100 people receiving blinatumomab **(AMG 103)**, more than 20 and up to 100 may have:”
		• Updated table text to add and delete risk information as follows:
		  • **Infection, especially when white blood cell count is low**
		
		2B) Under occasional, some may be serious:
		• Updated heading to read “In 100 people receiving blinatumomab **(AMG 103)**, from 4 to 20 may have:”
		• Updated table text to add and delete risk information as follows:
		  • Blood clot **which may cause swelling, pain, shortness of breath**
		  • ~~Infection, especially when white blood cell count is low~~
		  • Muscle ~~spasm or~~ weakness
		  • Change(s) in thinking patterns **or**~~,~~ voice ~~or personality~~
		  • Dizziness**, confusion**
		  • Abnormal body movement~~, difficulty talking~~
		  • **Worry**
		  • Fluid in the body **which may cause low blood pressure, shortness of breath, swelling of ankles**
		  • High blood pressure which may cause **headaches, dizziness,** blurred vision
		
		2C) Under rare and serious:
		• Updated heading to read “In 100 people receiving blinatumomab **(AMG 103)**, 3 or fewer may have:”
		• Updated table text to add and delete risk information as follows:
		  • **Damage to organs (brain, lungs, others) which may cause shortness of breath**
		  • **Restlessness**
		  • **Sensing things that are not there**
		  • **Change in personality**
		  • ~~Swelling of the lungs which may cause shortness of breath~~

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: CONSENT FOR ALL LOW-RISK PATIENTS ELIGIBLE TO TAKE PART IN LR RANDOMIZATION

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

Section	Page	Comments
All	Throughout	Version date has been updated.

What side effects or risks can I expect from being in the study?	10-12	1. Updated section "Risks of Study" to add the following:
		• **May not be able to take part in future studies**
		• Some side effects may be **mild. Other side effects may be very** serious and may even result in death.
		
		2. Updated Blinatumomab risk insert as follows:
		
		2A) Under common some may be serious:
		• Updated heading to read "In 100 people receiving blinatumomab **(AMG 103)**, more than 20 and up to 100 may have:"
		• Updated table text to add and delete risk information as follows:
		  • **Infection, especially when white blood cell count is low**
		
		2B) Under occasional, some may be serious:
		• Updated heading to read "In 100 people receiving blinatumomab **(AMG 103)**, from 4 to 20 may have:"
		• Updated table text to add and delete risk information as follows:
		  • Blood clot **which may cause swelling, pain, shortness of breath**
		  • ~~Infection, especially when white blood cell count is low~~
		  • Muscle ~~spasm or~~ weakness
		  • Change(s) in thinking patterns **or**~~,~~ voice ~~or personality~~
		  • Dizziness**, confusion**
		  • Abnormal body movement~~, difficulty talking~~
		  • **Worry**
		  • Fluid in the body **which may cause low blood pressure, shortness of breath, swelling of ankles**
		  • High blood pressure which may cause **headaches, dizziness,** blurred vision
		
		2C) Under rare and serious:
		• Updated heading to read "In 100 people receiving blinatumomab **(AMG 103)**, 3 or fewer may have:"
		• Updated table text to add and delete risk information as follows:
		  • **Damage to organs (brain, lungs, others) which may cause shortness of breath**
		  • **Restlessness**
		  • **Sensing things that are not there**
		  • **Change in personality**
		  • ~~Swelling of the lungs which may cause shortness of breath~~

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: CONSENT FOR PATIENTS WHO DID NOT RESPOND TO THERAPY AFTER BLOCK 1 (ALL PATIENTS) OR BLOCK 2 (HR/IR PATIENTS ON TREATMENT ARM A)

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

Section	Page	Comments
All	Throughout	Version date has been updated.

What side effects or risks can I expect from being in the study?	6-8	1. Updated section "Risks of Study" to add the following:
		• **May not be able to take part in future studies**
		• Some side effects may be **mild. Other side effects may be very** serious and may even result in death.
		
		2. Updated Blinatumomab risk insert as follows:
		
		2A) Under common some may be serious:
		• Updated heading to read "In 100 people receiving blinatumomab **(AMG 103)**, more than 20 and up to 100 may have:"
		• Updated table text to add and delete risk information as follows:
		  ◦ **Infection, especially when white blood cell count is low**
		2B) Under occasional, some may be serious:
		• Updated heading to read "In 100 people receiving blinatumomab **(AMG 103)**, from 4 to 20 may have:"
		• Updated table text to add and delete risk information as follows:
		  ◦ Blood clot **which may cause swelling, pain, shortness of breath**
		  ◦ ~~Infection, especially when white blood cell count is low~~
		  ◦ Muscle ~~spasm or~~ weakness
		  ◦ Change(s) in thinking patterns **or**~~,~~ voice ~~or personality~~
		  ◦ Dizziness**, confusion**
		  ◦ Abnormal body movement~~, difficulty talking~~
		  ◦ **Worry**
		  ◦ Fluid in the body **which may cause low blood pressure, shortness of breath, swelling of ankles**
		  ◦ High blood pressure which may cause **headaches, dizziness,** blurred vision
		
		2C) Under rare and serious:
		• Updated heading to read "In 100 people receiving blinatumomab **(AMG 103)**, 3 or fewer may have:"
		• Updated table text to add and delete risk information as follows:
		  ◦ **Damage to organs (brain, lungs, others) which may cause shortness of breath**
		  ◦ **Restlessness**
		  ◦ **Sensing things that are not there**
		  ◦ **Change in personality**
		  ◦ ~~Swelling of the lungs which may cause shortness of breath~~

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: CONSENT FOR COLLECTION OF ADDITIONAL BONE MARROW

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

Section	Page	Comments
All	Throughout	Version date has been updated.

AALL1331 SUMMARY OF CHANGES

SUMMARY OF CHANGES: Case Report Forms (CRFs)

- The protocol version date has been updated on all CRFs.
- **Eligibility CRF**
  1. Was patient consented to and enrolled on the most current version of protocol?
     a. Edit Check update
     b. Help text update

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

Memo

To: Principal Investigators and Clinical Research Associates

From: Christine Petrossian, Protocol Coordinator

Re: Amendment #10A

Study: **AALL1331,** *Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)*

Date: February 24, 2020

NOTE: THIS STUDY WAS CLOSED TO ACCRUAL EFFECTIVE 09/30/2019

AMENDMENT		**STATUS CHANGE**	
____	Change of Participants/Coordinator(s)	____	Reactivation
X	Editorial or Administrative Changes		
____	Scientific Changes		
X	Therapy Changes		
____	Eligibility Changes		
X	Informed Consent Changes		

REQUIRED ACTIONS FOR COG REGULATORY COMPLIANCE:

A. For sites utilizing a local IRB:

Local IRB approval is due within **90** days of the date on this memo.

B. For sites utilizing the Pediatric CIRB:

Sites are required to implement this study amendment within **30** days of the CIRB posting date of this amendment. New patients must be consented, enrolled **and treated with** this amended version of the protocol 30 days after the CIRB posting date.

Enclosed please find Amendment #10A to protocol AALL1331. All changes made to the protocol since Amendment #9 are detailed in the list of changes below and are contained in the tracked version of Amendment #10A.

The study has been amended in response to CTEP's request for rapid amendment (RRA) from Dr. Elad Sharon (sharone@mail.nih.gov). The protocol and consent forms have been revised to update new and/or modified risk information associated with Blinatumomab. The CAEPR list for Blinatumomab is revised from version 2.4 to version 2.5 along with the associated risk information in the ICDs. Refer to the action letter that was posted on 12/20/2019 on the protocol web page.

This amendment also describes the closure of the HR/IR randomization that occurred on September 18, 2019 as a result of a recent report that recommends treatment with blinatumomab on Arm B over standard chemotherapy on Arm A. Changes were also made in response to a request for amendment from CTEP to remove the in-line filter requirement during the administration of blinatumomab 7-day IV bags.

Several other administrative changes have been made; specific changes are detailed below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked in the protocol but not specified below.

Please Note: The CTEP amendment approval letter was issued with recommendations, which will be addressed in a forthcoming amendment.

TRAINING SLIDES AND HOME HEALTH CARE MANUAL

The AALL1331 Training Module, Prep & Admin Training slides and Home Health Care Manual have been revised to reflect changes made with this amendment and are posted on the protocol web page. The completion of the trainings is recommended/not required. Sites are strongly encouraged to review updated training modules as they become available, and are expected to remain current on study training.

AALL1331 SUMMARY OF CHANGES: PROTOCOL DOCUMENT

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

Section	Page	Comments
All	Throughout	Version date and amendment number have been updated.
Title page	1	Added study closure date: **09/30/19**
Table of Contents	3-11	Updated TOC due to repagination.
Study Committee	14	Updated contact information for Dr. Mini Devidas
Abstract	15	Added note about closure of the HR/IR randomization and further instructions for patients randomized to HR/IR arms.
Experimental Design Schema	16	• Removed treatment details related to Arm A and Callback 2 • Added note: **Randomization and accrual to the HR/IR arms is permanently closed effective 09/18/2019. All HR/IR patients receiving treatment on Arm A prior to Amendment #10 will receive blinatumomab in place of standard chemotherapy.**
1.0	17	Added note about closure of the HR/IR randomization to relevant aims.
2.2.3	22	Added note about closure of the HR/IR randomization and further instructions for patients randomized to HR/IR arms.

2.2.10	27	Added section that includes rationale for closure of HR/IR randomization
3.1.5	30	Added note about closure of the HR/IR randomization and further instructions for patients randomized to HR/IR arms.
3.1.6 3.1.7	31-32	Revised to inform that HR/IR patients are not eligible for post-Induction treatment on AALL1331 and removed details of callbacks related to the HR/IR randomization
4.1	40	Revised to inform that HR/IR patients are no longer eligible for post-Induction treatment on AALL1331 and the HR/IR randomization was closed 09/18/2019.
4.1.1.1	41-42	Added note: **Effective 09/18/2019, HR/IR patients are not eligible for post-Induction therapy on AALL1331 and will be removed from protocol therapy. Patients receiving therapy on Arm A prior to Amendment #10 who have not yet received Day 22 treatment on Block 3 will be offered the opportunity to cross over to Arm B to receive blinatumomab.**
4.2.7	47	Removed details of procedures related to HR/IR randomization and added note about closure of the HR/IR randomization and further instructions for patients randomized to HR/IR arms.
4.3 4.4	48-52	Removed HR/IR patients on Arm A from treatment sections since they are no longer eligible to receive post-Induction treatment on AALL1331.
4.5 4.7 4.15	55 61 90	Per the RRA, made the following edits: • Added that for patients treated for MRD-positive B-cell precursor ALL, hospitalization is recommended for the first **9** days of the first cycle, rather than the first ~~3~~ days of the first cycle, as previously suggested. • Added the language, **manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC).** • Added suggestion to **administer corticosteroids should be administered for severe or life threatening cytokine release syndrome.**
4.6, 4.8 4.16	58 64 93	Updated treatment plan to include Dexamethsone pre-medication is not required for the following cycles- • Blinatumomab Block: Cycle 2 (HR/IR Arm B) • Blinatumomab-S Cycle 2 (Salvage Therapy) • Blinatumomab Block: Cycle 2/3 (LR Patients in Arm D)

4.6, 4.8 4.16	58 64 92	Per the RRA, made the following edits: • Added the language, **manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC).** • Added suggestion to **administer corticosteroids for severe or life-threatening cytokine release syndrome.**
5.1	94	Added leading zero to the listed therapeutic dose of asparaginase.
6.1	115-125	• Updated Blinatumomab monograph date • Added language to indicate that an in-line filter is not required **during the administration of blinatumomab 7-day IV bag. This is to alleviate the IV pressure or backflow into the IV line during the IV infusion of 7-day bag.**
6.1	115-125	Per the RRA, inserted an updated blinatumomab CAEPR (Version 2.5, revised September 4, 2019). The following changes were made since the previous CAEPR: • The SPEER grades have been updated. • The footnotes have been reordered. • Added New Risk: o Rare but Serious: Blood and lymphatic system disorders - Other (hematophagic histiocytosis); Blood and lymphatic system disorders - Other (lymphadenopathy) o Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution: Adult respiratory distress syndrome; Amnesia; Anal mucositis; Cardiac troponin I increased; Delirium; Dysphagia; Electrocardiogram QT corrected interval prolonged; Facial muscle weakness; Hypercalcemia; Left ventricular systolic dysfunction; Leukemia secondary to oncology chemotherapy; Lymphocyte count increased; Malaise; Metabolism and nutrition disorders - Other (fluid overload); Multi-organ failure; Muscle weakness left-sided; Nervous system disorders - Other (difficulty following commands); Neuralgia; Optic nerve disorder; Papilledema; Photophobia; Psychiatric disorders - Other (altered mental status); Pulmonary edema; Restlessness; Treatment related secondary malignancy; Vascular access complication • Increase in Risk Attribution: o Changed to Less Likely from Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution: Generalized edema; Hyperuricemia o Changed to Rare but Serious from Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution: Injury, poisoning and procedural complications - Other (overdose) • Decrease in Risk Attribution:

		o Changed to Less Likely from Likely: Diarrhea o Changed to Rare from Less Likely: Tumor lysis syndrome o Changed to Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution from Less Likely: Abdominal distension; Hematuria; Leukocytosis; Muscle cramp; Pleural effusion • Provided Further Clarification: o Footnote #7 has been added: "Overdoses have been observed. Overdoses resulted in adverse reactions, which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care. Consider re-initiation of blinatumomab at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion." o Metabolism and nutrition disorders - Other (fluid retention) is now reported as generalized edema. Skin and subcutaneous tissue disorders - Other (petechiae) is now reported as Purpura.
6.2 6.6 6.8 6.11 6.13	127-151	Minor updates to the following drug monographs: • ASPARAGINASE Erwinia chrysanthemi • Dexamethasone • FILGRASTIM, TBO-FILGRATIM, FILGRATIM-SNDZ • leucovorin calcium • Methotrexate
6.15	156	Updated occasional toxicity table for Mycophenolate Mofetil to remove paresthesia.
8.1	174	Added off protocol criteria for patients risk stratified as HR/IR.
9.3	184-186	Included description of analysis that determined favorable results on Arm B and closure of the HR/IR randomization.
14.0	218	Revised to remove language about HR/IR randomization
Appendix II-A	233-234	• Revised to state that HR/IR patients are not eligible to continue to post-Induction treatment on AALL1331 and will be removed from protocol therapy at the end of Induction. • Corrected Block 1 TDM to remove observation "d" (bone marrow for immunophenotyping) on Day 29.
Appendix II-B	235-236	Removed HR/IR patients on Arm A from treatment sections since they are no longer eligible to receive post-Induction treatment on AALL1331.
Appendix II-B	235	Corrected Block 2 TDM footnote to read "^ All patients with M1 marrow **are recommended to await count recovery to** ~~must have~~ ANC ≥ 500/μL and platelets ≥ 50,000/μL prior to beginning Day 8 ID MTX. **Day 8 treatment must begin no later than 14 calendar days after giving the Day 1 vincristine and dexamethasone to continue to receive protocol therapy** ~~Day 8 treatment must begin no later than 14 calendar days after risk assignment for patient to continue to receive protocol therapy~~." The change was made to keep the roadmap consistent with treatment Section 4.2.7.
Appendix II-C	236-237	Removed details related to HR/IR patients on Arm A from treatment sections since they are no longer eligible to receive post-Induction treatment on AALL1331.

Appendix II-I	246	Corrected TDM for Continuation 1/2 Leucovorin PO important notes section to read "**CNS1/2** ~~CNS3~~ ONLY Begin 48 hrs after the START of day 22 PO Methotrexate" to keep it consistent with Section 4.11.3.
Appendix X	272-277	Revised to include additional procedures and methods of analysis for blinatumomab pharmacodynamics correlative study.
Appendix XIII	291	The CTSU registration procedures were revised to delete the paragraph regarding protocol-specific DTL since it does not apply to this study.
Appendix XIV	293-300	Updated Possible Drug Interactions tables.

AALL1331 SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENTS

CONSENT 1: CONSENT FOR RE-INDUCTION (BLOCK 1) THERAPY FOR ALL SUBJECTS

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

Section	Page	Comments
All	Throughout	Version date has been updated.
What will happen on this study that is research?	5	Updated Block 1 Therapy footnote to read "If an allergy develops, 6 injections of a different form of Asparaginase (called **Asparaginase Erwinia** ~~Erwinia L-asparaginase~~) may be substituted for each dose ~~for~~ of pegaspargase in future cycles"
What side effects or risks can I expect from being in the study?	8-9	Updated Reproductive Risks section to add "**If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately.**"
How long is this study?	9	Updated section to read "We would like to continue to follow your health ~~status~~ for about 10 years after you start the study."
Possible Side Effects of Methotrexate	16	• Added **and up to 100** when describing number of people with common side effects • Removed ~~cause tiredness~~ from occasional side effects • Moved bullet point for "difficulty with speaking" down within occasional side effects • Moved bullet point "damage to the brain which could lead to coma" up within rare side effects
Possible Side Effects of Dexamethasone	19	• Removed ~~the~~ • Removed an unnecessary comma
Possible Side Effects of Pegaspargase	21	• Removed ~~cause tiredness~~ from occasional side effects • Removed ~~Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat~~ from rare side effects

CONSENT 2: CONSENT FOR ALL HIGH-RISK AND INTERMEDIATE-RISK PATIENTS ELIGIBLE TO TAKE PART IN HR/IR RANDOMIZATION

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

Section	Page	Comments
All	Throughout	Version date has been updated.
Title page	1	Due to closure of the HR/IR randomization, added note: **THIS CONSENT FORM ONLY APPLIES TO PATIENTS ENROLLED BEFORE AMENDMENT #10.**
What will happen on this study that is research?	7	Per the RRA request, revised to state the patient may be hospitalized during the first **9 days** of the first blinatumomab cycle, instead of ~~3 days~~.
What side effects or risks can I expect from being in the study?	10-11	Added New Risk: • Rare: Damage to the bone marrow which may cause infection, bleeding, may require transfusions Decrease in Risk Attribution: • Changed to Occasional from Common: Diarrhea • Changed to Rare from Occasional: Kidney damage that may require dialysis • Changed to Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Bloating Provided Further Clarification: • Internal bleeding which may cause black tarry stool, blood in vomit, or blood in urine (under Occasional) is now reported as Internal bleeding which may cause black tarry stool, blood in vomit (Rare). • Fluid in the body which may cause low blood pressure, shortness of breath, swelling of ankles (under Occasional) is nor reported as Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles (under Rare). • Damage to the organs (brain, lungs) which may cause shortness of breath (under Rare) is now reported as Damage to organs (brain, lungs) which may cause shortness of breath (under Rare). Damage to the brain or nerves which may result in confusion, restlessness, worry, or sensing things that are not there (under Rare) is now reported as Damage to the brain or nerves (under Rare).
What side effects or risks can I expect from being in the study?	11	Updated Reproductive Risks section to add "**If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately.**"
How long is this study?	12	Updated section to read "We would like to continue to follow your health ~~status~~ for about 10 years after you start the study."

Attachment #1 Treatment and Procedures Common to all Patients receiving SCT for relapsed ALL	17	Corrected bullet point number four under Treatment Plan to read "The leukemia returned in your central nervous system (spinal fluid) and/or the testes 18 months or **more** ~~less~~ after you were first diagnosed with ALL…" to maintain consistency with the protocol.
Possible Side Effects of Cyclophosphamide	22	Added **and up to 100** when describing common side effects
Possible Side Effects of Cyclosporine	23	• Added **and up to 100** when describing common side effects • Removed ~~which may cause~~ from appearing before "headaches" under common side effects
Possible Side Effects of Dexamethasone	25	• Removed ~~the~~ from common side effects • Added **blurred vision** to occasional side effects
Possible Side Effects of Intrathecal Triples	30	Added **and/or confusion** to occasional side effects
Possible Side Effects of Mercaptopurine	32	• Added **in** to appear before "sperm" under occasional side effects • Remove ~~in~~ from appearing before "shortness" under rare side effects
Possible Side Effects of Methotrexate IT	33	• Added **cause** to appear before "changes" under occasional side effects • Moved bullet point for "difficulty with speaking" down within occasional side effects • effects • Removed ~~cause tiredness~~ from occasional side effects • Moved bullet point with "damage to the brain which could lead to coma" up within rare side effects
Possible Side Effects of Methotrexate PO or IV	34	Moved bullet point with "Scarring of the lungs which may cause shortness of breath" up within rare side effects
Possible Side Effects of Mycophenolate Mofetil	35	Removed the following from common side effects: • ~~Low or high levels of certain salts in the body which may require you to take another medicine to correct the salt level~~ • ~~High blood sugar~~ • ~~Increased blood level of liver tests which may mean there has been damage to the liver, may cause yellowing of the skin~~ Added the following from common side effects: • **loss of appetite, heartburn** • **cause tiredness, or may** • **Feeling of "pins and needles" in arms and legs** Removed the following from occasional side effects: • ~~Feeling of "pins and needles" in arms and legs~~ Removed the following from rare side effects: • ~~Scarring of the lungs~~ Added the following from rare side effects: • Replaced ~~earlier~~ with **a prior** • Replaced ~~belly~~ with **stomach**

		• Replaced ~~stomach~~ and ~~belly~~ with **bowels**
Possible Side Effects of Tacrolimus	37	Replaced ~~earlier~~ with **a prior** under rare side effects

CONSENT 3: CONSENT FOR ALL LOW-RISK PATIENTS ELIGIBLE TO TAKE PART IN LR RANDOMIZATION

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

Section	Page	Comments
All	Throughout	Version date has been updated.
What will happen on this study that is research?	7	Per the RRA request, revised to state the patient may be hospitalized during the first **9 days** of the first blinatumomab cycle, instead of ~~3 days~~.
What side effects or risks can I expect from being in the study?	11-12	Added New Risk: • Rare: Damage to the bone marrow which may cause infection, bleeding, may require transfusions Decrease in Risk Attribution: • Changed to Occasional from Common: Diarrhea • Changed to Rare from Occasional: Kidney damage that may require dialysis • Changed to Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Bloating Provided Further Clarification: • Internal bleeding which may cause black tarry stool, blood in vomit, or blood in urine (under Occasional) is now reported as Internal bleeding which may cause black tarry stool, blood in vomit (Rare). • Fluid in the body which may cause low blood pressure, shortness of breath, swelling of ankles (under Occasional) is nor reported as Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles (under Rare). • Damage to the organs (brain, lungs) which may cause shortness of breath (under Rare) is now reported as Damage to organs (brain, lungs) which may cause shortness of breath (under Rare). Damage to the brain or nerves which may result in confusion, restlessness, worry, or sensing things that are not there (under Rare) is now reported as Damage to the brain or nerves (under Rare).
What side effects or risks can I expect from being in the study?	12	Updated Reproductive Risks section to add "**If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately.**"
How long is this study?	13	Updated section to read "We would like to continue to follow your health ~~status~~ for about 10 years after you start the study."

Possible Side Effects of Cyclophosphamide	19	Added **and up to 100** when describing common side effects
Possible Side Effects of Asparaginase Erwinia	22	Moved bullet point with "diarrhea" up within rare side effects
Possible Side Effects of Methotrexate IT	26	• Added **and up to 100** when describing common side effects • Removed ~~vomiting~~ from common side effects • Moved bullet point for "difficulty with speaking" down within occasional side effects • Removed ~~cause tiredness~~ from occasional side effects • Moved bullet point with "paralysis, weakness" down within rare side effects
Possible Side Effects of Methotrexate PO or IV	27	Moved bullet point with "dizziness" down within rare side effects
Possible Side Effects of Mercaptopurine	28	Added **in** to appear before "sperm" under occasional side effects

CONSENT 4: CONSENT FOR PATIENTS WHO DID NOT RESPOND TO THERAPY AFTER BLOCK 1 (ALL PATIENTS) OR BLOCK 2 (HR/IR PATIENTS ON TREATMENT ARM A)

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

Section	Page	Comments
All	Throughout	Version date has been updated.
What will happen on this study that is research?	5	Per the RRA request, revised to state the patient may be hospitalized for the first **9 days** of the first blinatumomab cycle, instead of ~~3 days~~.
What side effects or risks can I expect from being in the study?	7-8	Added New Risk: • Rare: Damage to the bone marrow which may cause infection, bleeding, may require transfusions Decrease in Risk Attribution: • Changed to Occasional from Common: Diarrhea • Changed to Rare from Occasional: Kidney damage that may require dialysis • Changed to Also Reported on Blinatumomab (AMG-103) Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Bloating Provided Further Clarification:

		• Internal bleeding which may cause black tarry stool, blood in vomit, or blood in urine (under Occasional) is now reported as Internal bleeding which may cause black tarry stool, blood in vomit (Rare). • Fluid in the body which may cause low blood pressure, shortness of breath, swelling of ankles (under Occasional) is nor reported as Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles (under Rare). • Damage to the organs (brain, lungs) which may cause shortness of breath (under Rare) is now reported as Damage to organs (brain, lungs) which may cause shortness of breath (under Rare). Damage to the brain or nerves which may result in confusion, restlessness, worry, or sensing things that are not there (under Rare) is now reported as Damage to the brain or nerves (under Rare).
What side effects or risks can I expect from being in the study?	9	Updated Reproductive Risks section to add "**If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately.**"
How long is this study?	10	Updated section to read "We would like to continue to follow your health ~~status~~ for about 10 years after you start the study."
Funding support	11	Updated section to add "**This study includes providing specimens to the researcher. There are no plans for you to profit from any new product developed from research done on your specimens.**"
Attachment #1 Treatment and Procedures Common to all Patients receiving SCT for relapsed ALL	15	Corrected bullet point number four under Treatment Plan to read "The leukemia returned in your central nervous system (spinal fluid) and/or the testes 18 months or **more** ~~less~~ after you were first diagnosed with ALL…" to keep it consistent with the protocol.
Possible Side Effects of Cyclophosphamide	20	Removed ~~the~~ from common side effects
Possible Side Effects of Dexamethasone	22	Added **blurred vision** to occasional side effects
Possible Side Effects of Mercaptopurine	26	• Added **in** to appear before "sperm" under occasional side effects • Remove ~~in~~ from appearing before "shortness" under rare side effects
Possible Side Effects of Methotrexate IT	27	• Removed ~~vomiting~~ from common side effects • Moved bullet point for "difficulty with speaking" down within occasional side effects • Removed ~~cause tiredness~~ from occasional side effects • Moved bullet point with "damage to the brain which could lead to coma" down within rare side effects

Possible Side Effects of Methotrexate PO or IV	28	Moved "scarring of the lungs which may cause shortness of breath" up within rare side effects
Possible Side Effects of Mycophenolate mofetil	29	Removed the following from common side effects: • ~~Low or high levels of certain salts in the body which may require you to take another medicine to correct the salt level~~ • ~~High blood sugar~~ • ~~Increased blood level of liver tests which may mean there has been damage to the liver, may cause yellowing of the skin~~ Added the following from common side effects: • **loss of appetite, heartburn** • **cause tiredness, or may** • **Feeling of "pins and needles" in arms and legs** Removed the following from occasional side effects: • ~~Feeling of "pins and needles" in arms and legs~~ Removed the following from rare side effects: • ~~Scarring of the lungs~~ Added the following from rare side effects: • Replaced ~~earlier~~ with **a prior** • Replaced ~~belly~~ with **stomach** • Replaced ~~stomach~~ and ~~belly~~ with **bowels**

Consent 5: CONSENT FOR COLLECTION OF ADDITIONAL BONE MARROW

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

Section	Page	Comments
All	Throughout	Version date has been updated.
Consent For Collection Of Additional Bone Marrow	1	Revised first paragraph second sentence to read "When the **word** "you" appears in this consent form ~~from~~, it refers to your son or daughter."

SUMMARY OF CHANGES FOR CRFs

AALL1331 Amendment 10 CRF Revisions (Amendment and Non-Amendment Related)

The following forms have been updated to provide clarification and address errors.

Reporting Period – Block 1

1. **Absolute Lymphocyte Count**
    a. Revised edit check
2. **ANC**
    a. Revised edit check
3. **Peripheral Platelet Count**
    a. Revised edit check
4. **Reason patient is off protocol therapy:**
    a. Added SMN rollout
    b. Added new PV

Reporting Periods – Arm A

1. **Reporting Period Start Date**
    a. Revised edit check
2. **Absolute Lymphocyte Count**
    a. Revised edit check
3. **Peripheral Platelet Count**
    a. Revised edit check
4. **Reason patient is off protocol therapy:**
    a. Added SMN rollout

Reporting Periods – Arm B

1. **Reporting Period Start Date**
    a. Revised edit check
2. **Absolute Lymphocyte Count**
    a. Revised edit check
3. **Peripheral Platelet Count**
    a. Revised edit check
4. **Reason patient is off protocol therapy:**
    a. Added SMN rollout

Reporting Periods – Arm C

1. **Reporting Period Start Date**
    a. Revised edit check
2. **Absolute Lymphocyte Count**
    a. Revised edit check
3. **Peripheral Platelet Count**
    a. Revised edit check
4. **Reason patient is off protocol therapy:**
    a. Added SMN rollout
    b. Revised edit check

Reporting Period – Arm D

1. **Reporting Period Start Date**
    a. Revised edit checks
2. **Absolute Lymphocyte Count**

a. Revised edit check

3. **Peripheral Platelet Count**
    a. Revised edit check
4. **Reason patient is off protocol therapy:**
    a. Added SMN rollout
    b. Revised edit check

<u>Reporting Periods – Salvage Therapy (Blin-S) for Treatment Failures</u>

1. **Reporting Period Start Date**
    a. Revised edit checks
2. **Absolute Lymphocyte Count**
    a. Revised edit check
3. **Peripheral Platelet Count**
    a. Revised edit check
4. **Treatment plan after this reporting period:**
    a. Revised edit check
5. **Reason patient is off protocol therapy:**
    a. Added SMN rollout

<u>Reporting Period – Post-Transplant Observation</u>

1. **Reason patient is off protocol therapy:**
    a. Added SMN rollout

<u>Adverse Events: Treatment</u>

1. **Instructional text of Form Header**
    a. Revised instructional text

<u>Follow-Up</u>

1. **Was follow-up information obtained for this time-point**
    a. Revised edit check
2. **Has a new primary cancer or MDS been diagnosed that has not been previously reported?**
    a. Added SMN rollout
3. **Anti-cancer therapy -**
    a. Added instructional text
    b. Added three new questions:
        i. Did the patient start any anti-cancer therapy during this reporting period?
        ii. Type(s) of anti-cancer therapy the patient received started during this reporting period:
            - Added edit checks to rollout anti-cancer therapy forms
        iii. Other, specify:
    c. Inactivated three questions:
        i. Did the patient receive any anti-cancer therapy during this reporting period?
        ii. Type(s) of anti-cancer therapy the patient received:
        iii. Other, specify:
4. **Did patient reach the tenth anniversary of their study enrollment during this follow-up period?**
    a. New question

<u>Cytogenetics - Central Review</u>

1. **Sample Collection Date:**

    a. Revised edit checks
2. **Reason sample rejection:**
    a. Revised PV
3. **If Other, specify:**
    a. Revised question text
4. **Karyotype:**
    a. Revised edit check
5. **Number of Chromosomes:**
    a. Revised edit check
    b. Revised format
6. **Does patient have evidence of hypodiploidy?**
    a. Revised edit check
7. **Trisomy 4**
    a. Revised edit check
8. **Trisomy 10**
    a. Revised edit check
9. **t(9;22)(q34;q11.2)**
    a. Revised edit check
10. **t(4;11)(q21;q23)**
    a. Revised edit check
11. **t(8;14)(q24;q32) or other variant of B-ALL**
    a. Revised edit check
12. **Other translocation involving 11q23**
    a. Revised edit check
13. **Were karyotype changes made?**
    a. Revised edit check
14. **FISH Data**
    a. Revised edit check
15. **If Other, specify:**
    a. Revised question text
    b. Revised help text
16. **Text fields on Form**
    a. Revised character count to 1999

ALC and B & T Cell Subset Quantifications

1. **Absolute Lymphocyte Count:**
    a. Revised edit check
2. **Absolute CD 19 Lymphocyte Count:**
    a. Revised edit check
3. **Absolute CD 3 Lymphocyte Count:**
    a. Revised edit check

STF Protein Cell Stress Pathways (optional study)

1. **Instructional Header**
    a. Added Accession Number

SMN

1. **New Form**

Anti-cancer therapy Follow-up – New Forms

1. Chemotherapy Follow-up Data
2. Stem Cell Transplant Follow-up Data
3. Immunotherapy (non-cellular) Follow-up Data
4. CAR T-Cell Follow-up Data
5. Other Cellular Immunotherapy Follow-up Data
6. External Beam Radiation Therapy Follow-up Data
7. Other Anti-Cancer Therapy Follow-up Data

Activated: 12/08/14
Closed: 09/30/19

Version Date: 12/19/2019
Amendment #10A

CHILDREN'S ONCOLOGY GROUP

AALL1331

Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC# 765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

IND Sponsor for Blinatumomab: DCTD, NCI

A Groupwide Phase III Study
Participating Countries: Australia, Canada, New Zealand and United States

STUDY CHAIR

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ABBREVIATIONS

Abbreviation	Term
aGVHD	Acute graft versus host disease
B-ALL	B-Lymphoblastic Leukemia
CR	Complete remission
DFS	Disease free survival
GVHD	Graft vs. host disease
HR	High risk
HSCT	Hematopoietic stem cell transplant
IEM	Isolated extramedullary
IR	Intermediate risk
IS	Immune suppression
LR	Low risk
MRD	Minimal residual disease
PFS	Progression free survival
Ph^+	Philadelphia chromosome positive
TF	Treatment failure
TKI	Tyrosine kinase inhibitor
URD	Unrelated Donor

TABLE OF CONTENTS

ABSTRACT

AALL1331 is a group wide risk-stratified, randomized Phase III study to test whether incorporation of blinatumomab into the treatment of patients with childhood B-Lymphoblastic Leukemia (B-ALL) at first relapse will improve disease free survival. Blinatumomab is being tested in this population based on its demonstrated safety profile and single agent activity (induction of MRD-negative remissions in children with multiple relapsed refractory B-ALL).

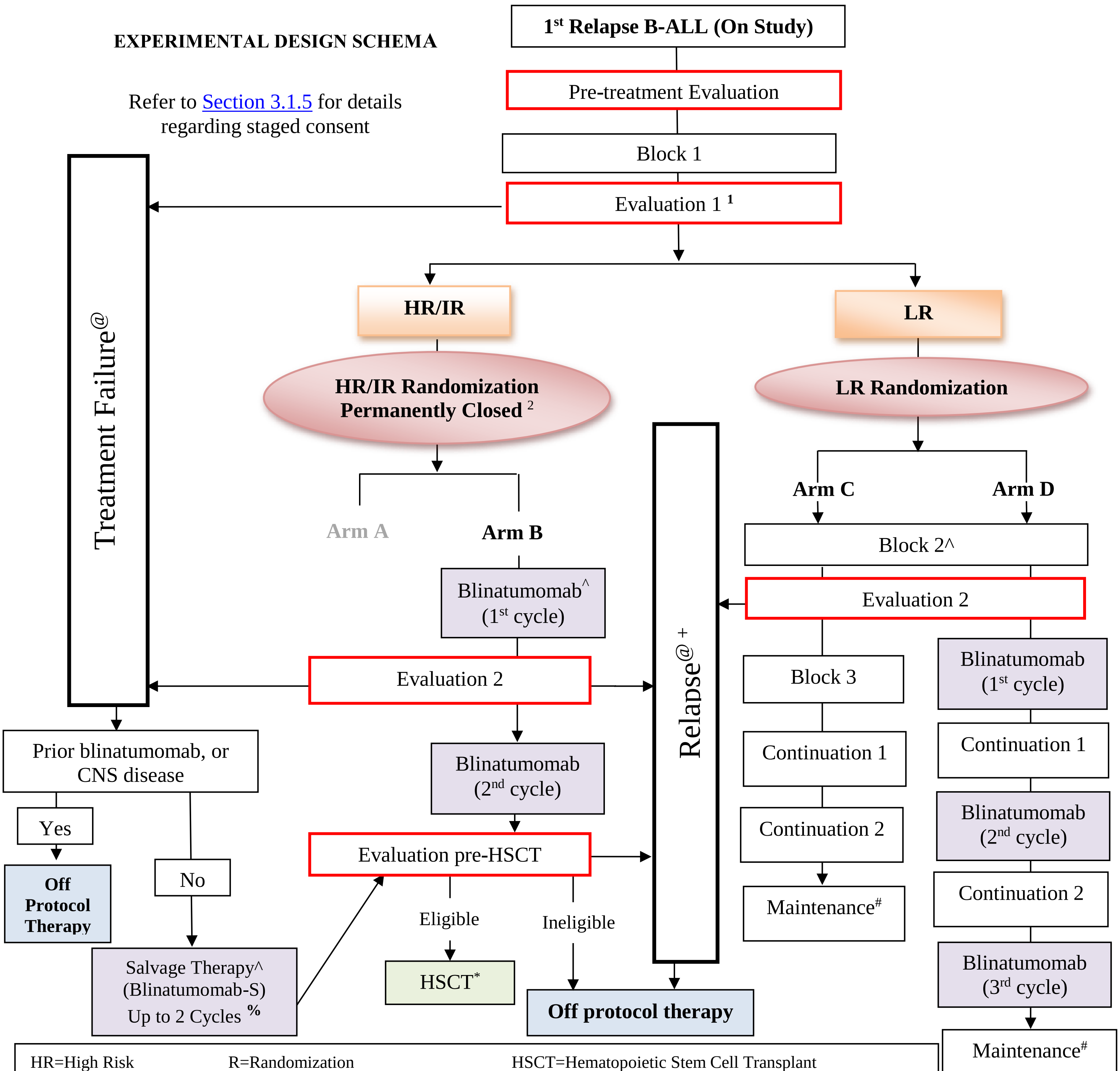
AALL1331 risk stratification is determined based on site of relapse [marrow versus isolated extramedullary (IEM)], time to relapse and minimal residual disease (MRD) status following a uniform first block of chemotherapy. High risk (HR) and intermediate risk (IR) patients will be eligible for randomization to either a control arm with two additional blocks of chemotherapy, or an experimental arm with two blocks of blinatumomab. Both arms will proceed to protocol-specified hematopoietic stem cell transplant (HSCT) that includes a rapid taper of immune suppression for patients with residual disease and no graft vs. host disease (GVHD). Low risk (LR) patients will be eligible for randomization to either a control arm with two blocks of chemotherapy followed by continuation and maintenance chemotherapy, or an experimental arm with one block of chemotherapy, 2 blocks of blinatumomab, each followed by continuation and a third additional block of blinatumomab followed by maintenance.

AALL1331 includes correlative laboratory studies to refine risk stratification, identify new targets for therapy, identify biomarkers to predict response to chemotherapy and blinatumomab, and to link host polymorphisms with various disease characteristics and toxicities.

Amendment #10 incorporates the High Risk/Intermediate Risk randomization closure as a result of COG DSMC's recommendation based on data that determined the experimental arm with blinatumomab (Arm B) has a significantly more favorable tolerability profile and similar or superior EFS/OS. Effective September 18, 2019, accrual and randomization on the HR/IR arms closed. At completion of Block 1, if patient is found to be HR/IR the patient comes off protocol therapy . HR/IR patients already assigned to Arm A (standard chemotherapy) who are at an appropriate point in their treatment program (prior to receiving Day 22 treatment on Block 3) will be offered the opportunity to cross over to Arm B to receive blinatumomab.

EXPERIMENTAL DESIGN SCHEMA

Refer to Section 3.1.5 for details regarding staged consent



HR=High Risk	R=Randomization	HSCT=Hematopoietic Stem Cell Transplant	
IR=Intermediate Risk	CR=Complete response	LR=Low Risk	TF: Treatment Failure

@ See Section 3.3 for definitions of treatment failure and relapse.

1 End Block 1 Callback (completed via OPEN, see Section 3.1.6-3.1.7)

2 **Randomization and accrual to the HR/IR arms is permanently closed effective 09/18/2019. All HR/IR patients receiving treatment on Arm A prior to Amendment #10 will receive blinatumomab in place of standard chemotherapy.**

CNS3 patients receive chemoradiation post Maintenance Cycles 1 * Patient may receive bridge therapy prior to HSCT

^ Patients with persistent testicular involvement after Block 1 will receive testicular radiation (TRT) during designated blocks

% Evaluation pre-HSCT at end of each cycle. See Section 4.7.6 and 4.8.5 for details

+ Patients who achieve remission at end-Block 1 or 2 but are no longer in remission on a subsequent evaluation will be removed from protocol therapy for relapse.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To compare disease free survival (DFS) of HR and IR relapse B-ALL patients who are randomized following Induction Block 1 chemotherapy to receive either two intensive chemotherapy blocks or two 5-week blocks of blinatumomab (HR/IR Randomization). **(Closed effective September 18, 2019)**

1.1.2 To compare DFS of LR relapse B-ALL patients who are randomized following Block 1 chemotherapy to receive either chemotherapy alone or chemotherapy plus blinatumomab (LR Randomization).

1.2 Secondary Aims

1.2.1 To compare overall survival (OS) of HR and IR relapse B-ALL patients who are randomized following Induction Block 1 chemotherapy to receive either two intensive chemotherapy blocks or two 5 week blocks of blinatumomab (HR/IR Randomization). **(Closed effective September 18, 2019)**

1.2.2 To compare OS of LR relapse B-ALL patients who are randomized following Block 1 chemotherapy to receive either chemotherapy alone or chemotherapy plus blinatumomab (LR Randomization).

1.3 Exploratory Aims

1.3.1 To compare the rates of MRD $\geq$ 0.01% at the end of Block 2 and Block 3 for HR and IR relapse B-ALL patients in HR/IR randomization. **(Closed effective September 18, 2019)**

1.3.2 To estimate, for treatment failure (TF) patients not previously receiving blinatumomab, the hematologic complete remission rate (CR), rate of MRD $<$ 0.01%, and proportion able to proceed to hematopoietic stem cell transplant (HSCT) in CR after treatment with blinatumomab.

1.3.3 To assess the feasibility and safety of rapid taper of immune suppression for the subset of HSCT patients with MRD $\geq$ 0.01% pre- and/or post-HSCT with no acute graft versus host disease (aGVHD).

1.3.4 To evaluate blinatumomab pharmacokinetics (PK) and explore exposure-response relationships for measures of safety and effectiveness.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

Note: This study is not on the CTSU Menu (i.e. it is not posted to the CTSU web site) but is supported by the CTSU Regulatory Office, OPEN and Rave.

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the 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 XIII for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

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.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix I.

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.

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

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

See Section 3.1.6 below for details regarding randomization and treatment assignment for patients.

3.1.4 Timing

Informed consent: Except for administration of intrathecal chemotherapy (methotrexate strongly preferred) administered at the time of the required diagnostic lumbar puncture to establish baseline CNS status, *informed consent/parental permission* MUST be signed before protocol therapy begins. See Section 3.1.5 for summary of time points to obtain informed consent.

Study enrollment: Study enrollment 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 that 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. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment.

3.1.5 Staged Consent

Informed consent will be obtained at critical stages of treatment for the different groups of patients on this study (see summary table below). Informed consent that describes Block 1 therapy (common to all patients on study) will be obtained before starting treatment, with the exception of intrathecal chemotherapy (methotrexate strongly preferred) administered at the time of the required diagnostic lumbar puncture to establish baseline CNS status. At the end of Block 1 therapy, after risk groups have been assigned, subsequent informed consent that describes further therapy will be obtained at the various time points detailed in Table 8 below. Also see Experimental Design Schema

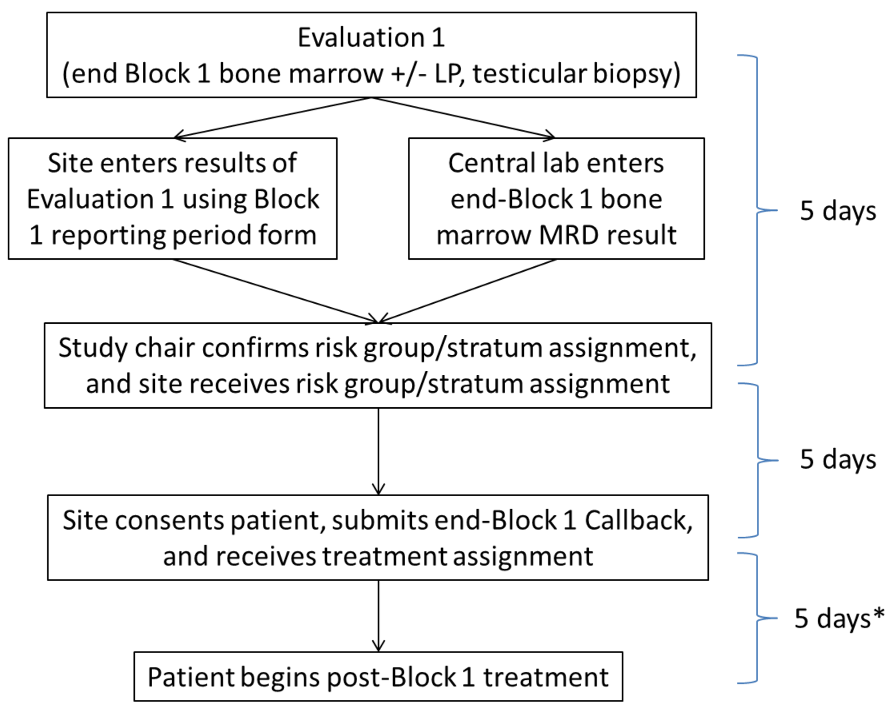
Effective September 18, 2019 the HR/IR randomization closed. Patients who meet criteria for HR/IR randomization should not be approached for post-Induction therapy on AALL1331 and will be removed from protocol therapy at the completion of Block 1.

Table 8: Summary of required consents for AALL1331

Consent Form	Time point to Obtain Consent	Population for Consent
Consent 5 – Consent for collection of additional marrow	Before study entry (prior to collection of bone marrow)	All potential subjects
Consent 1 – Re-induction (block 1) therapy for all subjects	Study Entry (Prior to shipment of bone marrow sample, enrollment, and initiation of therapy)	All subjects
Consent 2: All High-Risk and Intermediate-Risk patients eligible to take part in HR/IR randomization ***Closed effective 09/18/2019***	Evaluation 1 (prior to HR/IR randomization)	HR/IR subjects
Consent 3: All low-risk patients eligible to take part in LR randomization	Evaluation 1 (prior to start of LR randomization)	LR subjects
Consent 4: Patients who did not respond to therapy after Block 1 (all patients) or Block 2 (HR/IR Patients on Treatment Arm A)	Prior to start of Salvage Therapy (Blinatumomab-S): ●End Block 1 ●End Block 2	Treatment Failures (TF)

3.1.6 Risk Assignment, Randomization, and Treatment Assignment

- Evaluation 1 (detailed in Section 4.2.7).



*Exception: 14 days for HR/IR patients with M1 marrow assigned to Arm B

Evaluation 1 must occur no earlier than Day 29 (± 1 day); the evaluation may be delayed until no later than Day 36 (± 1 day) if ANC < 500 and/or platelets < 50,000 on Day 29.

Completion of risk group/stratum assignment must occur within 5 calendar days of Evaluation 1.

- Step 1: site enters results of local morphologic assessment (marrow/CSF/testes) using Block 1 RP form (form may be saved while incomplete)
- Step 2: central lab enters marrow flow MRD result using Block 1 MRD form
- Step 3: Study chair confirms risk group/stratum assignment using SC Risk Assignment form (using criteria outlined in Section 3.3)

Submission of end-Block 1 callback form must occur within 5 calendar days of risk group/stratum assignment.

Components of callback

1) Risk group/stratum
2) Confirmation that patient does not have severe residual toxicities
3) Confirmation that consent has been signed

Upon submission, site receives treatment assignment: Consenting LR patients will be randomized according to LR Randomization; HR/IR patients are not eligible for post-Induction treatment on AALL1331 and are removed from protocol therapy following completion of Block 1; patients deemed Treatment Failure at Evaluation 1 who are eligible for and consent to Salvage Therapy will be assigned to Salvage Therapy.

NOTE: Patients with residual non-heme toxicities that are likely to prevent beginning post-Block 1 treatment within required time frames should NOT submit the End-Block 1 callback.

3.1.7 Callbacks

Callback is performed using the Oncology Patient Enrollment Network (OPEN).

Callback	Timing	Population for Callback	Purpose
End Block 1 Callback **(ALL patients continuing to post-Block 1 therapy)**	Evaluation 1*	Consenting LR patients not off protocol therapy after completion of Block 1 therapy.	Randomize LR patients to either of 2 treatment arms: **Arm C** (Control Arm) or **Arm D** (Experimental Arm).
		Treatment Failure patients who are eligible for and consent to Salvage Therapy	Assign patients to Salvage Therapy (Blinatumomab-S)

*See Section 3.1.6 for timing details

3.1.8 Drug Preparation and Administration

Blinatumomab must be prepared in an ISO Class 5 containment device, ideally in an ISO Class 7 room as described in USP <797>, but ISO Class 7 is not required. US sites must attest that their drug preparation and administration guidelines comply with the USP 797. Documentation of participating site training with regard to the preparation and administration of blinatumomab must be submitted via RSS as protocol specific requirement at the time of site activation for participation on the trial.

3.1.9 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.

3.2 Patient Eligibility Criteria

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

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat the tumor imaging if necessary).

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age

Patients ≥1 year and < 31 years of age at the time of relapse will be eligible.

3.2.2 Diagnosis

First relapse of B-ALL, allowable sites of disease include isolated bone marrow, combined bone marrow and CNS and/or testicular, and isolated CNS and/or testicular.

Extramedullary sites are limited to the CNS and testicles. Please refer to Section 3.3 for definitions of relapse and criteria for risk classification.

3.2.3 Prior Therapy

Please see Section 4.1.2 for the concomitant therapy restrictions for patients during treatment.

3.2.3.1 No waiting period for patients who relapse while receiving standard Maintenance therapy

3.2.3.2 Patients who relapse on frontline therapy in phases other than Maintenance must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

3.2.3.3 Cytotoxic therapy: At least 14 days since the completion of cytotoxic therapy with the exception of hydroxyurea, which is permitted up to 24 hours prior to the start of protocol therapy, or Maintenance chemotherapy (see Section 3.2.3.1), or intrathecal chemotherapy (methotrexate strongly preferred) administered at the time of the required diagnostic lumbar puncture to establish baseline CNS status.

3.2.3.4 Biologic (anti-neoplastic) agent: At least 7 days since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

3.2.3.5 Stem cell transplant or rescue: Patient has not had a prior stem cell transplant or rescue.

3.2.3.6 Patient has not had prior treatment with blinatumomab.

3.2.3.7 With the exception of intrathecal chemotherapy (methotrexate strongly preferred; cytarabine is permissible) administered at the time of the required diagnostic lumbar puncture to establish baseline CNS status, patient has not received prior relapse-directed therapy (i.e., this protocol is intended as the INITIAL treatment of first relapse).

3.2.4 Performance Status

Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Please refer to performance status scale at: https://members.childrensoncologygroup.org/_files/protocol/Standard/PerformanceStatusScalesScoring.pdf

3.2.5 Organ Function Requirements

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 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
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.[37]

3.2.5.2 Adequate liver function defined as a direct bilirubin < 3.0 mg/dL.

3.2.5.3 Adequate Cardiac Function Defined As:
- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram.

3.2.6 Exclusion Criteria

3.2.6.1 Patients with Philadelphia chromosome positive/BCR-ABL1+ ALL are not eligible

3.2.6.2 Patients with Burkitt Leukemia/Lymphoma or mature B-cell leukemia are not eligible

3.2.6.3 Patients with T-Lymphoblastic Leukemia (T-ALL)/Lymphoblastic Lymphoma (T- LL) are not eligible

3.2.6.4 Patients with B-Lymphoblastic Lymphoma (B-LL) are not eligible

3.2.6.5 Patients with known optic nerve and/or retinal involvement are not eligible. Patients who are presenting with visual disturbances should have an ophthalmologic exam and, if indicated, an MRI to determine optic nerve or retinal involvement.

3.2.6.6 Patients known to have one of the following concomitant genetic syndromes: Down syndrome, Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome.

3.2.6.7 Patients with known HIV infection.

3.2.6.8 Patients with known allergy to mitoxantrone, cytarabine, or both etoposide and etoposide phosphate (Etopophos).

3.2.6.9 Lactating females who plan to breastfeed.

3.2.6.10 Patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.

3.2.6.11 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

3.2.6.12

a) Patients with pre-existing significant central nervous system pathology that would preclude treatment with blinatumomab, including: history of severe brain injury, dementia, cerebellar disease, organic brain syndrome, psychosis, coordination /movement disorder, or autoimmune disease with CNS involvement are not eligible. Patients with a history of cerebrovascular ischemia/hemorrhage with residual deficits are not eligible. (Patients with a history of cerebrovascular ischemia/hemorrhage remain eligible provided all neurologic deficits have resolved)

b) Patients with uncontrolled seizure disorder are not eligible. (Patients with seizure disorders that do not require antiepileptic drugs, or are well controlled with stable doses of antiepileptic drugs remain eligible.)

3.2.7 Regulatory Requirements

3.2.7.1 All patients and/or their parent or legal guardian must sign a written informed consent.

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

3.3 **Definitions**

Acute Lymphoblastic Leukemia (ALL)

Bone marrow with > 25% L1 or L2 lymphoblasts (M3 marrow). Patients with > 25% L3 marrow lymphoblasts and/or evidence of c-*myc* translocation are considered to have Burkitt or mature B-cell leukemia and are ineligible for this study.

Definitions of Relapse

- RELAPSE: Any recurrence of disease whether in marrow or extramedullary. For the purposes of eligibility for this trial, extramedullary sites are limited to the CNS and testicles. Relapse should be confirmed by pathology examination of appropriate tissue.

- ISOLATED BONE MARROW RELAPSE: Patients with an M3 marrow at any point after achieving remission without involvement of the CNS and/or testicles. Every effort should be made to confirm morphologic relapse using flow cytometry, FISH and/or cytogenetics.

- 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 that are, in the opinion of the investigator, more likely due to recurrent CNS leukemia than to alternative causes (e.g., viral infection or chemotherapy toxicity). If any CSF evaluation shows positive cytomorphology and WBC < 5/µL, a second CSF evaluation is recommended 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. Note that AALL1331 excludes patients with known optic nerve and/or retinal involvement (Section 3.2.6.5).

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

- ISOLATED EXTRAMEDULLARY (IEM) RELAPSE: CNS and/or testicular relapse with an M1 marrow. The presence of MRD in the bone marrow does NOT exclude IEM.

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

CNS Status:

NOTE: in this protocol "CNS-positive" means meeting the criteria for CNS Relapse (whether isolated CNS or combined relapse) at the time of AALL1331 study entry as listed in the Definitions of Relapse above. CNS 2 status first noted at the time of enrollment for concurrent relapse at another site (i.e. bone marrow) will not be considered 'CNS-positive'.

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 ≥ 5/µL WBCs 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, 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 algorithm should be used to distinguish between CNS 2 and CNS 3 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:

$$\frac{60}{1{,}500} = 0.04 > 2X \frac{46{,}000}{3.0 \text{ X } 10^6} = 0.015$$

Bone Marrow Status:

M1 Marrow: < 5% blasts in a bone marrow aspirate with at least 200 cells counted.

M2 Marrow: 5% - 25% blasts in a bone marrow aspirate with at least 200 cells counted.

M3 Marrow: > 25% blasts in a bone marrow aspirate with at least 200 cells counted.

For **initial remission** an M1 marrow must be achieved.

Treatment Failure: Failure to achieve the following:

	Marrow	CNS	Testicular
End-Block 1 (All patients)	M2 or better	Remission (clearance of CSF blasts, i.e. CNS1)	None; patients with persistent testicular disease will receive testicular radiation in Block 2 (LR and HR/IR randomized to the control arm) or during Blinatumomab Block: Cycle 1 (HR/IR randomized to the experimental arm)
End-Block 2, or End Blinatumomab Block, Cycle 1 (HR/IR only)	M1	Continued remission	Remission (clearance of testicular disease)

NOTE: Patients who achieve remission (M1 marrow and clearance of extramedullary disease) at end-Block 1 or Block 2 but are no longer in remission on a subsequent evaluation will be removed from protocol therapy for relapse.

Risk Assessment-End Block 1*:
Low Risk

- Late marrow (≥ 36 months), end-Block 1 MRD < 0.1%
- Late (≥ 18 months) Isolated Extramedullary (IEM), end-Block 1 MRD < 0.1% (or indeterminate MRD)

Intermediate Risk

- Late (≥ 36 months) marrow, end-Block 1 MRD ≥ 0.1%
- Late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%

High Risk

- Early (< 36 months) marrow
- Early (< 18 months) IEM

***** The timing of relapse (duration of first remission) is measured from the date of initial diagnosis to the date of relapse.

Complete Remission

Complete remission (CR) is defined as an M1 marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with peripheral count recovery, defined as absolute neutrophil count higher than or equal to 500/µL and platelet count higher than or equal to 50,000/µL.

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

All eligible patients with first relapse B-ALL who are enrolled on AALL1331 will receive standard chemotherapy during Block 1. All patients will then be risk assessed at the end of Block 1 as either HR, IR, LR or TF. Risk assessment is based on site of relapse, time to relapse, end Block 1 bone marrow morphology and MRD levels. Effective September 18, 2019, HR and IR patients are no longer eligible for post-Induction therapy on AALL1331 due to closure of the HR/IR randomization and will be removed from protocol therapy following completion of Block 1. LR patients will be eligible to participate in LR Randomization. See summary table below. Treatment failures are those patients whose disease status fails to meet pre-defined response criteria at end-Block 1 or end-Block 2. These patients are eligible to receive up to 2 blocks of blinatumomab if they have not previously received it on study and have no evidence of persistent CNS disease. These patients will also be eligible to continue on to HSCT if they achieve a CR. Otherwise, they will be removed from protocol therapy. See Section 3.3 for response definitions of TF CR.

Risk Stratification at end Block 1

Risk Group	Definition	Randomization Eligibility	Treatment Arms
High	• Early (< 36 months) marrow • Early (< 18 months) IEM	HR/IR ***Closed 09/18/2019***	• Arm A (Control) • Arm B (Experimental)
Intermediate	• Late (≥ 36 months) marrow, end-Block 1 MRD ≥ 0.1% • Late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%	HR/IR ***Closed 09/18/2019***	• Arm A (Control) • Arm B (Experimental)
Low	• Late (≥ 36 months) marrow, end-Block 1 MRD < 0.1% • Late (≥ 18 months) IEM, End-Block 1 MRD < 0.1%	LR	• Arm C (Control) • Arm D (Experimental)
Treatment Failure at end Block 1	Failure to achieve the following: • M2 or better • CNS remission (clearance of CSF blasts, i.e. CNS1)	None (treatment assignment)	• Salvage therapy (Blinatumomab-S)

<u>CNS Leukemia</u>

All patients with CNS3 involvement at the time of relapse will receive intrathecal triples (ITT) instead of IT MTX beginning on Day 8. During Block 1 these patients will receive two additional ITT doses (Days 15 and 22) and during Block 2 they will receive one additional ITT dose (Day 22). For LR patients with CNS3 involvement, AALL1331 will further intensify CNS-directed therapy by replacing lower dose oral MTX (25 mg/m^2 every 6 hours x 4 doses) with intermediate dose IV MTX (1 g/m^2 over 24 hours) during the each of the 2 continuation phases. All of these patients will then receive 1800 cGy cranial radiation and concurrent chemotherapy (including high dose dexamethasone) between and the first and second 12 week blocks of Maintenance. IR and HR patients will proceed to TBI-based HSCT and these patients will also receive a protocol-specified cranial radiation boost as part of their HSCT preparative regimen.

Testicular Leukemia

Patients with suspected isolated testicular relapse or equivocal testicular enlargement with concurrent bone marrow/CNS relapse must have a testicular biopsy performed at baseline. Patients with persistent or equivocal testicular enlargement at the end of Block 1 must have a testicular biopsy. Patients with persistent testicular leukemia at the end of Block 1 are eligible to continue on study and will receive 2400 cGy of testicular radiation during either Block 2 chemotherapy (for LR patients and HR/IR patients randomized to the control arm) or during blinatumomab (for HR/IR patients randomized to the experimental arm and TF.) Patients with extramedullary testicular leukemia that has resolved by end Block 1 will NOT receive testicular irradiation, with the exception of that which may be used in the HSCT preparative regimen for HR/IR patients.

HSCT

All patients enrolled on this protocol, their parents and full siblings should undergo HLA tissue typing as soon as possible after diagnosis of relapse, and should have transplantation consultation and initiation of a donor search. For HR/IR patients, and for TF patients who achieve CR with Salvage Therapy (Blinatumomab-S), the goal of this protocol is to move to transplant within 2 weeks of recovery from the last block/cycle of therapy prior to transplant. Because unrelated donor acquisition can take 8 - 12 weeks, centers must expedite the donor search process to meet this deadline.

Patient Pill Diary

It is recommended that patients use a Patient Pill Diary to keep track of oral medications.

4.1.1 TREATMENT ASSIGNMENTS

IMPORTANT NOTE:

In order to continue to receive protocol therapy, patients will need to begin post-Block 1 therapy within a specified time frame (see Section 4.2.7). If a patient has residual severe non-hematologic toxicities from Block 1 that are likely to preclude beginning post-Block 1 therapy within this time frame, please DO NOT complete end-Block 1 Callback for the patient. This is important to minimize the number of patients who are randomized/assigned but are unable to receive post-callback treatment.

4.1.1.1 **HR/IR Randomization**

Effective 09/18/2019, HR/IR patients are not eligible for post-Induction therapy on AALL1331 and will be removed from protocol therapy. Patients receiving therapy on Arm A prior to Amendment #10 who have not yet received Day 22 treatment on Block 3 will be offered the opportunity to cross over to Arm B to receive blinatumomab.

- **Arm A (Control Arm)**: Patients receive Block 2 and Block 3 of standard therapy followed by HSCT. ***Closed effective September 18, 2019.***

- **Arm B (Experimental Arm)**: Patients receive two 5 week blocks of Blinatumomab, followed by HSCT.

4.1.1.2 **LR Randomization**

Following submission of the end-Block 1 callback form LR patients will be randomized to receive treatment on either of 2 treatment arms (see Experimental Design Schema and Section 3.1.6):

- **Arm C (Control)**: Patients receive Block 2 and Block 3 of standard therapy followed by Continuation 1, Continuation 2, and Maintenance.

- **Arm D (Experimental)**: Patients receive Block 2 of standard therapy followed by a 5 week Blinatumomab Block, Continuation 1, a 5 week Blinatumomab Block, Continuation 2, a 5 week Blinatumomab Block, and Maintenance.

4.1.1.3 **Salvage Therapy (Blinatumomab-S)**

Following submission of the end-Block 1 or End-Block 2 callback form, eligible Treatment Failure patients will be assigned to Salvage Therapy (see Experimental Design Schema and Section 3.1.6).

4.1.2 Concomitant Therapy Restrictions

4.1.2.1 **Cytochrome P450 Interactions with Antileukemic Drugs.**

Since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with anti-leukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes.[38] Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsants. 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 anti-leukemic 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.[39,40]

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

4.1.2.2 **Possible Drug Interactions with 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://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf

4.1.3 Supportive Care for Patients 15 Years and Older

It is recommended that adolescent and young adult (AYA) patients enrolled on this protocol (defined as patients between the ages of 15 and 31 years) be *monitored in the hospital* during Block 1, Block 2 and Block 3 of chemotherapy until they show signs of bone marrow recovery (specifically until they show evidence that the absolute neutrophil count (ANC) is rising for 2 successive days) and the patient is afebrile and clinically stable. If a patient should experience profound myelosuppression at any other time, there should also be a very low threshold to hospitalize AYA patients, and to continue inpatient management until there is evidence of bone marrow recovery. *Antibiotic prophylaxis* against Gram-positive and Gram-negative organisms (e.g. levofloxacin) may be considered during these hospitalizations until patients meet the criteria for discharge. If the patient should develop febrile neutropenia while on antibiotic prophylaxis, the patient should be started on broad-spectrum intravenous antibiotics per institutional guidelines. *Antifungal prophylaxis* may also be considered during periods of myelosuppression. Options include an echinocandin such as caspofungin or micafungin, or an azole. **Azole antifungal agents (i.e., fluconazole, itraconazole, posaconazol, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Investigator caution is advised if azole antifungals are used.** If antibiotic and/or antifungal prophylaxis is utilized, consultation with Infectious Disease may be considered.

4.2 Block 1 (All patients) - 4 Weeks Duration

Block 1 therapy is common to all patients on study. See Experimental Design Schema. The therapy delivery map (TDM) for Block 1 is in APPENDIX II-A.

NOTE: The risks of significant morbidity and mortality, including sudden death in patients with relapsed leukemia, are sufficient to strongly recommend hospitalization during remission Induction, until patients show consistent neutrophil recovery and transfusion needs that are deemed to be manageable in the outpatient setting. Please see Appendix I for additional details.

4.2.1 Disease Evaluation Pre-Treatment

See Section 7.0, Evaluations/Material and Data to be Accessioned

4.2.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

Dosing should be based on actual BSA.

4.2.3 Block 1 Chemotherapy

Dexamethasone: PO (may be given IV)

Days: 1 - 5, 15 - 19

Dose: 10 mg/m²/dose (Total daily dose: 20 mg/m²/day, divided BID; dose capped at 40 mg per day)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 8, 15, 22

Dose: 1.5 mg/m²/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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Pegaspargase: **IV over 1 - 2 hours**
Days: 3, 17
Dose: 2,500 International Units/m²/dose
Administer through the tubing of a rapidly 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.

MitoXANTRONE: IV over 15 - 30 minutes, administered through the tubing of a rapidly infusing solution of D_5W or 0.9% NaCl.
Days: 1, 2
Dose: 10 mg/m²

Methotrexate: Intrathecal (IT) - ALL PATIENTS
Days: 1

Note: If intrathecal chemotherapy (methotrexate strongly preferred; cytarabine permissible) was given at the time of the diagnostic lumbar puncture, and if the treatment was given less than 7 days prior to the beginning of Day 1 systemic therapy, then the Day 1 IT treatment can be omitted at the discretion of the investigator. Otherwise, Day 1 intrathecal methotrexate must be given.

Age-based dosing:

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

Methotrexate: Intrathecal (IT) - CNS 1/2 PATIENTS ONLY
Days: 8
Note: For CNS2 patients continue weekly IT until 2 clear CSF samples (CNS1) are obtained.

Age-based dosing:

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

Intrathecal Triple Therapy (ITT) - ANY PATIENT WITH CNS3 AT THE TIME OF RELAPSE

Days 8, 15, and 22.

Age-based dosing:

Age (yrs)	Dose (mg)		
1 - 1.99	MTX: 8	HC: 8	ARAC: 16
2 - 2.99	MTX: 10	HC: 10	ARAC: 20
3 - 8.99	MTX: 12	HC: 12	ARAC: 24
≥ 9	MTX: 15	HC: 15	ARAC: 30

4.2.4 Disease Evaluation End Block 1

- The end-Induction evaluation should occur no earlier than Day 29 (± 1 day).
- The evaluation may be delayed no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- The evaluation includes a bone marrow aspirate for all patients, a diagnostic lumbar puncture should be performed for CNS2 or CNS3 patients for whom clearance of CSF blasts has not yet been documented, and a testicular biopsy for patients with definite or equivocal residual testiculomegaly at end of Block 1.
- See Sections 7.1 and 13.0 for details on specimen acquisition, handling and shipping.

4.2.5 Research Studies Block 1

See Section 7.2 for a full list of research studies.

4.2.6 HLA Tissue Typing for Hematopoietic Stem Cell Transplant

All patients enrolled on this protocol, their parents and full siblings should undergo HLA tissue typing as soon as possible after diagnosis of relapse, and should have transplantation consultation and initiation of a donor search. The goal of this protocol is to initiate transplantation within 2 weeks of recovery from Block 3. Since unrelated donor acquisition can take 8 - 12 weeks, centers must expedite the search process to meet this timeframe.

4.2.7 Evaluation 1 (Risk Assessment following Block 1)

Following completion of Block 1, patients will be risk assessed based on end-Block 1 criteria outlined in Section 3.3, and according to procedures in Section 3.1.6, as HR, IR, LR, or TF.

IMPORTANT NOTE:

In order to continue to receive protocol therapy, patients will need to begin post-Block 1 therapy within a specified time frame (see below). If a patient has residual severe non-hematologic toxicities from Block 1 that are likely to preclude beginning post-Block 1 therapy within this time frame, please DO NOT complete end-Block 1 Callback for the patient. This is important to minimize the number of patients who are randomized/assigned but are unable to receive post-callback treatment.

Post-Block 1 treatment should begin after submission of end-Block 1 Callback and receipt of treatment assignment as soon as clinically acceptable to the treating institution. Patients should have time for full or partial recovery (judged by the treating institution) from any toxicities experienced in the prior course(s) of therapy before proceeding to the next course. However, treatment must begin according to time frames below for patients to continue to receive protocol therapy.

HR B-ALL or IR B-ALL patients
Effective 09/18/2019, HR/IR patients are not eligible for post-Induction therapy on AALL1331 and will be removed from protocol therapy.

LR B-ALL Eligible for the LR Randomization

- All LR B-ALL patients (**Arm C and Arm D**) will receive Block 2 therapy (Section 4.3, APPENDIX II-B) and should proceed with Day 1 vincristine and dexamethasone without awaiting count recovery (no later than 5 calendar days after callback). It is recommended, but not required, that proceeding with Day 8 IV methotrexate treatment await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL. Day 8 treatment must begin no later than 14 calendar days after giving the Day 1 vincristine and dexamethasone to continue to receive protocol therapy.

Treatment failures Post-Block 1 (see Section 3.3 for definition) have the option to receive up to two 5 week cycles of Blinatumomab (Sections 4.7, 4.8 and APPENDIX II-F, and II-G respectively) and continue on to HSCT after achieving CR.

- TF patients with residual CNS disease (CNS2/3) regardless of marrow status should be removed from protocol therapy.
- TF patients with M3 marrow disease and no residual CNS disease (CNS1) should proceed to Blinatumomab-S Cycle 1 without awaiting count recovery (no later than 5 calendar days after callback).

NOTE: If residual non-hematologic toxicities prevent a patient from beginning post Block-1 treatment within the time frames noted above, then the patient should be removed from protocol therapy.

4.3 Block 2 (LR Patients: Post-randomization) – 4 weeks duration

Block 2 therapy is for all LR patients post LR randomization (**Arm C and Arm D**). See Experimental Design Schema.

The Therapy Delivery Map (TDM) for Block 2 is in APPENDIX II-B.

END-BLOCK 1 CALLBACK OCCURS PRIOR TO STARTING BLOCK 2 THERAPY. PLEASE SEE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON STAGED CONSENT, AND APPROPRIATE TIMING TO OBTAIN INFORMED CONSENT.

4.3.1 Criteria to Begin Block 2 Therapy

Block 2 should begin after submission of the appropriate end-Block 1 Callback and receipt of treatment assignment as soon as clinically acceptable to the treating institution. Patients should have time for full or partial recovery (judged by the treating institution) from any toxicities experienced in the prior course(s) of therapy before proceeding to the next course. To continue to receive protocol therapy, however, Block 2 must begin no later than 5 calendar days after callback. Count recovery is not required to proceed to Block 2.

4.3.2 Testicular Radiation Therapy (TRT)

Patients with persistent testicular leukemia at the end of Block 1 are eligible to continue on study and will receive 2400 cGy of testicular radiation during either Block 2 chemotherapy (all LR patients) or during the first cycle of Blinatumomab (for HR/IR patients).

- Patients with extramedullary testicular leukemia that has resolved by end Block 1 will NOT receive testicular irradiation with the exception of that which may be used in the HSCT preparative regimen.
- See Section 14.2 for detailed testicular radiation guidelines

4.3.3 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

Dosing should be based on actual BSA.

4.3.4 Block 2 Chemotherapy

Dexamethasone: PO (may be given IV)

Days: 1-5

Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Intermediate Dose Methotrexate (ID MTX): IV over 36 hours

Day: 8

Dose: 1,000 mg/m²/dose
Given as a 100 mg/m^2 bolus over 30 minutes followed by 900 mg/m^2 over 35.5 hours.

Be certain that the ID MTX infusion is completed in the 36 hour period. **Even if the infusion is not complete at this time point, it must be stopped.**

Leucovorin rescue: See below.

Suggested hydration and alkalinization for IDMTX: Prehydrate with D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m^2/hour to achieve a urine specific gravity ≤ 1.010 and pH between 7 and 8. 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 ≤ 1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m^2 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 using D 5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour throughout IDMTX infusion after its completion until the last dose of leucovorin has been given.

Timing of ID MTX:

- For patients beginning Block 2 with **M1** marrow, it is recommended to await count recovery to an ANC ≥ 500/μL and platelets ≥ 50,000/μL prior to beginning Day 8 IV methotrexate.

- Patients beginning Block 2 with **M2** marrow should proceed without awaiting count recovery.

Leucovorin: PO/IV
Day: 10, 11
Dose: 15 mg/m^2/dose every 6 hours beginning **48 hrs** after the **START** of ID MTX infusion.

- If 48 hr methotrexate level is ≤ 0.5 µM, do not give more than two doses of leucovorin (48 and 54 hours).
- If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.

See Section 5.8 for ID MTX/LCV rescue and infusion guidelines.

Methotrexate: Intrathecal (IT) – CNS1/2 PATIENTS ONLY
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

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).

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 8, 22

Age-based dosing:

Age (yrs)	Dose
1 – 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 – 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 – 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

When ITT therapy and ID MTX are scheduled for the same day, deliver the ITT 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).

Pegaspargase: IV over 1-2 hours
Administer 4 hours after completion of Day 8 IV MTX. (Day 9 or 10)
Dose: 2,500 International Units/m^2/dose

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 15-30 minutes (see note below)
Days: 15-19
Dose: 440 mg/m²/dose

Etoposide: IV over 1-2 hours (see note below)
Days: 15-19
Dose: 100 mg/m²/dose

NOTE: Await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 15 IV cyclophosphamide and etoposide.

4.3.5 Evaluation 2 (Disease Evaluation End Block 2)

- Evaluation 2 should not be done earlier than Day 29 (± 1 day);
- The evaluation may be delayed no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- See Sections 7.1 and 13.0 for details on specimen acquisition, handling and shipping.

4.3.6 Following Completion of Block 2:

For LR B-ALL patients post-Block 2:

- **Arm C**, Block 3 (Section 4.4, APPENDIX II-C) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.
- **Arm D**, therapy with Blinatumomab Block Cycle 1 (Section 4.15, APPENDIX II-M) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.4 Block 3 (LR Patients on Arm C) - 4 weeks

Block 3 therapy is for LR patients randomized to the control arm (**Arm C**). See Experimental Design Schema.

The Therapy Delivery Map (TDM) for Block 3 is in APPENDIX II-C.

4.4.1 Criteria to Begin Block 3 Therapy

Start when ANC $\geq$ 500/µL and platelets $\geq$ 50,000/µL

4.4.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.4.3 Block 3 Chemotherapy

Dexamethasone: PO (may be given IV)
Days: 1-5
Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Cytarabine: IV over 3 hours
Days: 1, 2, 8, 9
Dose: 3000 mg/m^2/dose every 12 hours

Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose of cytarabine and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, may administer artificial tears on an every 2-4 hour schedule.

Asparaginase (Erwinia): IM (may be given IV over 1 hour)
Day: 2, 4, 9, 11, 23
Dose: 25, 000 International Units/m^2/dose

- Asparaginase (Erwinia) should be given 4 hours after the completion of the last cytarabine infusion on Days 2 and 9.
- Asparaginase (Erwinia) should be given 4 hours after the MTX infusion is complete on Day 23.
- If Asparaginase (Erwinia) is not available, a single dose of Pegaspargase should be substituted 4 hours after the last cytarabine dose is complete on Day 9, and no asparaginase is given on Day 23.

Methotrexate: Intrathecal (IT)
Day: 1 **FOR ALL PATIENTS**
Day 22: **CNS1/2 PATIENTS 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

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).

NOTE: Await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 22 IV Methotrexate and intrathecal chemotherapy.

Triple Intrathecal Therapy (ITT) -
CNS3 PATIENTS ONLY
Day: 22

Age-based dosing:

Age (yrs)	Dose		
1 to < 1.99	MTX: 8 mg	HC: 8 mg	ARAC: 16 mg
2 to < 2.99	MTX: 10 mg	HC: 10 mg	ARAC: 20 mg
3 to < 8.99	MTX: 12 mg	HC: 12 mg	ARAC: 24 mg
≥ 9	MTX: 15 mg	HC: 15 mg	ARAC: 30 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).

Intermediate Dose Methotrexate: IV over 36 hours
Day: 22
Dose 1000 mg/m²/dose

See Sections 4.3.4 and 5.8 for ID MTX/LCV rescue and infusion guidelines

Leucovorin: PO/IV
Days: 24, 25
Dose: 15 mg/m^2/dose beginning **48 hrs** after the **START** of ID MTX infusion.

- If 48 hr methotrexate level is ≤ 0.5 µM, do not give more than two doses of leucovorin (48 and 54 hours).
- If MTX level at 48 hours is > 0.5 µM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 µM.

See Section 5.8 for ID MTX/LCV rescue and infusion guidelines.

4.4.4 Disease Evaluation End Block 3 (HR/IR Patients ONLY):

- The End Block 3 disease evaluation should not be done earlier than Day 29 (± 1 day);
- The evaluation may be delayed no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- See Sections 7.1 and 13.0 for details on specimen acquisition, handling and shipping.

Notes regarding End Block 3 Disease Assessment:

- BM assessment should be coordinated so that patients begin their preparative regimens no later than 2 weeks from BM documentation of M1.
- If delays > 14 days are required for donor timing or other reasons, patients may receive up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment is required to document remission and MRD status within 14 days of starting the HSCT preparative regimen.
- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

4.4.5 Following completion of Block 3:

For LR B-ALL patients:
Arm C, Continuation 1 (Section 4.11, APPENDIX II-I) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.5 Blinatumomab Block: Cycle 1 (HR/IR Patients in Arm B) - 5 weeks

With Amendment #10, HR/IR patients already assigned to Arm A (standard chemotherapy) who are at an appropriate point in their treatment program (prior to receiving Day 22 treatment on Block 3) will be offered the opportunity to cross over to Arm B to receive blinatumomab.

The therapy described in this section is for the 1st cycle of therapy with Blinatumomab for HR/IR patients. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab Block: Cycle 1 (**Arm B**) is in APPENDIX II-D.

NOTE: Hospitalization is STRONGLY recommended during the first 9 days of this cycle in case of a cytokine reaction. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Corticosteroids should be administered for severe or life threatening cytokine release syndrome.

Blinatumomab infusion interruptions for technical reasons:
The drug administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than one hour should be documented. If the interruption is longer than four hours, re- start of the infusion should be performed in the hospital, under supervision of the investigator. The patient should be observed overnight for possible side effects after the re-start in the hospital and can be discharged the following day if no difficulties arise. Administration of the premedication (dexamethasone) described in Section 4.5.4, is recommended. If possible, the infusion time before and after a break should sum up to 28 days treatment per cycle.

END BLOCK 1 CALLBACK OCCURS PRIOR TO STARTING BLINATUMOMAB BLOCK: CYCLE 1 THERAPY. PLEASE SEE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON STAGED CONSENT, AND APPROPRIATE TIMING TO OBTAIN INFORMED CONSENT.

4.5.1 Criteria to Begin Blinatumomab Block: Cycle 1

Blinatumomab Cycle 1 should begin after submission of end- Block 1 Callback and receipt of treatment assignment and as soon as clinically acceptable to the treating institution. Patients should have time for full or partial recovery (judged by the treating institution) from any toxicities experienced in the prior course(s) of therapy before proceeding to the next course.

For patients beginning Blinatumomab Cycle 1 with M1 marrow, it is recommended to await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL. To continue to receive protocol therapy, M1 patients must begin Blinatumomab Cycle 1 no later than 14 calendar days after callback.

For patients beginning Blinatumomab Cycle 1 with M2 marrow, it is recommended to proceed without awaiting count recovery. To continue to receive protocol therapy, M2 patients must begin Blinatumomab Cycle 1 no later than 5 calendar days after Callback.

4.5.2 Testicular Radiation Therapy (TRT)

- Patients with persistent testicular leukemia at the end of Block 1 are eligible to continue on study and will receive 2400 cGy of testicular radiation during the 1st cycle of Blinatumomab (for HR/IR patients).
- Patients with extramedullary testicular leukemia that has resolved by end-Block 1 will NOT receive testicular irradiation with the exception of that which may be used in the HSCT preparative regimen.
- See Section 14.2 for detailed testicular radiation guidelines.

4.5.3 General Chemotherapy Guidelines

See Section 6.0, DRUG INFORMATION, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA. There is no maximum dosing

4.5.4 Blinatumomab Block: Cycle 1 Chemotherapy

Blinatumomab: IV; Continuous Infusion over 28 days*

Days: 1-28

Dose: 15 micrograms/m²/day

***IV bag will be changed every 24 - 96 hours or every 168 hours (7 days), depending on the details of the infusion preparation**

Dexamethasone: PO/IV

Day: 1

Dose: Prior to day 1 therapy -

- A single dose of 5 mg/m^2/dose (maximum 20 mg/dose) will be administered 30 to 60 minutes prior to the start of the blinatumomab infusion and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
Day: 15, 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

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 15, 29

Age-based dosing:

Age (yrs)	Dose
1 – 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 – 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 – 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

4.5.5 Disease Evaluation End-Blinatumomab Block: Cycle 1

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

4.5.6 Following completion of Blinatumomab Block: Cycle 1 (Arm B)

a. For HR/IR B-ALL patients assigned to Arm B:
Blinatumomab Block Cycle 2 (Section 4.6, APPENDIX II-E) starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

b. Treatment Failures post-Blinatumomab Block:
Patients with a TF post Blinatumomab Block: Cycle 1 (see Section 3.3 for definition) will be taken off protocol therapy.

4.6 Blinatumomab Block: Cycle 2 (HR/IR Patients in Arm B) - 5 weeks

With Amendment #10, HR/IR patients already assigned to Arm A (standard chemotherapy) who are at an appropriate point in their treatment program (prior to receiving Day 22 treatment on Block 3) will be offered the opportunity to cross over to Arm B to receive blinatumomab.

The therapy described in this section is for the 2nd cycle of therapy with blinatumomab on Arm B. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab Block: Cycle 2 (Arm B) is in APPENDIX II-E.

NOTE: Hospitalization is STRONGLY recommended during the first 2 days of this cycle in case of a cytokine reaction. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Corticosteroids should be administered for severe or life threatening cytokine release syndrome.

Blinatumomab infusion interruptions for technical reasons:
The drug administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than one hour should be documented. If the interruption is longer than four hours, re- start of the infusion should be performed in the hospital, under supervision of the investigator. The patient should be observed overnight for possible side effects after the re-start in the hospital and can be discharged the following day if no difficulties arise. (*NOTE: Administration of the premedication (dexamethasone) is NOT RECOMMENDED for the second cycle of blinatumomab.)* If possible, the infusion time before and after a break should sum up to 28 days treatment per cycle.

4.6.1 Criteria to Begin Blinatumomab Block: Cycle 2

- Do not start Blinatumomab Cycle 2 before Day 36 after beginning of Cycle 1.
- Begin Blinatumomab Block: Cycle 2 therapy when ANC ≥ 500/μL and platelets ≥ 50,000/μL.

4.6.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA.

4.6.3 Blinatumomab Block: Cycle 2 Administration Guidelines

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1-28
Dose: 15 micrograms/m²/day

***IV bag will be changed every 24 - 96 hours or every 168 hours (7 days), depending on the details of the infusion preparation**

(*NOTE: Administration of the premedication (dexamethasone) is NOT RECOMMENDED for the second cycle of blinatumomab.)*

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
Days: 8, 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

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 8, 29

Age-based dosing**:**

Age (yrs)	Dose		
1 – 1.99	MTX: 8 mg	HC: 8 mg	ARAC: 16 mg
2 – 2.99	MTX: 10 mg	HC: 10 mg	ARAC: 20 mg
3 – 8.99	MTX: 12 mg	HC: 12 mg	ARAC: 24 mg
≥ 9	MTX: 15 mg	HC: 15 mg	ARAC: 30 mg

4.6.4 Disease Evaluation End-Blinatumomab Block: Cycle 2

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

Notes regarding End-Blinatumomab Block: Cycle 2 Disease Assessment:

- BM assessment should be coordinated so that patients begin their preparative regimens no later than 2 weeks from BM documentation of M1.
- If delays > 14 days are required for donor timing or other reasons, patients may receive up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment is required to document remission and MRD status within 14 days of starting the HSCT preparative regimen.
- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

4.6.5 Following completion of Blinatumomab Block: Cycle 2 (Arm B):

- Patients will continue on to HSCT (See Section 4.9).Patients may receive up to 6 weeks of bridging maintenance therapy prior to HSCT as described in Section 4.10.
- Treatment Failures post-Blinatumomab Block: Cycle 2 (see Section 3.3 for definition) will be taken off protocol therapy.

4.7 Blinatumomab-S: Cycle 1 (Salvage Therapy) - 5 weeks

Patients classified as treatment failures after Block 1 or Block 2 treatment (see Section 3.3 for definitions) who have not previously received blinatumomab on study and who are without evidence of CNS disease will have the option to be non-randomly assigned treatment with up to 2 blocks of salvage blinatumomab (Blinatumomab-S), and continue on study with HSCT therapy if a CR is achieved. Eligible patients should complete the appropriate callback (Section 3.1.7) before initiating Salvage Therapy treatment. **Note that blinatumomab dosing in Blinatumomab-S cycles differs from dosing in Blinatumomab Block cycles** (See Section 4.7.4.) The schedule below describes treatment for the 1st cycle only. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab-S: Cycle 1 is in APPENDIX II–F.

NOTE: Hospitalization is STRONGLY recommended during the first 9 days of this cycle in case of a cytokine reaction. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Corticosteroids should be administered for severe or life threatening cytokine release syndrome.

Blinatumomab infusion interruptions for technical reasons:
The drug administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than one hour should be documented. If the interruption is longer than four hours, re- start of the infusion should be performed in the hospital, under supervision of the investigator. The patient should be observed overnight for possible side effects after the re-start in the hospital and can be discharged the following day if no difficulties arise. Administration of the premedication (dexamethasone) described in Section 4.5.4, is recommended. If possible, the infusion time before and after a break should sum up to 28 days treatment per cycle.

OBTAIN INFORMED CONSENT PRIOR TO INITIATING THE FIRST CYCLE OF SALVAGE THERAPY. PLEASE SEE THE SUMMARY TABLE IN SECTION 3.1.5 FOR DETAILS ON TIMING TO OBTAIN INFORMED CONSENT. CALLBACK OCCURS PRIOR TO STARTING BLINATUMOMAB-S: CYCLE 1 THERAPY (See Section 3.1.7 for appropriate callback).

4.7.1 Criteria to Begin Blinatumomab-S: Cycle 1

- None

4.7.2 Testicular Radiation Therapy (TRT)

- All Treatment Failures on the basis of M3 marrow at the end of Block 1 who also have persistent testicular leukemia will receive 2400 cGy of testicular radiation during the 1st cycle of Salvage Therapy (Blinatumomab-S: Cycle 1).
- Patients with extramedullary testicular leukemia that has resolved by end Block 1 will NOT receive testicular irradiation with the exception of that which may be used in the HSCT preparative regimen for HR/IR patients.

- See Section 14.2 for detailed radiation guidelines.

4.7.3 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA.

4.7.4 Blinatumomab-S: Cycle 1 Chemotherapy Guidelines

Blinatumomab: IV; Continuous Infusion over 28 days*

Days: 1-28

Dose: 5 micrograms/m²/day (Days 1-7) followed by 15 micrograms/m²/day (Days 8-28)

***IV bag will be changed every 24 - 96 hours or every 168 hours (7 days), depending on the details of the infusion preparation**

Dexamethasone: PO/IV

Dose: Prior to day 1 and day 8 of therapy -

- A single dose of 5 mg/m²/dose (maximum 20 mg/dose) will be administered 30 to 60 minutes prior to the start of the blinatumomab infusion on Day 1, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Methotrexate: Intrathecal (IT)

Day: 15

Age-based dosing**:**

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

4.7.5 Disease Evaluation End Blinatumomab-S Cycle 1:

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

4.7.6 Following completion of Blinatumomab-S: Cycle 1:

a. Patients with M1 marrow after Blinatumomab-S Cycle 1:

- If patient has recovered counts to ANC ≥ 500/µL and platelets ≥ 50,000/µL (i.e., have achieved a CR), then proceed to HSCT on study as soon as possible. See Section 4.9.
- If patient has NOT recovered counts to ANC ≥ 500/µL and platelets ≥ 50,000/µL at the time of the marrow evaluation, but recovers counts within 1 week of the marrow evaluation, then this will be considered a CR and the patient should proceed to HSCT as soon as possible.
- If patient has NOT recovered counts to ANC ≥ 500/µL and platelets ≥ 50,000/µL at the time of the marrow evaluation, and does NOT recover counts within 1 week of the marrow evaluation, a repeat marrow every 1 - 2 weeks until either patient meets definition of CR (in which case the patient may proceed to HSCT) or develops an M2/M3 marrow (in which case proceed as detailed in Section 4.7.6.b).
- Patients should begin their preparative regimens no later than 2 weeks from BM documentation of M1.
- If patient achieves a CR but delays > 14 days are required for donor timing or other reasons, patients may receive Blinatumomab-S Cycle 2 as described in Section 4.8 or up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment will be needed to document remission and MRD status within 14 days of starting the HSCT preparative regimen.
- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

b. Patients with M2/M3 marrow after Blinatumomab-S: Cycle 1

Such patients proceed to Blinatumomab-S: Cycle 2 (Section 4.8, APPENDIX II-G) without awaiting count recovery.

4.8 **Blinatumomab-S: Cycle 2 (Salvage Therapy) - 5 weeks**

Blinatumomab-S: Cycle 2 is for patients with M2/M3 marrow after completion of Blinatumomab-S: Cycle 1. Patients who are M1 after completion of Blinatumomab-S: Cycle 1 and have delays >14 days before initiating HSCT may also receive treatment on Blinatumomab-S: Cycle 2 (See Section 4.7.6). **Note that blinatumomab dosing in Blinatumomab-S cycles differs from dosing in Blinatumomab Block cycles** (See Section 4.8.3.)

The schedule below describes treatment for the 2nd cycle only. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab-S: Cycle 2 is in APPENDIX II - G.

NOTE: Hospitalization is STRONGLY recommended during the first 2 days of this cycle in case of a cytokine reaction. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Corticosteroids should be administered for severe or life threatening cytokine release syndrome.

Blinatumomab infusion interruptions for technical reasons:

The drug administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than one hour should be documented. If the interruption is longer than four hours, re- start of the infusion should be performed in the hospital, under supervision of the investigator. The patient should be observed overnight for possible side effects after the re-start in the hospital and can be discharged the following day if no difficulties arise. *NOTE: Administration of the premedication (dexamethasone) is NOT RECOMMENDED for the second cycle of blinatumomab.)* If possible, the infusion time before and after a break should sum up to 28 days treatment per cycle.

4.8.1 Criteria to Begin Blinatumomab-S: Cycle 2

Do not start Blinatumomab-S: Cycle 2 before Day 36 after beginning of Cycle 1.

4.8.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA.

4.8.3 Blinatumomab-S: Cycle 2 Chemotherapy

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1-28
Dose: 15 micrograms/m²/day (Days 1-28)

***IV bag will be changed every 24-96 hours or every 168 hours (7 days), depending on the details of the infusion preparation**

(*NOTE: Administration of the premedication (dexamethasone) is NOT RECOMMENDED for the second cycle of blinatumomab.)*

Methotrexate: Intrathecal (IT)
Day: 8 & 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

4.8.4 Disease Evaluation End-Blinatumomab-S: Cycle 2

- The end block disease staging should be performed no earlier than Day 29 (± 1 day);
- The evaluation may be delayed to no later than Day 36 (± 1 day) if ANC < 500/µL and platelets < 50,000/µL on Day 29.
- Two (2 mL) of bone marrow will be collected and shipped to the flow cytometry laboratory for MRD determination
- See Sections 7.1 and 13.0 for details on specimen handling and shipping.

4.8.5 Following completion of Blinatumomab-S: Cycle 2:

a. Patients with M1 marrow after Blinatumomab-S Cycle 2:

- If patient has recovered counts to ANC ≥ 500/µL and platelets ≥ 50,000/µL (i.e., have achieved a CR), then proceed to HSCT on study as soon as possible. See Section 4.9.
- If patient has NOT recovered counts to ANC ≥ 500/µL and platelets ≥ 50,000/µL at the time of the marrow evaluation, but recovers counts within 1 week of the marrow evaluation, then this will be considered a CR and the patient should proceed to HSCT as soon as possible.
- If patient has NOT recovered counts to ANC ≥ 500/µL and platelets ≥ 50,000/µL at the time of the marrow evaluation, and does NOT recover counts within 1 week of the marrow evaluation, a repeat marrow

every 1-2 weeks until either patient meets definition of CR (in which case the patient may proceed to HSCT) or develops an M2/M3 marrow (in which case proceed as detailed in Section 4.8.5.b).

- Patients should begin their preparative regimens no later than 2 weeks from BM documentation of M1.
- If patient achieves CR but delays > 14 days are required for donor timing or other reasons, patients may receive up to 6 weeks of bridging maintenance therapy as described in Section 4.10.
- For patients who receive bridging therapy, a repeat BM assessment will be needed to document remission and MRD status within 14 days of starting the HSCT preparative regimen.
- Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

b. Patients with M2/M3 marrow after Blinatumomab-S Cycle 2

Remove from protocol therapy.

4.9 Hematopoietic Stem Cell Transplant

All transplants performed on COG trials must occur at FACT-accredited HSCT programs with the exception of adolescents/adults being treated on COG trials who are referred to an adult transplant facility. See the COG Administrative Policy 3.3 regarding the agreement requirements for these cases.

4.9.1 Overview

Stem cell transplantation in this study will be utilized in patients with HR/IR relapse ALL (see Section 3.3 for risk definitions).

All patients enrolled on this protocol and their full siblings should undergo HLA tissue typing as soon as possible after diagnosis of relapse. All high-risk patients should have transplantation consultation and initiation of a donor search early while undergoing their initial Block 1 therapy. It is recommended that all intermediate-risk patients also undergo transplantation consultation as soon as possible after Block 1 therapy, so that a donor search can be initiated immediately if they are noted to be MRD+ after initial induction. The goal of this protocol is to move to transplantation within 2 weeks of recovery from the final consolidation cycle or completion of Salvage Therapy (Blinatumomab-S). As unrelated donor acquisition can take 8 - 12 weeks, to meet this deadline centers must expedite the search process. Please see Section 7.1c for details of required evaluations.

Patients going on to HSCT will undergo an extensive pre-transplant evaluation to assess remission status, assure adequate organ system function, and document freedom from active viral, bacterial, and fungal infection. Patients should begin their preparative regimen no later than 2 weeks after obtaining the BM aspiration scheduled after recovery from their final consolidation cycle or completion of Salvage Therapy (Blinatumomab-S). If transplantation is delayed by 14 days for donor timing or other reasons, patients may receive up to 6 weeks of bridging maintenance therapy as described in Section 4.10, Appendix II-H. For patients who receive bridging therapy, a repeat BM assessment will be needed to document remission and MRD status within 14 days of starting the HSCT preparative regimen. Patients who are unable to begin the transplant preparative regimen within 8 weeks of initial BM assessment are off protocol therapy.

Patients will receive 1 of 3 designated preparative regimens (cyclophosphamide/total body irradiation (TBI) [cy/TBI] alone or with thiotepa or etoposide). Fludarabine will be added to cy/TBI for cord blood recipients. GVHD prophylaxis varies slightly according to stem cell source.

Patients who are high risk for relapse (MRD+ pre-HSCT with no evidence of GVHD by Day +55, or with + MRD post BMT) are eligible for early taper of immune suppression. The intent of the protocol will be for patients to undergo TBI-based myeloablative conditioning. If patients are not eligible for a myeloablative regimen and either do not undergo HSCT or undergo a reduced intensity procedure, limited data will be collected regarding post transplant survival and relapse.

In the recent COG ASCT0431 trial some variability was allowed in lung shielding with total body irradition. Review of ASCT0431 data showed that lung irradiation doses above 800 cGy were significantly associated with an increased risk of treatment-related mortality and relapse, largely due to toxicity (Pulsipher and Lu, unpublished data November 2014). Accordingly, AALL1331 mandates lung shielding with total body irradiation to limit the lung dose to less than 800 cGy (See Section 14.0 for Radiation Therapy Guidelines).

4.9.1.1 **Eligibility Criteria for Hematopoietic Stem Cell Transplant (HSCT)**

Patients who have an appropriately matched stem cell source (see Section 4.9.1.5) and who meet one of the following criteria:

1. Patients with HR relapse:
   - Early (< 36 months) marrow
   - Early (< 18 months) IEM

2. Patients with IR relapse with persistent MRD:
   - Late (≥ 36 months) marrow, end-Block 1 MRD ≥ 0.1%
   - Late (≥ 18 months) IEM, end-Block 1 MRD ≥ 0.1%

3. Patients with treatment failure (TF) who achieve a CR after receiving blinatumomab.

   NOTE: Patients must maintain an M1 marrow (< 5% blasts) through the BM assessment prior to transplant. (Patients who achieve a remission and relapse prior to HSCT can go to HSCT later, but as they have met a study endpoint (relapse), this procedure will be as per center preference and the patient will only be followed for survival.)

4.9.1.2 **Exclusion Criteria for Hematopoietic Stem Cell Transplant (HSCT)**

Interval development of significant pathology that would preclude HSCT including the following infectious and organ system pathologies:

1. Infections

   Patients with uncontrolled fungal, bacterial or viral infections are excluded.

   Patients acquiring fungal disease during Induction therapy may proceed if they have a significant response to antifungal therapy with no or minimal evidence of active disease remaining by CT evaluation.

2. Organ Function Requirements for HSCT

   Must meet the criteria for renal, biliary and cardiac function as outlined in Section 3.2.4. In addition, must have adequate pulmonary function defined as anFEV_1, FVC, and DLCO (corrected for Hgb) ≥ 60% by pulmonary function tests (PFTs).

   For children who are unable to cooperate for PFTs, the criteria are: no evidence of dyspnea at rest, no exercise intolerance, and not requiring supplemental oxygen therapy.

3. Performance Status
   Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Please refer to performance status scale at:
   https://members.childrensoncologygroup.org/_files/protocol/Standard/PerformanceStatusScalesScoring.pdf

4.9.1.3 **Eligibility for Accelerated Taper of Immune Suppression**

a. Patients who are MRD+ (≥ 0.01%) within 2 weeks of beginning HSCT preparative regimen who do not have any evidence of aGVHD by Day +55 post HSCT (pre-MRD+ group)

b. Patients who are MRD- (< 0.01%) within 2 weeks of beginning HSCT preparative regimen but are found to be MRD+ (≥ 0.01%) on peri-engraftment (Day +28-55) or Day +100 marrow who do not have any evidence of aGVHD by Day +55 (peri-engraftment group) or Day +100 (Day +100 group)

4.9.1.3.1 **Adjustment of TBI/chemotherapy During the Preparative Regimen**

The full dose of preparative regimen TBI and chemotherapy agents will be administered unless patients have a life threatening reaction thought likely to occur again with continued administration and an appropriate substitution cannot be made (i.e. etopophos for etoposide).

4.9.1.4 **Dose Adjustment of Chemotherapy for Patients Whose Weight Exceeds > 125% Ideal Body Weight (IBW)**

Chemotherapy given during the preparative regimen (thiotepa, cyclophosphamide, and etoposide) will be dosed based on actual weight for patients ≤ 125% IBW. Those > 125% IBW will be dosed based upon adjusted ideal body weight as follows:

Adjusted ideal body weight = IBW + 0.25 (Actual weight – IBW).

The following formulas for pediatric and adult IBW calculations are recommended, but IBW may be calculated according to institutional standard operating procedures (SOPs).

<u>Recommended Ideal Body Weight Calculation for Children Age 1 - 17 years</u>

$$\text{IBW} = \frac{\text{Height (cm)}^2 \times 1.65}{1000}$$

<u>Recommended Ideal Body Weight Calculation for Adults (Height > 5 feet/60 inches)</u>

IBW (females) = (cm ÷ 2.54 – 60) x 2.3 kg + 45.5 kg

IBW (males) = (cm ÷ 2.54 – 60) x 2.3 kg + 50 kg

4.9.1.5 **Stem Cell Source Requirements**

Molecular typing at high resolution of HLA A, B, C, and DRB1 is required, and DQB1 suggested, for all bone marrow or peripheral blood stem cell (PBSC) donors who are either unrelated or related but not matched siblings (i.e. matched parent, partially mismatched sibling, etc.). For matched sibling donors and cord blood units, intermediate level matching of class I antigens is acceptable, but allele level typing is required for DRB1 and encouraged for class I antigens and DQB1.

Hierarchy of stem cell choices is as follows:

1) Preferred: Genotypically HLA matched siblings

2) If genotypically matched sibling is not available, the following are equally acceptable:

   a) **Unrelated or "other" related (non-genotypically matched) donors** must be matched at 8/8 or 7/8 alleles (HLA-A, B, C and DRB1 at high resolution).

   b) **Unrelated cord blood units** must be matched at 4/6, 5/6, or 6/6 antigens (HLA A, B [intermediate), and DRB1 [high resolution]). Published data show lower non-relapse mortality when patients receive units matched at 8/8, 7/8, or 6/8 alleles (HLA-A, B, C and DRB1 at high resolution), therefore allele-level typing is strongly encouraged. Use of cords matched at 5/8 or 4/8 alleles leads to more TRM, but are acceptable if better matches are not available. It is recommended that units matching at the 3/8 allele level be avoided if possible. Minimum pre-thaw cell dose of 3×10^7 nucleated cells/kg recipient weight is required. Two cords may be used if this cell dose is not achieved with a single unit. The two units must each match the recipient at a minimum of 4/6 antigens and must match each other at a minimum of 3/6 antigens.

   NOTE: Centers using unlicensed cord blood must consent the patient on the NMDP cord blood IND protocol or other cord blood IND protocols as appropriate in order to use such units on this study

3) Use of Peripheral Blood Stem Cells (PBSC)
   Bone marrow should be requested from allogeneic donors. PBSC is allowed only if the donor is unable or unwilling to give marrow.

4.9.1.5.1 Recommended minimum cell doses:

HPC-M cell dose should be at least 1×10^8 TNC/kg
HPC-A cell dose should be at least 2×10^6 CD34/kg

4.9.1.6 **Preparative Regimens**

Preparative regimens allowed on this protocol are standard regimens used in ASCT0431 for related and unrelated BM/PBSC recipients and BMT CTN 0501 for cord blood recipients. ASCT0431 designated TBI 1200cGy/thiotepa/cyclophosphamide, but also allowed a variation substituting etoposide for thiotepa and a second variation substituting a slightly higher TBI dose (1320cGy) for thiotepa. BMT CTN 0501 used TBI 1320/cyclophosphamide/fludarabine for all patients.

4.9.2 Preparative Regimen Administration

4.9.2.1 **TBI Administration**

Fractionated TBI will be administered according to protocol guidelines (see Section 14.5 for radiotherapy guidelines). TBI may be delivered from either linear accelerator or Cobalt sources.

4.9.2.2 **Thiotepa Administration** (for centers choosing the thiotepa-containing regimen).

- Thiotepa will be administered intravenously over 3 hours. To minimize skin toxicity, frequent bathing (minimum 2 - 3x daily) is required on the days of thiotepa administration as per center standard.
- See above for dose modification if weight exceeds 125% of IBW

4.9.2.3 **Cyclophosphamide Administration**

- Cyclophosphamide will be administered intravenously over 1-6 hours.
- Hyperhydration, maintenance of significant urine output after administration, and the use of Mesna is required.
- Recommended mesna dosing: 360 mg/m^2 during cyclophosphamide followed by 120 mg/m^2/hour for 12 hours after each dose. Institutional standards or protocols for mesna administration may also be used.
- See above for dose modification if weight exceeds 125% of IBW

4.9.2.4 **Etoposide Administration** (for centers choosing etoposide regimen)

- Etoposide will be administered intravenously at a maximum infusion rate of 300 mg/m^2/hour for a minimum of 5 hours or per institutional standard.
- Patients should be given 1.5X maintenance fluids during etoposide administration to minimize the risk of hypotension.
- Etopophos substitution is allowed.
- See above for dose modification if weight exceeds 125% of IBW

4.9.2.5 **Fludarabine Administration**

- Fludarabine will be administered intravenously over 30 - 60 minutes each day.
- Fludarabine **will not** be adjusted for body weight.

4.9.3 Preparative Regimen Administration Tables

4.9.3.1 TBI 1200/thiotepa/cyclophosphamide Regimen (related and unrelated BM/PBSC)

Treatment	Route	Dose	Days	Notes
TBI		200 cGy BID	Day -8, -7, & -6	May deliver 1200 cGy fractionated TBI over 4 days per center preference
Thiotepa	IV over 3 hours daily	5 mg/kg/day	Day -5 & -4	
Cyclophosphamide	IV over 1-6 hours daily	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.3.2 TBI 1200/etoposide/cyclophosphamide Regimen (related and unrelated BM/PBSC)

Drug/Treatment	Route	Dose	Days	Notes
TBI		200 cGy BID	Day -7, -6, & -5	May deliver 1200 cGy fractionated TBI over 4 days per center preference
Etoposide	IV over a minimum of 5 hours or per institutional standard	1500 mg/m^2	Day -4	maximum rate of infusion is 300 mg/m^2/hour or per institutional standard
Cyclophosphamide	IV over 1-6 hours daily	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.3.3 TBI 1320/cyclophosphamide Regimen (related and unrelated BM/PBSC)

Treatment	Route	Dose	Days	Notes
TBI		165 cGy BID	Day -7, -6, -5, & -4	Total dose must be 1320 cCy
Cyclophosphamide	IV over 1-6 hours daily	60 mg/kg/day	Day -3 & - 2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.3.4 TBI 1320/fludarabine/cyclophosphamide Regimen (related and unrelated cord blood)

Treatment	Route	Dose	Days	Notes
Fludarabine	IV over 30 - 60 minutes daily	25 mg/m^2/day	Day -10, -9, -8	
TBI		165 cGy BID	Day -7, -6, -5, & -4	Total dose must be 1320 cCy
Cyclophosphamide	IV over 1-6 hours daily	60 mg/kg/day	Day -3 & -2	
Rest			Day -1	
Infusion of allogeneic HSCT			Day 0	

4.9.4 Sanctuary Site Therapy (see Section 14.0)

Prior to transplant, designated patients with extramedullary relapse must receive cranial or testicular radiotherapy boosting in addition to the doses of TBI associated with the preparative regimen. The cranial boost and/or testicular boosts should be given over 3 days prior to the beginning of TBI.

4.9.4.1 **Radiotherapy boost for patients with CNS leukemia (CNS3) at relapse**:

Patients with CNS3 involvement at the time relapse with or without a history of prior CNS leukemia and/or radiotherapy will receive a cranial radiotherapy boost just prior to TBI (3 doses, maximum 200 cGy daily: total dose to cranial axis = 1800 cGy (unless alternative TBI dose given in which case the dose will be 1920 cGy). If the patient is ≤ 3 years at the time of transplant, centers may elect not to give a boost because of developmental concerns. If the patient has CNS1 or CNS2 status at relapse, no boost will be given.

4.9.4.2 **Testicular boost for patients with testicular leukemia at relapse:**

The only patients that will receive a testicular boost prior to TBI (3 daily doses, 200 cGy fractions, total 600 cGy) are IR/HR/TF patients with extramedullary testicular leukemia at the time of relapse that DID resolve by end Block 1, since those without resolution have already received 2400 cGy of testicular radiation.

4.9.4.3 **Prophylactic testicular boosting**:

Prophylactic testicular boosting of 400 cGy for patients without testicular relapse is allowed, but not part of the designated therapy.

4.9.5 Growth Factor Administration

Filgrastim (G-CSF) at a dose of 5 micrograms/kg/day given IV or subcutaneously is required for recipients of cord blood starting at Day +1 and continuing until patients are fully engrafted. G-CSF is generally not necessary for BM/PBSC recipients and is not recommended, unless engraftment is delayed.

4.9.6 GVHD Prophylaxis

GVHD prophylaxis will consist of tacrolimus/methotrexate (TAC/MTX) for recipients of related and unrelated donor BM/PBSC and cyclosporine and mycophenolate mofetil (CYA/MMF) for cord blood recipients. Substitution of CYA for TAC or TAC for CYA according to center preference is allowed.

Drug	Route*	Dose	Days	Important Notes
BM Recipient				
Tacrolimus (TAC)	IV	0.02 mg/kg/day cont infusion	Begin Day -3	Target concentration 8 - 12 ng/mL
Methotrexate (MTX)	IV	5 mg/m^2 sib donor 10 mg/m^2 URD^	+1, +3, &+6 sibs +1, +3, +6, +11 URD	
Cord Recipient				
Cyclosporine A (CYA)	IV	Varies by age, adjusted to target	Begin Day -3	Target concentration 200 - 400 ng/mL
Mycophenolate mofetil (MMF)	IV	≥ 50 kg: 1000 mg q8h < 50kg: 15 mg/kg q8h	Begin Day -3	

* All drugs may be switched to PO after engraftment when patients are able to tolerate and absorb PO medications.

^ URD, unrelated donor

4.9.6.1 **Tacrolimus Administration, Monitoring and Dose Adjustments (related or unrelated BM/PBSC)**

Tacrolimus should be administered by continuous IV infusion until patients are able to take PO. Serum tacrolimus troughs and serum magnesium, potassium, and creatinine should be drawn at least twice per week while hospitalized, then as per good clinical practice thereafter unless a change in medication (e.g. use of concomitant CYP3A4 inhibitors) or renal function might result in an acute change in level.

At that point, concentrations will be measured as clinically indicated. Concentrations sent when dosing by continuous infusion are not true trough concentrations, however, the same target range of drug concentration will be used for both continuous IV and bolus PO routes of administration.

When converting patients at a therapeutic tacrolimus level from IV to PO formulation, multiply total daily IV dose times 4 and administer in 2 divided oral doses per day, every 12 hours (e.g., 1 mg of IV tacrolimus per day equates to 4 mg of PO tacrolimus per day). Younger children (eg. < 6 years of age) may require more frequent PO tacrolimus dosing (every 8 hours) to maintain target trough concentrations. The oral dose should be administered 8 - 12 hours after the end of the tacrolimus continuous infusion.[41]

The target serum trough concentration for tacrolimus is 8 - 12 ng/mL. Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level.

4.9.6.2 **Methotrexate Administration, Monitoring and Dose Adjustments (related or unrelated BM/PBSC)**

For patients receiving sibling donors, methotrexate should be given at a dose of 5 mg/m^2 on Days +1, 3, and 6 after transplant. For patients receiving unrelated BM or PBSC, methotrexate should be given at a dose of 10 mg/m^2 on Days +1, 3, and 6, and 11. All doses of methotrexate should be administered as scheduled if possible, but centers may modify or hold methotrexate for significant toxicity (see Section 5.8 for methotrexate dose modification guidelines).

4.9.6.3 **Leucovorin Administration**

Leucovorin may be given at the physician's discretion for patients at risk for methotrexate toxicity. Patients at risk for methotrexate toxicity include those with extravascular fluid collections (ascites, pleural effusions) or with decreased renal function (see Section 5.8).

4.9.6.4 **Cyclosporine Administration, Monitoring and Dose Adjustments (related and unrelated cord blood)**

Cyclosporine should be administered by IV infusion until patients are able to take PO. Cyclosporine levels as well as serum magnesium, potassium, and creatinine levels should be drawn at least twice per week while hospitalized, then weekly or monthly thereafter unless a change in medication (e.g. use of concomitant CYP3A4 inhibitors) or renal function might result in an acute change in level. At that point, levels will be measured as clinically indicated. When converting patients at a therapeutic tacrolimus level from IV to PO formulation, multiply the IV dose times 2.5 if using the modified formulation (i.e., Neoral or Gengraf) or times 3 if using the non-modified formulation (i.e., SandIMMUNE).

The target serum trough concentration for cyclosporine is 200 – 400 ng/mL. Variations in dosing levels based upon laboratory methodology (e.g. tandem mass-spec analysis) allowed. Dose adjustments are based on clinical judgment of the treating physician after considering clinical toxicity, serum levels, GVHD, concomitant drug use and the rate of rise or decline of the serum level.

4.9.6.5 **Mycophenolate Mofetil (MMF) Administration and Dose Adjustments (related and unrelated cord blood)**

MMF should be given at a dose of 1 gram IV q8 hours for patients ≥ 50kg or 15 mg/kg IV q8 hours for patients < 50 kg beginning the morning of Day -3. MMF should be given IV until patient can tolerate oral medications. MMF should be dosed upon actual body weight.

The FDA has determined that a REMS (Risk Evaluation and Mitigation Strategy) program is necessary to ensure the benefits of mycophenolate outweigh the risks of first trimester pregnancy loss and congenital malformations associated with mycophenolate use during pregnancy. Mycophenolate REMS is a program to tell doctors, nurses, pharmacists and patients about the risks of taking mycophenolate during pregnancy. The program also contains important information about patient education and reporting details for pregnancy. Please refer to the website for additional information (https://www.mycophenolaterems.com/). If ≤ Grade 1 acute GVHD, MMF will be discontinued by Day +30. For patients with > Grade 1 acute GVHD, the MMF taper will be per institutional protocols. Patients may transition to PO formulations at a 1:1 IV to PO conversion when clinically appropriate. Refer to Section 5.13 for dose adjustments based upon clinical and laboratory findings.

4.9.7 Standard Taper of Immune Suppression

This applies to all patients who are MRD negative pre- and at all times post-transplant who have not developed aGVHD requiring systemic therapy. (Patients who develop significant aGVHD will be tapered at the discretion of the transplant center.)

Drug	Stem Cell Source	Taper Schedule
Tacrolimus	Matched Sibling BM/PBSC	Start Day +42 over 8 weeks, off by Day +98
Tacrolimus	Unrelated Donor BM/PBSC	Start Day +100 off by Day +180
Cyclosporine	Unrelated Cord	Start Day +100 off by Day +180
Mycophenolate Mofetil	Unrelated Cord	Continue until Day +45 or 7 days after engraftment, whichever day is later. Stop without a taper.

4.9.8 Accelerated Taper of Immune Suppression

See Section 4.9.1 for eligibility requirements.

4.9.8.1 Taper for patients who are MRD positive pre-HSCT with no aGVHD by Day +55 and for patients who are MRD positive > 0.01% by flow cytometry at their peri-engraftment BM test (approx. Day +30)

Drug	Stem Cell Source	Taper Schedule
Tacrolimus	Matched Sibling BM/PBSC	Taper already started by Day +42. At Day +55 increase rate of taper to complete taper by Day +70
Tacrolimus	Unrelated Donor BM/PBSC	Start Day+55 off by Day +100
Cyclosporine	Unrelated Cord	Start Day+55 off by Day +100

Mycophenolate Mofetil	Unrelated Cord	Continue until Day +45 or 7 days after engraftment, whichever day is later. Stop without a taper.

4.9.8.2 Taper for patients who are MRD negative pre- HSCT with no aGVHD by Day +55 who are MRD positive > 0.01% by flow cytometry at their Day +100 test.

Drug	Stem Cell Source	Taper Schedule
Tacrolimus	Matched Sibling BM/PBSC	Taper already started by Day +42 and pt should be off immune suppression. Stop tacrolimus without taper if still on medication.
Tacrolimus	Unrelated Donor BM/PBSC	Taper over 2-3 weeks as soon as MRD report is received.
Cyclosporine	Unrelated Cord	Taper over 2-3 weeks as soon as MRD report is received.
Mycophenolate Mofetil	Unrelated Cord	Should be off this medication.

4.10 **Bridging Maintenance Therapy (All HR/IR Patients, as required) – up to 6 weeks**

This therapy is for all HR/IR patients who have completed either Blocks 2 and 3 of chemotherapy or both cycles of blinatumomab and due to stem cell source or facility scheduling issues have a lag time > 2 weeks after count recovery prior to starting HSCT therapy. Patients should start bridging therapy when clinically able after meeting count requirements and continue until approximately one week prior to beginning the transplant preparative regimen.

The Therapy Delivery Map (TDM) for Bridging therapy is in Appendix II-H.

4.10.1 Criteria to Begin Bridging Maintenance Therapy

Start when peripheral counts recover to ANC ≥ 500/μL and platelets ≥ 50,000/μL.

4.10.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines**.**

Dosing should be based on actual BSA.

4.10.3 Bridging Maintenance Chemotherapy Guidelines

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Mercaptopurine: PO
Days: 1 - 42
Dose: 75 mg/m^2/dose* once daily

Other Considerations:

- ***See** Section 5.9 for suggested starting dose based on TPMT status (if status is known)
- Mercaptopurine should be taken consistently at the same time every day.
- The liquid or tablet formulation may be used. If using tablets, adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible

Methotrexate: PO
Days: 1, 8, 15, 22, 29, 36
Dose: 20 mg/m^2/dose

Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water).

4.11 Continuation 1/Continuation 2 (All LR Patients) - 8 weeks

The therapy described in this section is for all LR patients in either **Arm C** or **Arm D** and represents therapy given during Continuation 1 and Continuation 2. See Experimental Design Schema.

The therapy delivery map for Continuation 1 and Continuation 2 is in APPENDIX II-I.

4.11.1 Criteria to Begin and During Continuation Therapy

a. Begin Continuation when ANC ≥ 500/µL and platelets ≥ 50,000/µL.
b. All Patients should have ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to starting therapy on Days 22 and 43.

- If at Day 22 the ANC is < 500/µL and platelets < 50,000/µL, it is permissible to delay the divided dose oral methotrexate (ddMTX) (25 mg/m^2/dose for CNS1/2) or ID MTX (for CNS3) by until counts recover.

- If counts are not recovered after one (1) week, then omit the Day 22 ddMTX or ID MTX for this cycle. After counts recover, resume with the Day 29 standard dose MTX.

4.11.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.11.3 Continuation 1/Continuation 2 Chemotherapy Guidelines

Dexamethasone: PO (may be given IV)

Days: 1 - 5

Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Methotrexate: Intrathecal (IT) –CNS1/2 PATIENTS ONLY

Days: 1, 43

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).

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 1, 43

Age-based dosing**:**

Age (yrs)	Dose
1 – 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 – 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 – 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

When ITT therapy and ID MTX are scheduled for the same day, deliver the ITT 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: PO
Days: 1 - 42
Dose: 75 mg/m²/dose* once daily

Other Considerations:

- ***See Section 5.9** for suggested starting dose based on TPMT status, if known
- Mercaptopurine should be taken consistently at the same time every day.
- The liquid or tablet formulation may be used. If using tablets, adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m^2/week as possible

Methotrexate: PO
Days: 8, 15, 29, 36
Dose: 20 mg/m^2/dose
Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water).

Divided Dose Methotrexate (dd MTX): PO - CNS1/2 PATIENTS ONLY
Day: 22
Dose: 25 mg/m^2/dose Q6H x 4 doses

Other Considerations:

- ANC must be ≥ 500/µL and platelets must be ≥ 50,000/µL prior to Day 22 therapy.
- Administer on an empty stomach (at least 1 hour before or 2 hours after food or drink except water).

Leucovorin: PO CNS 1 AND 2 PATIENTS ONLY
Day: 24

Dose: 10 mg/m²/dose for 2 doses 6 hours apart beginning **48 hrs** after the **START** of Day 22 Methotrexate

Intermediate Dose Methotrexate (ID MTX): IV over 36 hours - CNS3 PATIENTS ONLY
Day: 22
Dose: 1000 mg/m²/dose
Given as a 100 mg/m² bolus over 30 minutes followed by 900 mg/m² over 35.5 hours.
Be certain that the ID MTX infusion is completed in the 36 hour period. **Even if the infusion is not complete at this time point, it must be stopped.**

Leucovorin rescue: See below.

Suggested hydration and alkalinization for IDMTX: Prehydrate with D5 ¼ NS with 30 mEq NaHCO3/L at 125 mL/m²/hour to achieve a urine specific gravity ≤ 1.010 and pH between 7 and 8. 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 ≤ 1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m² 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 using D 5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m²/hour throughout IDMTX infusion, and until the last dose of leucovorin has been given. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is < 0.1 μM.

Timing of ID MTX
ANC must be ≥ 500/μL and platelets must be ≥ 50 000/μL prior to ID MTX.

Leucovorin: PO/IV CNS 3 PATIENTS ONLY
Days: 24, 25
Dose: 15 mg/m²/dose every 6 hours beginning **48 hrs** after the **START** of ID MTX infusion.

- If 48 hr methotrexate level is ≤ 0.5 μM, do not give more than two doses of leucovorin (48 and 54 hours).
- If MTX level at 48 hours is > 0.5 μM, then continue hydration and leucovorin rescue at 15 mg/m²/dose po/IV every 6 hours until MTX levels are < 0.1 μM.

See Section 5.8 for ID MTX/LCV rescue and infusion guidelines.

Cyclophosphamide: IV over 15 - 30 minutes
Days: 43, 50
Dose: 300 mg/m²/dose (see note below)

Etoposide: IV over 1 - 2 hours
Days: 43, 50
Dose: 150 mg/m²/dose

Note: ANC must be ≥ 500/µL and platelets must be ≥ 50,000/µL prior to Day 43 therapy. Once the Day 43 cyclophosphamide/etoposide is given, the Day 50 cyclophosphamide/etoposide doses should be given regardless of blood counts (hold only for presumed or proven significant infection).

Thioguanine: PO
Days: 43 - 49.
Dose: 40 mg/m^2/dose once daily

Other Considerations:
- Administer consistently at the same time every day.
- Adjust daily dose using the dosing nomogram in Appendix IV to attain a weekly cumulative dose as close to 280 mg/m^2/week as possible.
- An oral suspension can also be compounded for patients who cannot swallow pills. The compounded oral suspension is recommended for patients with a BSA between 0.27 and 0.48 m^2. (see Section 6.18)

Cytarabine: IV over 1 - 30 minutes or SQ
Days: 44 - 47, 51 -54
Dose: 50 mg/m^2/dose once daily

4.11.4 Following Continuation 1:

a. LR B-ALL patients randomized to the control arm (**Arm C**) will receive Continuation 2 (Section 4.11, APPENDIX II-I) when ANC ≥ 500/µL and platelets ≥50,000/µL.
b. LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Blinatumomab Block: Cycle 2 (**Arm D**) - (Section 4.16, APPENDIX II-N) when ANC ≥ 500/µL and platelets ≥50,000/µL.

4.11.5 Following Continuation 2:

a. LR B-ALL patients randomized to the control arm (**Arm C**) will receive Maintenance Cycle 1 therapy (Section 4.12, Appendix II-J) when ANC ≥ 500/µL and platelets ≥ 50,000/µL.
b. LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Blinatumomab Block: Cycle 3 (**Arm D**) - (Section 4.16, APPENDIX II-N) when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.12 Maintenance Cycle 1 (All LR patients) – 12 weeks

Maintenance Cycle 1 therapy is for common for all LR B-ALL patients randomized to either **Arm C** or **Arm D**. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for Maintenance Cycle 1 is in Appendix II-J.

CNS3 patients ONLY are to be given Chemoradiation (Section 4.13, Appendix II-K) BETWEEN Maintenance Cycle 1 and subsequent Maintenance cycles (Maintenance-Post Cycle 1, Section 4.14, Appendix II-L).

All other patients receive **Maintenance-Post Cycle 1 treatment** (Section 4.14, Appendix II-L) immediately following Maintenance Cycle 1.

4.12.1 Criteria to Begin Maintenance Therapy

- Maintenance begins when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/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. Triple Intrathecal therapy (ITT), vincristine and prednisone will be delivered as scheduled, despite myelosuppression.

4.12.2 Duration of Cycles in Maintenance Therapy

- **Maintenance consists of 12 week cycles repeated until total duration of therapy is 2 years from start of Block 1 therapy for both male and female patients.**
- Therapy may be **s**topped on anniversary date if the 5-day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

4.12.3 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.12.4 Maintenance Chemotherapy Cycle 1

Dexamethasone: PO (may be given IV)
Days: 1 - 5, 29 - 33, & 57 - 61
Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days: 1, 29, 57
Dose: 1.5 mg/m²/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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Mercaptopurine: PO
Days: 1 - 84
Dose: 75 mg/m²/dose* once daily
Other Considerations:

- ***See Section 5.9** for suggested starting dose based on TPMT status, if known
- Mercaptopurine should be taken consistently at the same time every day.
- The liquid or tablet formulation may be used. If using tablets, adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m²/week as possible

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Day: 1
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 – 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 – 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
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

Methotrexate: PO
Days: 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78
Dose: 20 mg/m^2/dose

4.12.5 Following Maintenance Cycle 1:

- **ONLY** CNS3 will receive Chemoradiation (see Section 4.13, APPENDIX II-K) prior to moving on to subsequent Maintenance cycles (Maintenance-Post Cycle 1, Section 4.14, APPENDIX II-L).
- All other patients in both Arm C and Arm D will continue on to **Maintenance-Post Cycle 1** (Section 4.14, APPENDIX II-L).

4.13 **Maintenance Chemoradiation - 3 weeks**
The CNS-directed therapy described in this section is for LR B-ALL CNS3 Patients ONLY (Patients with late B-ALL isolated CNS3 or CNS3 combined relapse).

The Therapy Delivery Map for this additional CNS-directed therapy during Maintenance is in APPENDIX II-K.

4.13.1 Criteria to Begin Maintenance Chemoradiation
Start when ANC ≥ 500/µL and platelets ≥ 50,000/µL.

4.13.2 Cranial Radiation Therapy
Cranial radiation will be administered during this phase of therapy, which is between the 1st and 2nd cycles of Maintenance therapy. Patients with CNS3 and isolated CNS relapse will receive 1800 cGy cranial radiation to the brain in 10 daily fractions along with concurrent chemotherapy. See Section 14.1 for details on cranial irradiation.

4.13.3 General Chemotherapy Guidelines
See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.13.4 Chemotherapy Guidelines for Maintenance Chemoradiation
Dexamethasone: PO (may be given IV)
Days: 1 - 7, 15 - 21
Dose: 5 mg/m²/dose (Total daily dose: 10 mg/m²/day, divided BID; dose capped at 40 mg per day)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days: 1, 8, and 15
Dose: 1.5 mg/m²/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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Pegaspargase: IV over 1-2 hours
Day: 1
Dose: 2,500 International Units/m^2/dose

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.

4.13.5 Following Maintenance Chemoradiation:
- All patients will continue on to Maintenance-Post Cycle 1 (see Section 4.14, APPENDIX II-L).

4.14 **Maintenance-Post Cycle 1 (All LR patients)**
Maintenance-Post Cycle 1 therapy is common for all LR B-ALL patients randomized to either **Arm C** or **Arm D**. See Experimental Design Schema.

NOTE: CNS3 and Isolated CNS Relapse ONLY are to be given Chemoradiation (see Section 4.13, APPENDIX II-K) between Maintenance Cycle 1 and subsequent Maintenance cycles (Maintenance-Post Cycle 1). All other patients receive Maintenance-Post Cycle 1 immediately following Maintenance Cycle 1.

4.14.1 Criteria to Continue Maintenance Therapy

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. Triple Intrathecal therapy, vincristine and prednisone will be delivered as scheduled, despite myelosuppression.

4.14.2 Duration of Cycles in Maintenance Chemotherapy

- **Maintenance consists of 12 week cycles repeated until total duration of therapy is 2 years from start of Block 1 therapy for both male and female patients.**
- Therapy may be **s**topped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e. complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

4.14.3 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA.

4.14.4 Chemotherapy Guidelines for Maintenance-Post Cycle 1

Dexamethasone: PO (may be given IV)
Days: 1 - 5, 29 - 33, & 57 - 61
Dose: 3 mg/m²/dose (Total daily dose: 6 mg/m²/day, divided BID)
If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days: 1, 29, 57
Dose: 1.5 mg/m²/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®). Use conventional vinCRIStine only; the conventional and liposomal formulations are NOT interchangeable.

Mercaptopurine: PO
Days: 1 - 84
Dose: 75 mg/m²/dose* once daily

Other Considerations:
- *See Section 5.9 for suggested starting dose based on TPMT status (if status is known)
- Mercaptopurine should be taken consistently at the same time every day.
- The liquid or tablet formulation may be used. If using tablets, adjust daily dose using the dosing nomogram in Appendix III to attain a weekly cumulative dose as close to 525 mg/m²/week as possible

Methotrexate: PO - CNS3 PATIENTS ONLY
Day: 1
Dose: 20 mg/m²/dose

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
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

Methotrexate: PO
Days: 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78
Dose: 20 mg/m²/dose

4.15 Blinatumomab Block: Cycle 1 (Patients in Arm D) - 5 weeks

The therapy described in this section is for the 1st cycle of therapy with Blinatumomab on **Arm D**. See Experimental Design Schema.

The Therapy Delivery Map (TDM) for the Blinatumomab Block: Cycle 1 (Arm D) is in APPENDIX II-M.

NOTE: Hospitalization is STRONGLY recommended during the first 9 days of this cycle in case of a cytokine reaction. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Corticosteroids should be administered for severe or life threatening cytokine release syndrome.

Blinatumomab infusion interruptions for technical reasons:
The drug administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than one hour should be documented. If the interruption is longer than four hours, re- start of the infusion should be performed in the hospital, under supervision of the investigator. The patient should be observed overnight for possible side effects after the re-start in the hospital and can be discharged the following day if no difficulties arise. Administration of the premedication (dexamethasone) described in Section 4.5.4, is recommended. If possible, the infusion time before and after a break should sum up to 28 days treatment per cycle.

4.15.1 Criteria to Begin Blinatumomab

Start when ANC ≥ 500/µL and platelets ≥ 50,000/µL

4.15.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA. There is no maximum dosing.

4.15.3 Blinatumomab Block: Cycle 1 (Patients in Arm D) Chemotherapy

Blinatumomab: IV; Continuous Infusion over 28 days*
Days: 1 - 28
Dose: 15 micrograms/m²/day

***IV bag will be changed every 24 - 96 hours or every 168 hours (7 days), depending on the details of the infusion preparation**

Dexamethasone: PO/IV
Day: 1
Dose: Prior to day 1 therapy -

- A single dose of 5 mg/m^2/dose (maximum 20 mg/dose) will be administered 30 to 60 minutes prior to the start of the blinatumomab infusion and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed

Methotrexate: Intrathecal (IT) - CNS1/2 PATIENTS ONLY
Day: 8, 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

Triple Intrathecal Therapy (ITT) - CNS3 PATIENTS ONLY
Days: 8, 29
Age-based dosing:

Age (yrs)	Dose
1 – 1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2 – 2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3 – 8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

4.15.4 Following Blinatumomab Block: Cycle 1 (Arm D)

The next phase of therapy is Continuation 1 (Section 4.11, APPENDIX II-I).

4.16 **Blinatumomab Block: Cycle 2/3 (**LR Patients in **Arm D) - 5 weeks**

The therapy described in this section is therapy given during Blinatumomab Block Cycle 2 and Blinatumomab Block Cycle 3. Do not start Blinatumomab Cycle 2 before Day 56 after beginning of Continuation 1. Do not start Blinatumomab Cycle 3 before Day 56 after beginning of Continuation 2. See Experimental Design Schema.

NOTE: Hospitalization is STRONGLY recommended during the first 2 days of these cycles in case of a cytokine reaction. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Corticosteroids should be administered for severe or life threatening cytokine release syndrome.

The Therapy Delivery Map (TDM) for the Blinatumomab Block: Cycle 2/3 (Arm D) is in APPENDIX II-N.

Blinatumomab infusion interruptions for technical reasons:

The drug administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistic reason the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than one hour should be documented. If the interruption is longer than four hours, re- start of the infusion should be performed in the hospital, under supervision of the investigator. The patient should be observed overnight for possible side effects after the re-start in the hospital and can be discharged the following day if no difficulties arise. If possible, the infusion time before and after a break should sum up to 28 days treatment per cycle.

4.16.1 Criteria to Begin Blinatumomab Block: Cycle 2/3

Start when ANC ≥ 500/µL and platelets ≥ 50,000/µL

4.16.2 General Chemotherapy Guidelines

See Section 6.0, Drug Information, and the Parenteral and Oral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions associated with chemotherapy administration. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Appendix VII-A for the management options of blinatumomab in the outpatient setting.

See Section 5.0 for Dose Modifications based on Toxicities and Appendix I for Supportive Care Guidelines.

Dosing should be based on actual BSA. There is no maximum dosing.

4.16.3 Blinatumomab Block: Cycle 2/3: Chemotherapy Guidelines

Blinatumomab: IV; Continuous Infusion over 28 days*

Days: 1 - 28

Dose: 15 micrograms/m²/day

***IV bag will be changed every 24 - 96 hours or every 168 hours (7 days), depending on the details of the infusion preparation**
(*NOTE: Administration of the premedication (dexamethasone) is NOT RECOMMENDED for the second or third cycle of blinatumomab.)*

4.16.4 Following Blinatumomab Block Cycle 2:

LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Continuation 2- (Section 4.11, APPENDIX II-I)

4.16.5 Following Blinatumomab Block Cycle 3:

LR B-ALL patients randomized to the experimental arm (**Arm D**) will receive Maintenance Cycle 1 therapy- (Section 4.12, Appendix II-J.)

5.0 DOSE MODIFICATIONS FOR TOXICITIES

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

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

Systemic Allergic Reactions/Anaphylaxis:
For severe allergic reaction, discontinue pegaspargase and substitute *Erwinia*. Erwinia therapy should begin within 72 hours of the pegaspargase reaction or as soon as possible. Erwinia dosing: 25,000 international units (IU)/m^2 IM M-W-F for six doses substituted for each dose of pegaspargase. If Erwinia is given IV it should be given as a 1-2 hour infusion. Note that the M-W-F schedule documenting acceptable activity was established using IM not IV Erwinia; thus consideration should be given to administer IV Erwinia at the above dose every other day for 2 weeks (7 total doses).

For mild-moderate reversible reaction:

1. If the infusion was completed, consider sending an asparaginase activity level. Note that a therapeutic level of asparaginase of at least 0.1 IU/mL 14 days after administration is considered therapeutic. Please see the table below for guidance on using levels to switch to Erwinia asparaginase. Management decisions for levels obtained on other days are up to the treating physician.

Time point after completion of pegaspargase infusion	Asparaginase activity level	Action
1 hour – 1 day	< 0.5 IU/mL	Substitute *Erwinia* asparaginase
7 days	< 0.3 IU/mL	Substitute *Erwinia* asparaginase
14 days	< 0.1 IU/mL	Substitute E*rwinia* asparaginase

2. If the infusion was discontinued early, consider re-challenging with pegaspargase after premedication and send asparaginase levels as above.

Premedication with antihistamines in the absence of prior hypersensitivity has been discouraged in the past since antihistamine use may mask the appearance of systemic allergy and fail to alert the provider of the presence of asparaginase neutralizing antibodies. The use of asparaginase activity assays, as described above, are commercially available and may help determine if neutralizing antibodies are present.

If there is a question of silent inactivation, check levels as described above between 1 hour and 7 days after the dose. Change to Erwinia based on activity levels described above. Of note, Erwinia asparaginase is recommended only for pegaspargase hypersensitivity reactions and/or in the presence of silent antibody. It is not recommended as a substitute 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 dose adjustment guidelines are provided in the manufacturer's labeling. Below are proposed dose adjustment guidelines from published literature:[42]

Direct Bilirubin	Dose Modification
≤ 3.0 mg/dl	Full dose
3.1 – 5.0 mg/dl	Hold pegaspargase and resume when direct bilirubin is < 2 mg/dl; consider switching to alternate asparaginase product
>5.0 mg/dl	Hold the dose of pegasparagase; do not substitute other asparaginase products; do not make up the missed dose

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: Discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until symptoms and signs subside, and amylase/lipase levels return to normal and then resumed.

Thrombosis (including CNS and non-CNS events): Withhold asparaginase until resolved, and treat with appropriate antithrombotic therapy and consider repletion of AT-III, as indicated. Upon resolution of symptoms consider resuming asparaginase, while continuing low molecular weight heparin (LMWH) or antithrombotic therapy. Do not withhold dose for abnormal laboratory findings without clinical correlate. Consider measurement and repletion of AT-III during subsequent courses of asparaginase if unable to achieve therapeutic Anti-Xa levels. For significant thrombosis, which is not catheter-related, consider evaluation for inherited predisposition to thrombosis.

5.2 Blinatumomab

The most frequent serious adverse events noted in patients treated with blinatumomab to date are disorders of the nervous system, both peripheral and central, and systemic cytokine release syndrome (CRS), though both are less likely to occur in patients with lower burden of disease at the time of administration. Both categories of events are more likely to occur within the first week of treatment with blinatumomab, and both categories of events are usually reversible and able to be managed with attentive supportive care.

AEs related to blinatumomab that require treatment interruption (according to table below) and do not resolve to CTCAE ≤ Grade 1 within 14 days will require permanent discontinuation of blinatumomab treatment. If the patient is otherwise eligible to continue protocol therapy (standard chemotherapy and/or HSCT), then the patient may, at the discretion of the investigator and family, continue to receive protocol therapy.

In the case that the AE(s) **DO resolve within 14 days**, blinatumomab treatment may resume at a **reduced dose of 5 mcg/m^2/day** to complete the 28 day course (not counting the duration of treatment interruption). **NOTE**: **For Grade 4 Central Nervous**

System/Psychiatric, Grade 4 thromboembolic or Grade 4 CRS AEs, blinatumomab must be permanently discontinued.

For patients who had experienced a ≥ Grade 2 Neurologic Systems and Psychiatric AE related to blinatumomab, **no dose escalation beyond 5 mcg/m^2/day will be permitted** for subsequent cycles. For patients who experienced other AEs related to blinatumomab, subsequent cycles will begin at the reduced dose of 5 mcg/m2/day, **but may escalate to 15 mcg/m^2/day** after 7 days if there are no significant blinatumomab-related AEs.

A **second occurrence of the same AE** that requires interruption **will require permanent discontinuation** of blinatumomab. If the patient is otherwise eligible to continue protocol therapy (standard chemotherapy, and or HSCT), then the patient may, at the discretion of the investigator and family, continue to receive protocol therapy.

The resumption of the infusion at the reduced dose should be accompanied by **dexamethasone premedication** as indicated in the relevant subsection of Section 4.0, and should be performed in the hospital under supervision of the investigator. Patients should be observed for at least 72 hours after the start of the next infusion at the reduced dose before considering discharge to the outpatient setting.

Table: Dose modifications for Adverse Events (AE) Possibly, Probably or Definitely Related to Blinatumomab:

Category: AE (CTCAE v4.03)	AE Grade	Stop Infusion?	Supportive Care (in addition to institutional guidelines)*	Restart allowed (with dex premeds) if Gr 1 within 14 days?	Restarting dose (mcg/m^2/day)	Escalation to 15 mcg/m2/day after 7 days (with dex premed) in subsequent cycle allowed?
Nervous system/ Psychiatric[1]: (Confusion, Hallucination, Delerium, Psychosis), Dysarthria, Tremor	1	N	CNS	-	-	-
	2	N	CNS	-	-	-
	3	Y	CNS, DEX	Y	5	N
	4	Y	CNS, DEX	N	-	-
Central Nervous system: Seizure	1, 2, 3	Y	SZ, CNS, DEX	Y	5	N
	4	Y	SZ, CNS, DEX	N	-	-
Immune system: Cytokine release syndrome- NOTE that it is NOT recommended to use the CTCAE grading[3]	1	N	-	-	-	-
	2	N, unless patient is unable to tolerate symptoms (e.g. due to other comorbidities)	TOCI,DEX only if patient is unable to tolerate symptoms (e.g. due to other comorbidities)	Y	5	Y
	3	Y	TOCI, DEX	Y	5	Y
	4	Y	DEX	N	-	-

Blood and lymphatic system[4]: Disseminated intravascular coagulation, hemolysis, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura	1, 2	N	-	-	-	-
	3, 4	Y	-	Y	5	Y
Blood and lymphatic system[5]: All others (lymphopenia, neutropenia, anemia, thrombocytopenia, etc.)	1, 2, 3, 4	N	-	-	-	-
Vascular: Thromboembolic event	1	N	-	-	-	-
	2, 3	Y	-	Y	5	Y
	4	Y	-	N	-	-
Investigations[6,7] Metabolism and Nutrition: All **(if not considered clinically relevant or responding to routine medical management**)	1, 2, 3, 4	N	-	-	-	-
Investigations[6,7] Metabolism and Nutrition: All **(if clinically relevant and not responding to routine medical management)**	1,2	N	-	-	-	-
	3,4	Y	-	Y	5	Y
All other AE	1,2	N	-	-	-	-
	3,4	Y	-	Y	5	Y

<u>Table Footnotes:</u>

[1] **Most neurologic AEs associated with blinatumomab are central in nature (e.g. dysarthria, encephalopathy, tremor). Peripheral neurologic AEs are very unlikely to be secondary to blinatumomab, and are far more likely to be secondary to other causes such as vincristine. Discontinuation of blinatumomab secondary to peripheral neurologic AEs should be avoided when possible. Most AEs in the psychiatric disorders category are unlikely to be caused by blinatumomab and generally require supportive care rather than dose modification or discontinuation of blinatumomab (e.g., Insomnia, Depression, Anxiety). Psychiatric AEs that may reflect underlying central nervous system toxicity (e.g., Confusion, Delirium, Hallucinations, Psychosis) are of greater interest, particularly if accompanied by other AEs in the nervous system disorders category.**

[2] **Close monitoring of fluid status by intake and output should be undertaken for the first 48 hours of blinatumomab infusion. Efforts to keep patients balanced between intake and output should be maintained, even if diuretic therapy (furosemide or similar) is needed to do this. Careful attention to fluid status may prevent deterioration from capillary leak, however even with meticulous attention some patients may experience pulmonary edema and require more aggressive respiratory support. Treating physicians should use their clinical judgment and institutional standards for whatever supportive care measures are needed during this period of time.**

[3] **Grading of cytokine release syndrome (CRS) severity should be performed according to that of Lee et al (see below table).[43] As many of the symptoms of CRS overlap with those of other medical complications such as infection, attribution should be carefully considered. Accurate application of this grading system requires clinical judgment to confirm that the symptoms are most likely due to CRS rather than to another medical condition. In all grades of CRS, aggressive supportive care is required. In grade 2 or 3 CRS, careful monitoring of cardiac function is strongly suggested.**

Grade 1	**Symptoms are not life threatening and require symptomatic treatment only, eg. fever, nausea, fatigue, headache**
Grade 2	**Symptoms require and respond to moderate intervention** **Oxygen requirement <40%, or** **Hypotension responsive to fluids or low dose of one vasopressor, or** **Grade 2 organ toxicity**
Grade 3	**Symptoms require and respond to aggressive intervention** **Oxygen requirement >=40%, or** **Hypotension requiring high dose of one vasopressor or multiple vasopressors, or** **Grade 3 organ toxicity or grade 4 transaminitis**
Grade 4	**Life-threatening symptoms** **Requirement for ventilator support, or** **Grade 4 organ toxicity (excluding transaminitis)**

[4] **In the first days of treatment, transient DIC-like pictures may develop. Because patients are at risk for capillary leak syndrome and cytokine release syndrome, appropriate supportive care with dexamethasone (described above), blood products and factors (packed red cells, platelets, cryoprecipitate, fresh frozen plasma), vitamin K, and/or albumin should be considered according to institutional standards of care. Particularly in the first week of infusion, when the risk of capillary leak and cytokine release is more prominent, appropriate use of blood products and factors is preferred if laboratory indications suggest the need for replacement, as large volumes of crystalloid fluids tend to exacerbate the capillary leak.**

[5] **In the first days of treatment, a rapid transient drop in platelets, neutrophils and/or hemoglobin may be observed. These effects are not necessarily cytokine-mediated. Counts typically recover to baseline during treatment, and usually within two weeks of starting blinatumomab. Transfusion of blood and platelets should be performed according to appropriate institutional standards.**

[6] **In the first days of treatment, transient increases in transaminases up to over 1000 U/L may develop. These have generally returned to baseline in the 1st week of treatment.**

[7] **Decrease in serum immunoglobulins have been observed in patients treated with blinatumomab. Intravenous immunoglobulin should be administered according to institutional standards, but is recommended for any patient with a total IgG level below 400. Immunoglobulin must not be administered through the line through which blinatumomab is actively being infused.**

* Definitions of supportive care abbreviations:

DEX: Given its potential to interfere with the efficacy of blinatumomab, the use of dexamethasone should be reserved for serious side effects that are unresponsive to other treatments (supportive care, discontinuation of blinatumomab infusion, tocilizumab) and for clinically significant neurologic toxicity. If required, dexamethasone should be administered at a total daily dose of at least 0.2 - 0.4 mg/kg/day (maximum 24 mg per day) administered preferably intravenous divided 3 - 4 times daily for at least 1 day but no more than 4 days. The dose should then be stopped or tapered as clinically indicated.

SZ: Appropriate imaging should be performed to evaluate for possible hemorrhage or thrombosis, and other diagnostic procedures should be performed as clinically appropriate. Prophylactic anticonvulsant treatment with a therapeutic dose of institutional standard agents (e.g., lorazepam, phenytoin, levetiracetam) should be administered if seizures develop, and continued throughout the blinatumomab infusion. Anti-convulsant therapy should be considered starting at least 24 - 48 hours prior to any subsequent blinatumomab infusions, and continuing for the remainder of those treatment cycles. Diagnostic measures to exclude potential infectious causes should be conducted once the patient has stabilized (i.e., a lumbar puncture to evaluate for bacterial, viral or fungal sources should be performed). Any identified pathology should be treated as clinically appropriate.

CNS: A daily finger-nose-finger or writing sample test is recommended according to age-appropriate activities for patients. In adults treated with blinatumomab, it has been found that a daily handwriting sample can often predict future nervous system toxicity before the clinical toxicity develops. Dexamethasone should be used for clinically significant neurologic toxicity. In case of a change in finger-nose-finger or handwriting test it is recommended to start dexamethasone on the schedule above to prevent possible deterioration of nervous system toxicity. Patients who experience nervous system toxicity in the first cycle typically do not experience it again in subsequent cycles, although it is possible.

TOCI: In patients with CRS who respond to tocilizumab, fever and hypotension often resolve within 6 hours, and pressors and other supportive care measures can be weaned quickly thereafter. In some cases, however, symptoms may not completely resolve, and continued aggressive support may be necessary for several days. If the patient's condition does not improve or stabilize within 24 hours of the tocilizumab dose, administration of a second dose of tocilizumab and/or a second immunosuppressive agent, such as dexamethasone, should be considered. Tocilizumab is generally not used in the management of CNS symptoms without significant hemodynamic instability or other life-threatening symptomatology.

TOCI Suggested Dosing:

- <30 kg: 12 mg/kg
- ≥30 kg: 8 mg/kg

5.3 Cyclophosphamide

Gross Hematuria: Omit in the presence of macroscopic hematuria.

Microscopic hematuria: Begin pre-hydration as in the treatment section of the protocol. Increasing the rate and duration of post-hydration should be considered (eg., 200 mL/m^2/hr x 12-24 hours). Give IV mesna at a total dose that is 100% of the cyclophosphamide dose divided to 5 doses. Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat at Hours 3, 6, 9 and 12 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 12 hours after the start of cyclophosphamide infusion. If the child develops gross hematuria, continue mesna infusion for 24 hours from the start of the 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.

5.4 **Cytarabine (ARAC)**

Cytarabine Syndrome: Do not withhold cytarabine for fever if it is likely to have been caused by the cytarabine. 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.

Myelosuppression: Do not interrupt high dose (3,000 mg/m^2/dose) cytarabine, once started, for uncomplicated myelosuppression; do hold for proven or presumed serious infection and do not make up missed doses during Block 3.

Once Continuation 1 and 2 have started, do not interrupt for uncomplicated myelosuppression; do hold for proven or presumed serious infection.

Stipulations for High Dose Cytarabine: Adequate renal function (defined as creatinine within normal range) is required for the administration of high dose (3,000 mg/m^2/dose) cytarabine. Creatinine clearance (CrCl) should be measured for patients with elevated creatinine or suspected renal insufficiency. For CrCl < 60 mL/min/1.73 m^2, hold pending recovery and omit if CrCl < 30 mL/min/1.73 m^2 or if recovery requires > 3 weeks.

Neurotoxicity: Discontinue cytarabine immediately for $\geq$ Grade 2 CNS toxicity, (e.g., ataxia, nystagmus, dysarthria, dysmetria, seizures and/or encephalopathy).

5.5 **Anthracycline-Mitoxantrone**

Consider Dexrazoxane prior to each dose for patients with:

- Anticipated cumulative anthracycline dose $\geq$150 mg/m^2.
- Past or anticipated radiotherapy including the myocardium (including whole-abdomen or left flank irradiation).
- Recommended dose of dexrazoxane is 10 x the DAUNOrubicin/DOXOrubicin dose or 30 x the mitoXANtrone dose, given over 5-15 minutes immediately before the chemotherapeutic agent.

Monitoring Cardiac Echocardiogram:
At baseline and then recommended after cumulative dose of 175, 300, 375, and 450 mg/m^2.

Dose modification for cardiac toxicity:
If left ventricular ejection fraction (EF) < 50% (as determined by the Biplane Simpson method), or if EF inevaluable shortening fraction (SF) < 24%, hold the anthracycline or anthracenedione and repeat the echocardiogram in one week. If EF remains < 50% (or if EF inevaluable, SF < 24%), discontinue the anthracycline or anthracenedione and deliver alternate therapy as per the protocol or provider decision. Resuming cardiotoxic therapy depends on the cause of the cardiac dysfunction and the results of further cardiac evaluation.

Myelosuppression (beyond Induction):
If patient has severe infection or severe mucositis, consider modifying or omitting

anthracycline.

Hyperbilirubinemia:

Direct Bilirubin	Dose Adjustment
$\leq$ 3.0 mg/dl	Full dose
3.1 – 5.0 mg/dl	Administer 50% of calculated dose
5.1 – 6.0 mg/dl	Administer 25% of calculated dose
> 6.0 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://cogmembers.org/_files/disc/pharmacy/ExtravasationReference.pdf for COG reference.

5.6 Etoposide

Allergic Reaction: Premedicate with diphenhydramine (1-2 mg/kg slow IV push, maximum dose is 50 mg). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension. Etoposide phosphate is a water soluble prodrug that does not contain polysorbate 80 and polyethyleneglycol, the solubilizing agent in etoposide that may induce allergic reactions and hypotension. Etoposide phosphate is rapidly converted to etoposide *in vivo* and provides total drug exposure, as represented by AUC (0-infinity), that is statistically indistinguishable from that measured for etoposide at equimolar doses.

Hypotension: If diastolic or systolic blood pressure (BP) falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of NS 10 mL/kg if BP fails to recover or falls further. Stop infusion if BP does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% NaCl at 10 mL/kg/hr for 2 hours prior to any subsequent infusion.

Renal Insufficiency: If renal function decreases, adjust etoposide as follows: CrCl 10-50 mL/min/1.73 m^2, decrease dose by 25%; if CrCl < 10 mL/min/1.73 m^2, decrease dose by 50%.

Hyperbilirubinemia: If direct bilirubin is > 2 mg/dL, decrease dose by 50%. If direct bilirubin is > 5 mg/dL, hold etoposide.

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 6 hours x 2 doses, beginning 24 hours after the IT therapy may be administered in an attempt to reduce the risk of worsening already existent myelosuppression (ANC < 500/µL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

Dose modifications following an episode of acute neurotoxicity:
Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.[44-46]

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. 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.[47]

Complete clinical evaluation including imaging of the brain is strongly recommended.
For patients who return to their baseline pre-event neurological status, clinicians may:

1. hold the next dose planned dose of IT therapy, or
2. substitute IT cytarabine or IT cytarabine/hydrocortisone for 1 dose of IT methotrexate or
3. proceed with IT methotrexate and include leucovorin rescue at a dose of 5 mg/m^2 IV/PO q 6 hrs x 2 doses beginning 24 hours after the LP.

If the event does not recur, resumption of standard therapy should be considered for subsequent intrathecal therapy.

For patients who do not return to baseline pre event neurological status or for those with recurrent events, or evidence of progressive encephalopathy, additional evaluations may be warranted and the treating physician may consider a more prolonged or definitive change in therapy upon discussion with the Study Chair.

Leucovorin rescue of IT MTX *without* acute neurotoxicity
Prevention of neurotoxicity by using leucovorin after IT MTX has not been studied in a randomized fashion. Neither the BFM, DFCI, nor COG have routinely introduced leucovorin rescue to prevent acute neurotoxicity, however SJCRH protocols use leucovorin rescue during remission induction and consolidation phases. The cumulative incidence of all neurotoxicities among non-DS patients enrolled on AALL0932 and AALL1131 indicate a less than 1% incidence of acute neurotoxicity during induction. For non-DS patients enrolled on AALL0932, the incidence during consolidation was 0.3%. For non-DS patients receiving consolidation therapy on AALL1131, the incidence was 3.3%.

For the reasons above, it is permissible for patients receiving augmented consolidation such as that prescribed for NCI-SR-High (AALL1731) or NCI-HR (AALL1732) patients to receive leucovorin during consolidation therapy after the 4 doses of weekly IT MTX on the following schedule:

1. Leucovorin, 5 mg/m2 IV/PO at hours 24 and 30 after IT MTX.

It is not known if providing leucovorin rescue after IT MTX during consolidation as a measure to reduce acute neurotoxicity will reduce therapeutic efficacy in the context of

COG protocols.

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 Intermediate-Dose Methotrexate (ID MTX) and Leucovorin Rescue

[*Please note that* ***IDMTX*** *refers to* IV *MTX* ***1000 mg/m²*** ***given over 36*** **hrs**]

5.8.1 ID MTX Infusion Guidelines and dose modifications for toxicity

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 0.5 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: to start at least 6 hours prior to commencement of intravenous methotrexate. **Fluid:** D5 ¼ NS with 30 - 50 mEq $NaHCO_3$/L at 125 mL/m^2/hour. 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 ≤ 1.010 and pH between 7 and 8. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Hour 0: MTX 100 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 900 mg/m^2 given by continuous IV infusion over 35.5 hours. Be certain that the ID MTX infusion is completed in the 36 hour period. **Note, even if the infusion is not complete at this time point, it must be stopped.**

Recommended Posthydration: Continue hydration using D 5 ¼ NS with 30 – 50 mEq $NaHCO_3$/L at 125 mL/m^2/hour (3 L/m^2/day) throughout IDMTX infusion until the last dose of leucovorin has been given. In patients with delayed MTX clearance, continue hydration until the plasma MTX concentration is below 0.1 μM.

Leucovorin rescue: 15 mg/m^2 PO/IV at 48 and 54 **hrs** after the start of the MTX infusion. If 48 hr methotrexate level is ≤ 0.5 μM, then only two doses of leucovorin are administered (at 48 and 54 hours). If MTX level at 48 hours is > 0.5 μM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 μM.

Hour 48: Check plasma methotrexate level at 48 hours after start of the methotrexate infusion. If the level is ≤ 0.5 μM, then do not give more than two doses of leucovorin (48 and 54 hours). If MTX level at 48 hours is > 0.5 μM, then continue hydration and leucovorin rescue at 15 mg/m^2/dose po/IV every 6 hours until MTX levels are < 0.1 μM.

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 (> 100% in 24 hours), assure appropriate urine pH and urine volume as above and consider glucarpidase If urine output fails to continue at 80% of the fluid intake, consider furosemide or acetazolamide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see below).

48 hr MTX level	Leucovorin Rescue
≤ 0.5 μM	Continue 15 mg/m^2 IV/PO q 6hrs for 2 doses.
0.5 – 1 μM	Increase to 15 mg/m^2 q 6 hrs until MTX level < 0.1 μM (draw q 6-24 hrs).
1 – 5 μM	Increase to 15 mg/m^2 q 3 hrs until MTX level < 0.1 μM (draw q 6-24 hrs).
5 – 10 μM	Increase to 100 mg/m^2 q 6hrs until MTX level < 0.1 μM (draw q 6-24 hrs).
> 10 μM	Increase to 1000 mg/m^2 q 6hrs until MTX level < 0.1 μM (draw q 6-24 hrs). Consider glucarpidase.

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 there is a rising creatinine (> 100% in 24 hours) or the 48 hour methotrexate level is > 10 μ/L consider using glucarpidase. If renal function does not recover, omit MTX. Do not give ID 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™).[48,49] 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 https://www.voraxaze.com/Order-Voraxaze regarding product availability through ASD Healthcare, Cardinal, and McKesson. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300 – 046 – 774 (local) or medicalinformationAUS@hospira.com. Patients requiring glucarpidase rescue will remain on study.

Stop leucovorin 2 hours before administering glucarpidase as it is a competitive substrate and may compete with MTX for glucarpidase binding sites.

Dose of glucarpidase: 50 units/kg administered by intravenous bolus over 5 minutes. Reconstitute each vial with 1 mL sodium chloride 0.9% (do not further dilute). Each vial contains 1,000 units/mL (after reconstitution) and round dose up to vial size. No further dose is required.

Maintaining alkalinization of urine with sodium bicarbonate is essential to maintain urinary pH > 7.

It is essential that patients are NOT co-prescribed the following medicines which reduce MTX excretion: NSAIDS, aspirin, ciprofloxacin, co-trimoxazole, penicillins, probenecid, omeprazole (or other proton pump inhibitors).

Two hours after administration of glucarpidase, leucovorin should be administered at a dose of 250 mg/m^2 every 6 hours by IV bolus (maximum rate: 160 mg/min) for up to 48 hours and then decreased based on plasma MTX concentrations to 15 mg/m^2 intravenously or orally every 6 hours until the plasma MTX concentration is < 0.2 μM.

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 in Appendix I for trimethoprim-sulfamethoxazole (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 2 to 4 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3 - 4 mucositis, attempt to decrease the number of leucovorin doses to 2. 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.

See Section 5.13 for dose modifications when MTX is used post HSCT.

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

During Continuation:

ANC < 500/µL and/or platelets < 50,000/µL:

Discontinue dose until ANC is ≥ 750/µL and platelets are ≥ 75,000/µL. Restart mercaptopurine and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-week intervals provided ANC remains ≥ 750/µL and platelets remain ≥ 75,000/µL. Consider a marrow evaluation in the face of persistent or prolonged neutropenia.

Prolonged cytopenia is defined as ANC < 750/µL and/or platelets < 75,000/µL after withholding therapy for > 2 weeks. Perform a bone marrow examination after 2 weeks of withholding chemotherapy, if no recovery is apparent. If monocyte count is increasing or viral myelosuppression is clinically suspected, the bone marrow examination may be postponed for 1 - 2 weeks and omitted if ANC and platelets fully recover by the 4th week after therapy is withheld.

If patient develops severe or unexpected myelosuppression, i.e., doesn't tolerate at least half dose MP, see section below on thiopurine pharmacology testing.

During Maintenance:

Myelosuppression: If absolute neutrophil count (ANC) falls below 500/µL or if platelet count falls below 50,000/µL during Maintenance, mercaptopurine and methotrexate should be held until recovery above these levels.

1. For the first drop below 500/µL ANC or platelet count < 50,000/µL, resume mercaptopurine and methotrexate at the same dose the patient was taking prior to the episode of myelosuppression when ANC ≥ 500 /µL and platelet count ≥ 50,000/µL.
2. If ANC falls below 500/µL or if platelet count falls below 50,000/µL for a second (or greater) time, hold mercaptopurine and methotrexate until ANC is ≥ 750/µL and platelets are ≥ 75,000/µL. Consider discontinuing trimethoprim/sulfamethoxazole (TMP/SMX) in favor of an alternative approach to Pneumocystis prophylaxis.
    a. When ANC ≥ 750/µL and platelet count ≥ 75,000/µL, restart mercaptopurine and methotrexate at 50% of the dose prescribed at the time that the medications were stopped.
    b. Increase doses of mercaptopurine and methotrexate to 75% and then 100% of dose prescribed prior to stopping the medications at 2-4 week intervals provided ANC remains > 750 /µL and platelets remain > 75,000/µL. May increase both mercaptopurine and methotrexate simultaneously.
    c. Once at 100% of the dose prescribed prior to stopping, see below for instructions regarding further dose escalation.

Continue to follow ANC q 2-4 weeks with target ranges ANC 500 – 1,500/µL and platelet count ≥ 50,000/µL

If patient develops severe or unexpected myelosuppression, i.e., doesn't tolerate at least half dose mercaptopurine, in the absence of TMP/SMZ or other myelosuppressive agents, strongly consider evaluation of TPMT and/or NUDT15 status if not already done)

Prolonged cytopenia is defined as ANC < 500/µL and/or platelets < 50,000/µL after withholding therapy for > 2 - 4 weeks. Consider a marrow evaluation in the face of persistent or prolonged neutropenia if no recovery is apparent. If monocyte count is increasing or viral myelosuppression is clinically suspected, the bone marrow examination may be postponed for 1-2 weeks and omitted if ANC and platelets fully recover by the 4th week after therapy is withheld.

Inadequate Myelosuppression: For persistent ANC ≥ 1,500/µL, no dose escalations are recommended during the first cycle of Maintenance.

- For ANC ≥ 1,500/µL on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s), alternately increase doses of methotrexate or mercaptopurine by 25%. Always wait at least 4 weeks before making another dose adjustment.
- If both methotrexate and mercaptopurine are increased once without a fall in ANC, consider noncompliance as a possibility. Noncompliance can be assessed by obtaining a sample for thiopurine metabolites. Although there are no specific values to use to indicate non-adherence, low concentrations of TGN and methylated derivatives in a sample taken after at least three weeks after continuous dosing may indicate non-adherence. Also consider observing the administration of an oral dose of methotrexate and checking plasma methotrexate concentration 2-4 hours later; this value should be ≥ 0.2 µM.
- If ANC remains high after intervention for possible noncompliance.
    - For patients who are heterozygous or homozygous deficient for TPMT/NUDT15 and have high ANCs as described above, increase methotrexate alone by 25% and repeat evaluation. Unless noncompliance is suspected, increase methotrexate preferentially over mercaptopurine Consider carefully increasing mercaptopurine doses as well, if high ANCs persist. Increase the mercaptopurine dose in 25% increments until ANC is in target. Always wait at least 4 weeks before making another dose adjustment or re-measuring TGN. If ANC remains high, alternate mercaptopurine dose increases with methotrexate dose increases.
    - If the methylated derivatives are significantly elevated, in concert with abdominal symptoms or Grade 4 SGPT/ALT, SGOT/AST and or direct bilirubin ≥ 2 mg/dl, and ANC indicates that the 6-MP should be increased, consider adding allopurinol at a dose of 50 mg/m^2 with a dose of 6-MP that has been decreased by 50-75%.[50]

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 Grade 3 toxicity, increase in hepatic transaminases (SGPT/ALT or SGOT/AST to greater than >5.0 - 20.0 x ULN), obtain total direct bilirubin. Monitor SGPT/ALT or SGOT/AST and total direct bilirubin weekly during Consolidation as long as transaminases remain over 5x ULN.
- Continue full dose therapy unless either of the following occurs:
- Direct bilirubin > 2 mg/dL
- Grade 4 SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) elevation on 2 determinations at least 1 week apart.
- If either of these occurs, hold mercaptopurine and monitor labs as above, weekly. Restart at full dose therapy when the transaminase elevation is < Grade 3 (are less than 5x ULN), as long as direct bilirubin is < 2 mg/dL
- Exclude infectious hepatitis for persistent (> 1 month) Grade 3 elevations in SGPT/ALT or SGOT/AST(above 5x ULN). Consider discontinuing trimethoprim/sulfamethoxazole (TMP/SMX) in favor of an alternative approach to Pneumocystis prophylaxis

For dose modifications when MTX is given for GVHD prophylaxis see Section 5.13.3.

Thiopurine Pharmacology Testing and Dosage Adjustments:

Mercaptopurine and thioguanine 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). [10,51-53] 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 6 MP (10 to 30 mg/m^2/day 3 days per week). About 35% of heterozygotes require a lower dose of 6-MP to avoid dose-limiting myelosuppression. [54]

There are now CLIA certified tests for TPMT genotype and phenotype, and for thiopurine metabolites (6-methyl mercaptopurine [6-MMP] and 6-TGN) measurements. Only 3 SNPs constitute well over 90% of the inactivating mutations in the gene, based on studies in numerous racial and ethnic groups worldwide. [51,55-58] 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 patients who have received full dose thiopurine therapy during the 2 weeks immediately preceding the test, RBC thiopurine metabolites will likely predict TPMT status and actual thiopurine exposure.
- In the absence of RBC transfusions for 3 months prior, TPMT activity will accurately reflect TPMT status
- TPMT genotyping will be informative in all patients, if at least 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 patient is *homozygous deficient* for TPMT, the thiopurine dose should be *reduced to* 10 - 20 mg/m^2/day 3 days per week. If the patient is *heterozygous for TPMT and* has experienced significant myelosuppression, the thiopurine dose should be reduced by 30% - 50%. Do not increase the dose in response to a high ANC for 4 weeks to allow for achievement of steady state. All other myelosuppressive medications should be delivered at full dose, and the thiopurine dose should be titrated based on blood counts. Further thiopurine pharmacologic measures are not often necessary.
- If the patient is homozygous wild-type (high activity) for TPMT, then discontinue TMP/SMX and use pentamidine or dapsone. For modifications of the oral MP and MTX see the beginning of this section.

5.10 Steroids (Dexamethasone)

Hypertension: Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension.

Hyperglycemia: Dose should not be reduced for hyperglycemia.

Pancreatitis: Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiographic findings only), steroids should be held until symptoms and signs subside, and amylase/lipase levels return to normal and then consider resuming steroids.

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

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

Inability to use oral doses:
For dexamethasone, substitute the IV preparation mg for mg.

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

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

Continuation:
Infection: Oral TG will be held for suspected or proven serious infection.

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

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[59,60]:

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

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://cogmembers.org/_files/disc/pharmacy/ExtravasationReference.pdf for COG reference.

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.

5.13 Stem Cell Transplant Regimen Agents

5.13.1 Tacrolimus

Tacrolimus commonly causes mild/moderate hypertension and alopecia and less commonly kidney or liver dysfunction, transplant associated microangiopathy (TAM), and neurological changes associated with significant hypertension. When trough levels are kept in the therapeutic range and patients receive adequate hydration and magnesium replacement, most of these side effects can be minimized. Hypertension should be managed with single or combination antihypertensive therapy. Tacrolimus should be held for severe toxicities thought to be related to its administration (significant neurological changes/malignant hypertension, TAM, kidney failure, etc.). Other immune suppressive medications may be substituted if tacrolimus is not tolerated (MMF, cyclosporine, etc.).

5.13.2 Cyclosporine

Cyclosporine commonly causes mild/moderate hypertension and less commonly kidney or liver dysfunction, TAM, and neurological changes associated with significant hypertension. When trough levels are kept in the therapeutic range and patients receive adequate hydration and magnesium replacement, most of these side effects can be minimized. Hypertension should be managed with single or combination antihypertensive therapy. Cyclosporine should be held for severe toxicities thought to be related to its administration (significant neurological changes/malignant hypertension, TAM, kidney failure, etc.). Other immune suppressive medications may be substituted if cyclosporine is not tolerated

5.13.3 Methotrexate

The most common acute side-effects of methotrexate include delay of count recovery, worsened mucositis, and kidney and liver damage (can contribute to VOD). Toxicity is directly related to the length of exposure to the drug. While methotrexate is generally excreted rapidly, delayed excretion of methotrexate occurs with decreased renal function and in circumstances where patients have third-space fluid collections (pulmonary effusions, ascites, joint effusions, etc.). The attending transplant physician should assess each patient prior to delivery of each dose and decide whether full dose methotrexate should be administered. Guidelines for modification of methotrexate dosing are listed in the tables below.

Table 5.13.3.1: Methotrexate Dose Modification for Renal Impairment

	Mild	Moderate	Severe	Life-Threatening
Serum creatinine	> 1.5 - 2x baseline	> 2 - 2.5x baseline	> 2.5 - 3x baseline	> 3x baseline or dialysis
% Methotrexate Dose reduction (Day +1, 3, 6, 11)	0 - 50%	50 - 100%	100% (no drug)	100% (no drug)

Table 5.13.3.2: Methotrexate Dose Modification for Significant Mucositis

Stomatitis, mucositis	**Painless ulcers, erythema, mild soreness or mild dysphagia**	**Painful erythema, edema, ulcers or moderate dysphagia, but can eat without narcotics**	**Cannot eat solids or requires narcotics to eat, requires parenteral or enteral support.**	**Complete obstruction or perforation**
% Methotrexate Dose reduction (Day +1, 3, 6, 11)	0%	0%	0 - 50%	50 - 100%

For significant third spacing (ascites, effusions, significant edema or weight gain > 5 - 10% above baseline) consider dose reductions of 50% and leucovorin rescue.

5.13.4 Guidelines for Leucovorin Rescue

Dose: Patients at risk for methotrexate toxicity should receive leucovorin at a dose of 5 - 10 mg/m^2 IV Q6H x 4 doses beginning 24 hours after administration of methotrexate. While most patients will need only 4 doses of leucovorin, if methotrexate levels are elevated due to renal dysfunction or other problems, leucovorin doses should be continued until serum methotrexate concentration is < $1x10^{-7}$M. If serum methotrexate concentration is > $5x10^{-6}$M, increase dose to 100 mg/m^2/dose IV Q3H until the serum methotrexate level is < $1x10^{-8}$M.

5.13.5 Mycophenolate Mofetil (MMF)

MMF can cause decreased counts, nausea, vomiting, diarrhea, hypertension, dizziness, insomnia, hyperglycemia, electrolyte imbalances, rash, leg cramps, and bone pain. For significant diarrhea or low counts (neutropenia, etc.), a decrease of MMF by approximately 20% is usually sufficient to decrease the toxicity. Further dose modifications for significant toxicity likely caused by MMF are allowed.

5.13.6 Adjustment of TBI/chemotherapy During the Preparative Regimen.

The full dose of preparative regimen TBI and chemotherapy agents will be administered unless patients have a life threatening reaction thought likely to occur again with continued administration and an appropriate substitution cannot be made (i.e. etopophos for etoposide).

5.13.7 Dose Adjustment of Chemotherapy for Patients Whose Weight Exceeds > 125% Ideal Body Weight (IBW)

Chemotherapy given during the preparative regimen (thiotepa, cyclophosphamide, and etoposide) will be dosed based on actual weight for patients ≤ 125% IBW. Those > 125% IBW will be dosed based upon adjusted ideal body weight as follows:

Adjusted ideal body weight = IBW + 0.25 (Actual weight – IBW).

The following formulas for pediatric and adult IBW calculations are recommended, but IBW may be calculated according to institutional standard operating procedures (SOPs).

Recommended Ideal Body Weight Calculation for Children Age 1- 17 years

$$IBW = \frac{Height\ (cm)^2 \times 1.65}{1000}$$

Recommended Ideal Body Weight Calculation for Adults (Height > 5 feet/60 inches)

IBW (females) = (cm ÷ 2.54 – 60) x 2.3 kg + 45.5 kg

IBW (males) = (cm ÷ 2.54 – 60) x 2.3 kg + 50 kg

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

7.1 Required and Optional Clinical, Laboratory and Disease Evaluations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated. **Obtain other studies prior to start of phase unless otherwise indicated.**

7.1a HR/IR Patients

STUDIES TO BE OBTAINED	Baseline	Block 1	Block 2	Block 3	Blinatumomab Blocks
Hx/PE with VS/Wt (BSA)	X		start of phase	start of phase	start of phase*
CBC/diff/plts	X	weekly	weekly	weekly	weekly
Bilirubin[0], ALT, creatinine, BUN	X	weekly	weekly	weekly	weekly
Local Bone Marrow (BM) Evaluation	X[1]	end of phase	end of phase	end of phase	end of phase
Bone Marrow (BM) for central flow MRD[2]		end of phase+	end of phase++	end of phase+++	end of Cycle 1++, end of Cycle 2+++
Bone Marrow (BM) for Immunophenotyping	X[2,7]				
Bone Marrow (BM) for future research banking	X[8]	X[8]			
CSF cell count and cytospin	X	with each IT	with each IT	with each IT	with each IT
Peripheral Blood for Pharmacokinetics (PK)					Cycle 1: Day 2 and Day 14[6]
Peripheral Blood for Immunogenicity					• Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1) • End of Cycle 2[$]
Peripheral Blood for future research banking	X[8]	X[8]	X[8]		X[8]
Echocardiogram	X				
Pregnancy test[3]	X				
Testicular exam	X	end of phase	end of phase		
Testicular biopsy	X[4]	X[5]			

[0] Adequate liver function as defined by direct bilirubin is required for eligibility (see Section 3.2.5.2).

[1] BM evaluation to confirm relapse and/or detect marrow disease in presumed isolated extramedullary relapse patients should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively by the COG Cytogenetics Committee. See Section 13.2 for details.

[2] See Section 13.3 for details on shipping and handling

[3] Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.

[4] Patients with suspected testicular involvement at relapse (either isolated or with concurrent BM/CNS relapse) must have biopsy performed at baseline.

[5] Patients with definite or equivocal residual testiculomegaly at end of Block 1 must have a biopsy to determine whether TRT is to be given during designated blocks of therapy (see Experimental Design Schema).

[6] See lab manual on protocol webpage for sample collection and shipping details

[7] Includes optional sample for CRLF2 expression for consenting patients (see Section 7.2 and Section 13.4).

[8] Optional for future research (see Section 7.2 and Section 13.1).
* See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e
[$] In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1.
+ Evaluation 1 ++ Evaluation 2 +++ pre-HSCT evaluation

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.1b LR Patients

STUDIES TO BE OBTAINED	Baseline	Block 1	Block 2	Block 3, Blinatumomab blocks, Continuation	Maintenance and post-therapy
Hx/PE with VS/Wt (BSA)	X		start of phase	start of phase*	every 28 days during maintenance
CBC/diff/plts	X	weekly	weekly	weekly	every 28 days during maintenance
Bilirubin[0], ALT, creatinine, BUN	X	weekly	weekly	weekly	every 28 days during maintenance
Local Bone Marrow (BM) Evaluation	X[1]	end of phase	end of phase		
Bone Marrow (BM) for central flow MRD[2]		end of phase+	end of phase++		
Bone Marrow (BM) for Immunophenotyping	X[2,7]				
Bone Marrow (BM) for future research banking	X[9]	X[9]			
CSF cell count and cytospin	X	with each IT	with each IT	with each IT	with each IT
Absolute lymphocyte count with T and B subset quantification					At end of each 12 week maintenance cycle, and every 3 months after completion of therapy for 1 year
Peripheral Blood for Pharmacokinetics (PK)				Blinatumomab Cycle 1:Day 2 and Day 14[6]	
Peripheral Blood for Immunogenicity				•Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1) •End of Cycle 2[$]	Prior to start of Maintenance Cycle 1 therapy[8]
Peripheral Blood for future research banking	X[9]	X[9]	X[9]		X[9]
Echocardiogram	X				
Pregnancy Test[3]	X				
Testicular Biopsy	X[4]	X[5]			

[0] Adequate liver function as defined by direct bilirubin is required for eligibility (see Section 3.2.5.2).
[1] BM evaluation to confirm relapse and/or detect marrow disease in presumed isolated extramedullary relapse patients should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively by the COG Cytogenetics Committee. See Section 13.2 for details.
[2] See Section 13.3 for details on shipping and handling
[3] Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.

4 Patients with suspected testicular involvement at relapse (either isolated or with concurrent BM/CNS relapse) must have biopsy performed at baseline.
5 Patients with definite or equivocal residual testiculomegaly at end of Block 1 must have a biopsy to determine whether TRT is to be given during designated blocks of therapy (see Experimental Design Schema).
6 See lab manual on protocol webpage for sample collection and shipping details
7 Includes optional sample for CRLF2 expression for consenting patients (see Section 7.2 and Section 13.4).
8 **Arm D ONLY.** Prior to start of Maintenance therapy for eligible patients (see Section 13.7 and lab manual for details)
9 Optional for future research (see Section 7.2 and Section 13.1).
* See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e
$ In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1.
\+ Evaluation 1 ++ Evaluation 2

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.1c **HSCT**

Observation	Prior to transplant (Tx)	1-2 weeks after ANC> 500/µL	3 mo Post-Tx	6 mo Post-Tx	9 mo Post-Tx	1 yr. Post-Tx	2 yrs. Post-Tx	3 yrs. Post-Tx	4 yrs. Post-Tx	5 yrs. Post-Tx	At subsequent relapse
Bone Marrow (BM) for central MRD[1]	X+++	X*	X**								
CSF cell count and cytospin	X										X
CBC, differential, platelets	X	X	X	X	X	X	X				X
BUN, Creatinine	X										
LFT	X	X	X	X	X	X	X				
Pulmonary function test	X										
Performance score	X	X	X	X	X	X	X	X	X	X	X

1 See Section 13.3 for details on shipping and handling; (see Section 7.2)
+++ pre-HSCT evaluation
* Day 30 (25-30)
** Day100 (+/- 3 weeks)

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.1d **Salvage Therapy (Blinatumomab-S)**

STUDIES TO BE OBTAINED	Blinatumomab Blocks
Hx/PE with VS/Wt (BSA)	Start of phase*
CBC/diff/plts	weekly

Bilirubin, ALT, creatinine, BUN	weekly
Local Bone Marrow (BM) Evaluation	end of phase
Bone Marrow (BM) for central flow MRD[2]	pre-HSCT
CSF cell count and cytospin	with each IT
Peripheral Blood for Pharmacokinetics (PK)	Cycle 1: Day 2 and Day 14**
Peripheral Blood for Immunogenicity	•Prior to (Hour 0) start of first blinatumomab infusion (Cycle 1) •End of Cycle 2[$]

* See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

** See lab manual on protocol webpage for sample collection and shipping details

$ In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1.

7.1e Recommended Observations: Blinatumomab Blocks

The investigator is recommended to monitor the patient's vital signs (body temperature, heart rate and blood pressure) approximately every 4 hours during the first 12 hours after the start of a cycle, and upon resumption after suspension for adverse event. On Day 2 and 3 vital signs should be measured once daily.

7.2 Research Studies

The following are correlative biology studies for which patient participation is optional. Please see Section 13.0 for details on volumes of specimen collection and shipping information. **Note: Patient consent is required.**

Study (see section for details)	**Summary of Sample and Timing**
Banking for Future Research * (Section 13.1)	**Peripheral blood:** • Baseline • End Block 1 • End Block 2 (Arm A, C or D, End of Blinatumomab Cycle 1 (Arm B) • Relapse **Bone marrow:** • Baseline • End Block 1 Relapse
CRLF2 expression (Section 13.4)	No separate specimen required – cell pellet from required baseline central flow bone marrow will be used
Protein Cell Stress (Section 13.6)	**Peripheral blood:** • Day 1 of Block 1 ○ Before chemotherapy (Hour 0) ○ After Chemotherapy (Hour 6 and Hour 24)
Blinatumomab Pharmacodynamics (PD) (Section 13.5)	**Bone marrow:** • End Block 1 (All patients) • End Block 2 (LR patients on Arm D only)

	Peripheral blood: • Prior to (Hour 0) start of first blinatumomab infusion • During (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion**

* For cases with a limited amount of tissue available for analysis, please prioritize specimen for tissue banking.

**In the event that the infusion is interrupted, the peripheral blood collection should likewise be delayed to account for the interruption. i.e. collect the timed sample after X days of infusion rather than X days from start of infusion.

7.3 At Relapse

Patients who relapse and have consented to cell banking at time of enrollment should have samples of bone marrow sent to the Molecular Reference Laboratory for cell banking (see Section 13.1.)

7.4 Follow-up

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Treatment failure but not eligible to receive blinatumomab salvage
b) Treatment failure that receives blinatumomab salvage but does not achieve CR after 2 cycles of blinatumomab
c) Adverse events requiring removal from protocol therapy
d) Refusal of further protocol therapy by patient/parent/guardian.
e) Completion of planned therapy.
f) Physician determines it is in patient's best interest.
g) Development of a second malignancy.
h) Second relapse at any site.
i) Repeat eligibility studies are outside the parameters required for eligibility (if applicable, see Section 3.2).
j) Inevaluable
k) Found to be ineligible for HSCT (See Section 4.9.1)
l) **Pre-Randomization (HR/IR or LR):** Interval development of significant central nervous system pathology that would preclude treatment with blinatumomab (see Section 3.2.6.12 for definition).
m) **Amendment #10:** Patient found to be HR/IR at the completion of Block 1.

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

8.2 Off Study Criteria

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

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

9.1.1 <u>Primary Endpoint</u>

A primary objective (HR/IR Randomization) of AALL1331 is to compare disease-free survival (DFS) of HR and IR relapse patients randomized to Block 2 and 3 chemotherapy (Control) vs. two blocks of blinatumomab (Experimental), followed by allogeneic HSCT. DFS is defined as time from start of randomization to event (treatment failure, relapse, second malignancy, death) or last follow-up for those who are event-free. DFS event date will be set at Day 1 if patients are deemed as TF after randomization.

Another primary objective (LR Randomization) of AALL1331 is to compare DFS of LR relapse patients randomized to chemotherapy alone (Control: Block 3, Continuation 1, Continuation 2 and Maintenance) vs. blinatumomab/chemotherapy (Experimental: blinatumomab, Continuation 1, blinatumomab, Continuation 2, blinatumomab, Maintenance). DFS is defined as time from start of randomization to first event (relapse, second malignant neoplasm, remission death) or last follow up for those who are event-free.

The primary analyses of DFS will include all randomized patients provided that randomization is performed per protocol. The analyses will be based on the intent-to-treat principle.

9.1.2 <u>Secondary Endpoints</u>

A secondary objective (HR/IR Randomization) of AALL1331 is to compare overall survival (OS) of HR and IR relapse patients randomized to Block 2 and 3 chemotherapy (Control) vs. two blocks of blinatumomab (Experimental), followed by allogeneic HSCT. OS is defined as time from start of randomization to death or last date of contact.

Another secondary objective (LR Randomization) of AALL1331 is to compare OS of LR relapse patients randomized to chemotherapy alone (Control: Block 3, Continuation 1, Continuation 2 and Maintenance) vs. blinatumomab/chemotherapy (Experimental: blinatumomab, Continuation 1, blinatumomab, Continuation 2, blinatumomab, Maintenance). OS is defined as time from start of randomization to death or last date of contact.

9.1.3 Exploratory Endpoints

The exploratory endpoints associated with HR/IR Randomization are to compare the rates of MRD positivity (>0.01%) at the end of Block 2 and 3 between randomized arms for HR and IR relapse patients.

Other exploratory endpoints include estimating the CR rate, MRD negativity (< 0.01%) rate and proportion that proceed to HSCT after treatment with blinatumomab for treatment failure patients not previously receiving blinatumomab, assessing the feasibility and safety of rapid taper of immune suppression for subset of HSCT patients with MRD ≥ 0.01% pre- and/or post-HSCT with no aGVHD, and collecting biologic samples for the prospective correlative biology studies described in Section 7.0.

Blinatumomab PK will be evaluated by summarizing blinatumomab steady state concentrations and systemic clearance obtained from non-compartmental analysis. In addition, a population PK approach using a non-linear mixed effect model will also be used to assess blinatumomab PK. Exposure-response analyses will be performed to explore associations among blinatumomab exposure, relevant clinical covariates and clinical measures of saftery and efficacy.

9.2 Patient Accrual and Expected Duration of Trial

9.2.1 Stratification to be used in the randomization

All patients are assigned to Stratum 1 at enrollment. All HR/IR relapse patients who do not meet the treatment failure criteria at the end of Block 1 will be eligible for HR/IR randomization and randomized equally between experimental (blinatumomab) and control (chemotherapy) arms. The randomization will occur upon recovery from Block 1 of therapy, and will be stratified by: 1) Risk Group (HR vs. IR); 2) For HR patients, site of relapse (marrow vs. IEM); 3) For HR – marrow patients, duration of first remission (< 18 months vs. 18-36 months from diagnosis); 3) For HR-marrow patients, MRD level end Block 1 (< 0.1% vs. ≥ 0.1%) to ensure balanced randomization within these subsets (see table below).

Stratum #	Risk-Site	CR1 mos	MRD status
2	HR-Marrow	< 18	MRD < 0.1%
3	HR-Marrow	< 18	MRD ≥ 0.1%
4	HR-Marrow	18-36	MRD < 0.1%
5	HR-Marrow	18-36	MRD ≥ 0.1%
6	HR-IEM	<18	-
7	IR	-	-

All late B-ALL marrow and late B-ALL IEM relapse patients with end Block 1 MRD < 0.1% will eligible for LR randomization and randomized equally between experimental (blinatumomab) and control (chemotherapy) arms. The randomization will occur upon recovery from Block 1 of therapy, and will be stratified by: 1) site of relapse (marrow vs. IEM); and 2) MRD level at time of randomization (< 0.01% vs. ≥ 0.01%) to ensure balanced randomization within these subsets.

Stratum #	Site	CR1 mos	MRD status
8	LR-Marrow	≥ 36	MRD < 0.01%
9	LR-Marrow	≥ 36	MRD ≥ 0.01% or MRD < 0.1% with sensitivity 1/1000
10	LR-IEM	≥ 18	MRD < 0.01%
11	LR-IEM	≥ 18	MRD ≥ 0.01% or MRD < 0.1% with sensitivity 1/1000

9.2.2 Sample size with power calculation (Activation Protocol)

Sample size calculations driving this study are based on the two randomized questions HR/IR Randomization and LR Randomization.

For HR/IR Randomization, approximately 170 evaluable HR/IR B-ALL patients are to be randomized between experimental (blinatumomab) and control (chemotherapy) arms after recovery from Block 1. As described in Section 9.3.1, the test of the randomization question has a power of 80.0% at a one-sided significance level of 2.5% to detect the desired improvement in 2-year DFS rate. The 170 evaluable HR/IR B-ALL patients are expected to take 3 years to be enrolled with the total rate of accrual to HR/IR Randomization to be 56 per year after adjusting for approximate 10% refusal rate to randomization. This estimate is based on the following estimates of annual accrual and dropout rate from past studies AALL01P2, AALL02P2, AALL0433 and ADVL04P2:

	Early marrow	Early IEM	Late marrow	Late IEM
# entering study	60	5	44	28
Rate of MRD ≥ 0.1%	-	-	38%	12%
Rate of not dropping out prior to block 2 (due to toxicity and/or treatment failure)	70%	70%	90%	90%
# eligible for randomization	42	3	15	3

For LR randomization, approximately 206 evaluable LR B-ALL patients are to be randomized between experimental (blinatumomab) and control (chemotherapy) arms after recovery from Block 1. As described in Section 9.3.2, the test of the randomization question has a power of 80.4% at a one-sided significance level of 5% to detect the desired improvement in 3-year DFS rate. The 206 evaluable LR B-ALL patients are expected to accrue over 5.6 years with total rate of accrual to LR Randomization to be 37 per year after adjusting for approximate 10% refusal rate to randomization. This estimate is based on the following estimates of annual accrual and dropout rate from past studies AALL01P2, AALL02P2, AALL0433 and ADVL04P2:

	Late marrow	Late IEM
# entering study	44	28
Rate of MRD < 0.1%	62%	88%

Rate of not dropping out prior to block 2 (due to toxicity and/or treatment failure)	80%	80%
# eligible for randomization	22	20

Therefore, in order to enroll 170 and 206 evaluable patients for HR/IR and LR Randomization respectively, a total of 195 early marrow/IEM and 403 late marrow/IEM patients are expected be accrued at the beginning of the study.

9.2.3 Extension of accrual duration for both the LR cohort and the HR/IR cohort (Amendment #8)

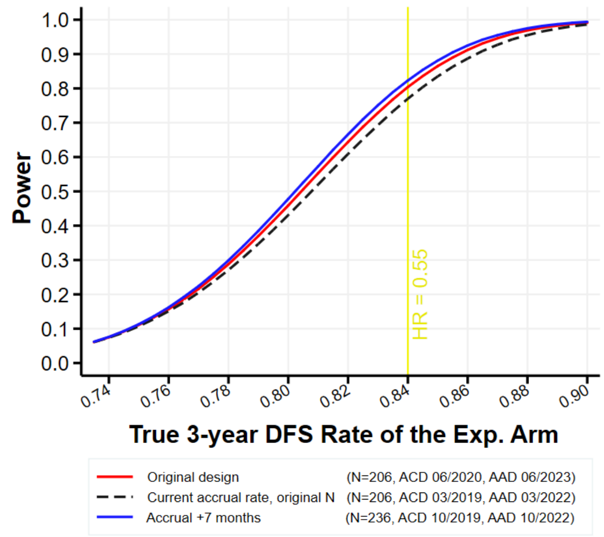
With Amendment #8, for both the LR cohort and the HR/IR cohort, the accrual duration will be extended until 10/31/2019, provided that there is no prolonged interruption of study enrollment.

The AALL1331 study has demonstrated a steady accrual rate for both the LR cohort and the HR/IR cohort. The observed accrual rate is approximately 53 patients/year in the LR cohort, much faster than the anticipated 37/year, and is 50 patients/year in the HR/IR cohort, slightly smaller than but very close to the anticipated 56/year. With the faster accrual rate in the LR cohort and steady observed accrual rate in HR/IR, we amend the accrual duration for both cohorts to be until 10/31/2019 to ensure that the primary analyses maintain sufficient statistical power for the LR cohort and that the timing of completion of accrual be the same between the two cohorts. This amendment in accrual target will increase the power of statistical analyses and the sensitivity of the study, help us to gather more accurate information regarding the treatment regimens, and will not cause delay in addressing the primary objectives of the study or delay in opening the planned successor trial to AALL1331 (AALL1821). AALL1331 is the first pediatric ALL study to substitute blocks of immunotherapy for conventional chemotherapy and the increased power of the analyses may be very beneficial in moving this general approach forward in future studies.

9.2.3.1 The LR Cohort

For the LR cohort, the study was originally designed to have approximately power of 0.80 to detect a hazard ratio of 0.55 with a one-sided logrank test and Type I error of 0.05, which corresponds to an increase in 3-year DFS rate from 73% in the control arm to 84% in the experimental arm. This cohort was planned to enroll a total of 206 randomized, evaluable patients. It was expected to accrue for 5.6 years, with 3 years of additional follow-up after completion of enrollment. With the observed accrual rate of 53 patients/year, the anticipated accrual completion date (ACD) with the original sample size of 206 is approximately 03/2019, and the anticipated analysis date (AAD) is 3 years after that, i.e., 03/2022.

Given the faster-than-expected observed accrual rate, if this cohort follows the original plan to enroll 206 evaluable patients and have 3 years of additional follow-up, the power of the study will be smaller than planned due to the shorter average follow-up time among the patients. This is demonstrated by the comparison of the dotted black line to the solid red line in the figure below. As shown by the dotted black line, with the observed accrual rate of 53/year, the study will only have power of 0.77 to detect a hazard ratio of 0.55, smaller than the planned power of 0.80.



The faster observed accrual rate in the LR cohort gives us the opportunity to address this issue by enrolling more patients, resulting in an increase in the power of the analysis, an increase in the sensitivity of the study, and the ability to gather more accurate information regarding the treatment regimens. With Amendment #8, we extend the accrual duration for the LR cohort to be until 10/31/2019. This will increase the number of evaluable patients from 206 to approximately 236. With this extended accrual duration, the ACD and AAD will be 10/2019 and 10/2022, respectively (please see Section 9.3.2.1 for more details on the primary analysis with Amendment #8). (Note that the AAD of 10/2022 is still earlier than the AAD had the accrual rate been the assumed 37 patients/year.) With 236 evaluable patients, the study will have approximately power of 0.83 to detect a hazard ratio of 0.55, and power of 0.75 to detect a hazard ratio of 0.59.

The following table presents a comparison in characteristics of the trial for the LR cohort under the scenarios of (1) the original accrual target with the expected accrual rate, (2) the original accrual target with the observed accrual rate, and (3) the extended accrual duration with Amendment #8.

	Characteristics	**Original Accrual Target (assuming expected accrual rate)**	**Original Accrual Target (with observed accrual rate)**	**Extended Accrual Duration (Amendment #8)**
1	Accrual rate	37 pts/year	53 pts/year	53 pts/year
2	Sample size	206	206	236
3	Accrual completion date (ACD)	06/2020	03/2019	10/2019
4	Anticipated analysis date (AAD)	06/2023	03/2022	10/2022

5	Power of detecting a hazard ratio of 0.55 (corresponding to 3-year DFS of 84% vs. 73%)	0.80	0.77	0.83
6	Power of detecting a hazard ratio of 0.59 (corresponding to 3-year DFS of 83% vs. 73%)	0.72	0.69	0.75
7	Sample size for evaluation of toxicities and biologic aims	--	--	Increased by 14%
8	Delay in addressing primary aim, compared to the original accrual target	--	--	No delay
9	Timing of completion of accrual compared to the HR/IR cohort	--	5~6 more months of accrual if without amendment of accrual target of the two cohorts.	The same as the HR/IR cohort with Amendment #8.

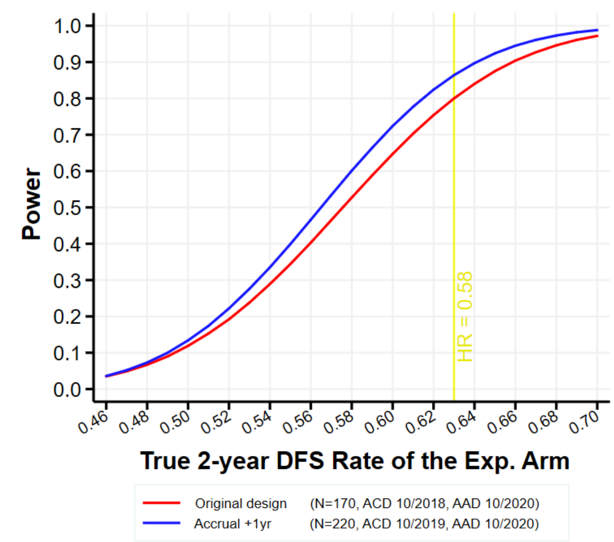
9.2.3.2 The HR/IR Cohort

For the HR/IR cohort, the study was originally designed to have approximately power of 0.80 to detect a hazard ratio of 0.58 with a one-sided logrank test and Type I error of 0.025, which corresponds to an increase in 2-year DFS rate from 45% in the control arm to 63% in the experimental arm. This cohort was planned to enroll a total of 170 randomized, evaluable patients. It was expected to accrual for approximately 3 years, with 2 years of additional follow-up after completion of enrollment. With the original sample size of 170 patients, the ACD is approximately 10/2018, and the AAD is 2 years after that, i.e., 10/2020.

If staying with the originally planned accrual target, the HR/IR randomization would be closed approximately 5-6 months earlier than the LR cohort. After closure of the HR/IR randomization, we would need to continue to enroll patients with late relapses to fulfill the accrual target for the LR cohort. A subset of patients with late relapses would be assigned the IR group at the completion of the induction therapy, and would subsequently need to be taken off therapy due to the closure of the HR/IR randomization.

To avoid having to reject patients from further protocol therapy, with Amendment #8, we extend the accrual duration for HR/IR so that this cohort will complete accrual at the same time as the LR cohort. That is, we extend accrual duration of HR/IR to be until 10/31/2019, the same as the LR cohort. We plan that the primary analysis for the HR/IR cohort be conducted approximately 1 year later (please see Section 9.3.1.1 for more details on the primary analysis with Amendment #8). Hence the AAD will be approximately 10/2020. Given that the protocol therapy duration for HR/IR patients is typically 7 months, by 10/2020 all patients in the HR/IR cohort should have completed protocol therapy. This AAD is the same as the AAD for HR/IR if we did not amend the accrual target.

In summary, the increased accrual target of the HR/IR cohort will give us the same timing of completion of accrual between the HR/IR cohort and the LR cohort, without causing any delay in addressing the primary objectives. The increased accrual target will also improve the sensitivity of this cohort and increase the power to detect a smaller difference in treatment effect between the experimental arm vs. the control arm. As shown in the figure below, the sample size of 220 evaluable patients will increase the power to detect a hazard ratio of 0.58 from 0.80 to 0.85.



The following table presents a comparison in characteristics of the trial for the HR/IR cohort under the scenarios of (1) the original accrual target, and (2) the extended accrual duration with Amendment #8.

	Characteristics	**Original Accrual Target**	**Extended Accrual Duration (Amendment #8)**
1	Sample size	170	220
2	Accrual completion date (ACD)	10/2018	10/2019
3	Anticipated analysis date (AAD)	10/2020	10/2020
4	Power of detecting a hazard ratio of 0.58 (corresponding to 2-year DFS of 63% vs. 45%)	0.80	0.85
5	Sample size for evaluation of toxicities and biologic aims	--	Increased by 29%
6	Delay in addressing primary aim, compared to the original accrual target	--	No delay
7	Timing of completion of accrual compared to the LR cohort	5~6 months ahead if without amendment of accrual target of the two cohorts.	The same as the LR cohort with Amendment #8.

9.2.3.3 Accrual target (Amendment #8)

With Amendment #8, both the LR cohort and the HR/IR cohort will enroll until 10/31/2019, provided that there is no prolonged interruption of study enrollment. Based on the observed accrual rates, it is anticipated, but not required, that we will enroll approximately a total of 220 randomized HR/IR patients and a total of 236 randomized LR patients. By 10/31/2019, it is expected that the total accrual on this study will not surpass 700 patients, including patients who are not eligible for or refuse randomization.

9.3 Statistical Analysis Methods

9.3.1 HR/IR Randomization for HR and IR relapse patients

9.3.1.1 Primary endpoint: intent-to-treat DFS

The original design (Activation Protocol)

The primary efficacy analysis for HR/IR Randomization will be an intent-to-treat comparison of the DFS curves between the randomized arms based on the Log-rank test. All HR/IR relapse patients who are not deemed as treatment failures at the end of Block 1 will be eligible for HR/IR Randomization. The randomization will occur upon recovery from Block 1 of therapy, and will be stratified as described in Section 9.2. From the past studies of AALL01P2, AALL02P2 and ADVL04P2, the overall 2-year DFS rate for HR/IR patients was approximately 45%. Although most events are projected to occur within 2 years, events continue to occur in subsequent years, and hence an exponential distribution is considered more appropriate than a cure-rate model for comparing survival curves for this cohort of patients at the time of final analysis. Assuming a minimum of 2 years of follow up, an estimate of 170 evaluable patients will need to be randomized to achieve the goal of 18% improvement in 2-year DFS rate with blinatumomab over the expected 2-year DFS rate of 45% with chemotherapy backbone alone, with 80.0% power at a one-sided significance level of 2.5%, which represents a 42.1% reduction in hazard rate. The power calculations are based on the assumption of proportional hazards and using the log rank test.

Interim analysis will be conducted to monitor for efficacy and futility. The efficacy stopping boundaries to be used will be based on the O' Brien-Fleming spending function. The futility boundaries are based on testing the alternative hypothesis at the 0.024 level.[62] This monitoring rule can be applied to any interim analysis schedule and maintains the overall significance level of 0.025. Assuming exponential distribution and the final analysis is performed at the 2 years after the completion of enrollment, the expected maximum number of events to be observed is estimated to be 109. The first interim analysis will be performed after 36 events have been observed. The cumulative power to detect the desired improvement is approximately 78%. The sample of monitoring boundaries for efficacy and futility with 3 interim analyses are given in the table below.

Looks	# of events	Information	Efficacy Boundary	Futility Boundary
1	36	33%	3.731	-0.392
2	73	67%	2.504	0.280
3	109	100%	1.994	1.994

Re-design for the HR/IR cohort (Amendment #8)

Summary of the original design

For the HR/IR cohort, the study was originally designed to have approximately power of 0.80 to detect a hazard ratio of 0.58 using a one-sided logrank test with Type I error of 0.025, which corresponds to an increase in 2-year DFS rate from 45% in the control arm to 63% in the experimental arm. This cohort was originally planned to enroll a total of 170 randomized, evaluable patients. It was expected to accrual for approximately 3 years, with 2 years of additional follow-up after completion of enrollment.

Extended accrual duration and increased sample size

With the extended accrual duration, the HR/IR cohort will continue to enroll until 10/31/2019. Based on the observed accrual rate of 50 patients/year, this extended accrual duration will lead to a sample size of approximately 220 randomized patients in the HR/IR cohort. As initially planned, the primary analysis on efficacy will be based on a one-sided logrank test, with one-sided Type I error of 0.025. The primary analysis is planned to be conducted 1 year after completion of accrual provided that the expected total number of events is observed by then. Otherwise the primary analysis will be conducted when the expected total number of events is observed, or at 1.5 years after completion of accrual, whichever comes first. Assuming exponential distribution for the survival function, with 4.4 years of enrollment and 1 year of additional follow-up, the expected total number of events is 131. With the sample size of 220, the study will have approximately power of 0.85 to detect a hazard ratio of 0.58.

Interim analysis performed to date

One interim analysis of DFS has been conducted for the HR/IR cohort using data freeze as of 12/31/2017. At the time of this first interim analysis, the observed number of events was 39 (35.8% of the information based on the original full information of 109 events), and the alpha (Type I error) that was spent was 0.00018. The first interim analysis did not cross either the efficacy or futility boundaries.

Amended statistical monitoring plan for DFS

With the extension of the accrual duration, the full information now increases from the original 109 events to 131 events. With the increased expected number of events, the first interim analysis was actually conducted when we had 29.8% of information (rather than 35.8%), and the alpha that would have been spent would be 0.00004 instead of 0.00018. That is, more alpha was spent in the first interim analysis.

A new interim monitoring plan for the future looks for the HR/IR cohort was developed by an independent statistician.

The new monitoring plan for the HR/IR cohort accounts for the alpha-spending that has already occurred.[63,64] Specifically, with the new monitoring plan, the overall alpha to be expended is the original significance level minus the alpha expended with the initial interim monitoring that has been conducted.[63,64] In the case of the HR/IR cohort, given that for the first look the alpha expended was 0.00018, the remaining alpha of 0.02482 can be used for the new monitoring plan. A monitoring plan that includes two more looks (the second look and the final look) was developed using the O'Brien-Fleming boundaries,[65,66] with an overall significance level of 0.02482, scheduled at 66.4% and 100% of the total expected information. This way the cohort-wide significance level of 0.025 is maintained. The futility boundaries are based on testing the alternative hypothesis at the 0.024 level.[62] The boundaries are shown in the following table.

		Original Efficacy Boundaries				**New Efficacy Boundaries**					**Futility**
Looks	**# of Events**	**Inf. Time**	**Upper Boundary of Z value**	**Nominal Alpha**	**Cumu. Alpha**	**Inf. Time Revised**	**Upper Boundary of Z value**	**Nominal Alpha**	**Cumu. Alpha**	**Overall alpha**	**Futility Boundary of Z value**
1 (done)	39	35.8%	3.568	0.00018	0.00018	29.8%				0.00018	-0.327
2	87					66.4%	2.519	0.00588	0.00588	0.00606	0.363
3	131					100%	1.995	0.02301	0.02482	0.025	1.995

<u>Confirmatory follow-up analysis of DFS of the HR/IR randomized cohort (Amendment #10)</u>

On 09/18/2019, the COG DSMC has recommended closing accrual to the HR/IR arms of AALL1331 and releasing the results of the HR/IR cohort to the study committee. This recommendation is primarily based on the significantly more favorable tolerability profile of the experimental (blinatumomab) arm, coupled with trending or superior DFS and OS of the blinatumomab arm (per interim analyses performed using data as of 06/30/2019). DSMC has recommended that HR/IR patients assigned to the control arm (Arm A) who are at an appropriate point in their treatment program (prior to receiving Block 3) be offered the opportunity to cross over to the experimental arm (Arm B) to receive blinatumomab.

The following table summarizes the analysis of DFS (the second look) using data as of 06/30/2019.

			Original Efficacy Boundaries				New Efficacy Boundaries					Futility	Observed Z Statistic
Looks	Data Cutoff	# of Events	Inf. Time	Upper Boundary of Z value	Nominal Alpha	Cumu. Alpha	Inf. Time Revised	Upper Boundary of Z value	Nominal Alpha	Cumu. Alpha	Overall alpha	Futility Boundary of Z value	
1	12/31/2017	39	35.8%	3.568	0.00018	0.00018	29.8%				0.00018	-0.327	1.233
2	06/30/2019	80					61.1%	2.644	0.00409	0.00409	0.00427	0.267	1.649

A confirmatory follow-up analysis comparing DFS of the control arm vs. the experimental arm will be conducted using the 12/31/2020 data freeze or when 131 events are observed, whichever occurs earlier. This confirmatory analysis will use the HR/IR patients randomized on or prior to 06/30/2019 (103 in the control arm and 105 in the experimental arm).

9.3.1.2 Secondary Endpoint: Intent-to-treat OS

From the past studies of AALL01P2, AALL02P2 and ADVL04P2, the 3-year OS rate for HR/IR patients was approximately 48%, and most deaths occurred within the first 3 years. Therefore, a cure-rate model with exponential distribution assumed during the first 3 years followed by a flat curve is considered for OS analysis. An interim OS analysis will be conducted at the time of the final DFS analysis, i.e. when all the 170 randomized patients are followed up for 2 years. Assuming 17% improvement in 3-year OS rate with blinatumomab over the expected 3–year OS rate of 48% with chemotherapy backbone alone, approximate 70 deaths are to be observed by the time of the interim OS analysis. The power to detect such improvement at a one-sided significance level of 2.5% is approximate 61% based on the log-rank test.

If DFS analysis meets its target level of improvement (i.e. one-sided p–value < 0.025), the formal OS analysis will be performed at at 1 year after the interim OS analysis, by which time approximate 74 deaths are to be observed. The power to detect the above desired improvement is approximately 63%.

Power of the analysis of OS with the extended accrual duration (Amendment #8)

With the accrual duration extended to 10/31/2019, the power of the analysis of OS for the HR/IR cohort will be approximately 0.67 if conducted at 1 year after completion of accrual, and will be approximately 0.72 if conducted at 2 years after completion of accrual.

Confirmatory follow-up analysis of OS of the HR/IR randomized cohort (Amendment #10)

A confirmatory follow-up analysis comparing OS of the control arm vs. the experimental arm will be conducted at the time of the confirmatory analysis of DFS, as well as one year following it. Same as for DFS, this analysis will also be utilizing the HR/IR patients randomized on or prior to 06/30/2019 (103 in the control arm and 105 in the experimental arm).

9.3.1.3 Secondary endpoint: MRD+ rates

MRD comparisons (using an MRD+ threshold of 0.01%) will be performed at the end of Blocks 2 and 3 for marrow relapse patients participating in HR/IR Randomization. From past experience with studies AALL01P2, ADVL04P2, AALL07P1 and AALL0433, we anticipate that over the 3 years of the study, there will be 56 patients per arm evaluable for the MRD comparison at the end of Block 2 and 50 patients per arm evaluable for the MRD comparison at the end of Block 3 (see table below for derivation).

	Early marrow	**Late marrow with MRD ≥ 0.1%**	**Total**
# randomized on HR/IR Randomization (per arm)	61	24	85
Rate of not dropping out prior to end Block 2	63%	75%	
# evaluable for end Block 2 MRD testing	38	18	56
Rate of not dropping out prior to end Block 3	89%	88%	
# evaluable for end Block 3 MRD testing	34	16	50

Further, we anticipate that the rates of MRD ≥ 0.01% in the control arm will be 67% (67% for early and 68% for late) at the end of Block 2 and 47% (43% for early and 55% for late) at the end of Block 3. A two-sample Fisher’s exact test of proportions (one-sided, alpha = 5%) will be used to test the hypothesis that the proportion of patients who are MRD+ on each experimental arm (with blinatumomab) is smaller than the control arm (without blinatumomab) at the end of Block 2 and 3. The corresponding power to detect various degrees of reduction in MRD+ rates is shown in the table below:

	Expected # per arm with successful MRD determination	**% MRD+ (control arm)**	**Reduction in MRD+ rates (investigational arm)**			
			10%	15%	20%	25%
End Block 2	56	67%	22.6%	41.8%	63.2%	81.2%
End Block 3	50	47%	19.2%	37.1%	59.5%	79.8%

With the accrual duration extended to 10/31/2019, the analysis on MRD+ rates should have more statistical power.

9.3.1.4 Safety monitoring (Activation Protocol)

According to the past study ALLR3, the cumulative toxic death rate of Blocks 2 and 3 of chemotherapy was estimated to be 4% (1.6% for Block 2 and 2.7% for Block 3). The toxic death rate is expected to be lower in the experimental arm than the control arm because the myelosuppressive cytotoxic chemotherapy blocks are replaced with targeted immunotherapy. Therefore, toxic deaths will be closely monitored on all patients enrolled to each arm of HR/IR Randomization separately through blocks 2 and 3 of therapy. HR/IR Randomization will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths in either arm is greater than or equal to that specified in the table. The boundary of toxic death was computed based on Pocock-type spending function at one-sided 20% significant level.

Looks	# evaluable patients	Information	Pocock boundary of excessive toxic death	Excessive toxic death rate
1	28	33%	4	14.29%
2	57	67%	5	8.77%
3	85	100%	7	8.24%

Either arm of HR/IR Randomization will be rejected for excessive toxicity if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring an arm too toxic are approximately 95.2%, 80.8%, 47.2% and 10.1% when the true toxic death rate is 13%, 10%, 7% and 4%, respectively.

In addition, occurred during Block 2 and 3 of chemotherapy the toxic deaths and all toxicities of all grades between the two arms will be monitored/compared during the study. If the toxic death rate or the rate for any specific toxicity is significantly higher on the blinatumomab arm compared to the control arm (ALLR3 backbone), the data will be reviewed for possible suspension of the randomization and modification of therapy.

9.3.1.5 Amended Safety Monitoring (Amendment 6)

As of April 2017, there have been 4 deaths during blocks 2 and 3, among 47 randomized patients on Arm A. Of these, three deaths occurred in 14 AYA patients (ages 17, 23, and 26 years), with a death rate of 21.4%. The death rate among the younger patients is 1/33 (3%). The published UKALLR3 clinical trial only enrolled patients up to 18 years of age at the time of first relapse. Hence the toxic death rate from that study (used as the baseline rate on this study), was based on a younger population than those enrolling on AALL1331. About 15% of enrollments on this study are currently greater than 18 years old. Based on prior studies in COG and other groups, it is known that the risk of toxic deaths may be higher in older patients relative to younger ones.

Based on this, the monitoring for toxic deaths during Blocks 2 and 3, among HR/IR patients randomized to Arm A, has been modified to apply only to patients ≤ 18 years of age at enrollment. The modified rule is given in the table below.

	#Evaluable patients	Pocock Boundary of Excessive Toxic deaths
Monitoring (HR/IR patients ≤18 years of age on Arm A)	4-40	4
	41-57	5
	58-72	6

With this rule, the probability of stopping due to excessive toxic deaths is 12% if the true toxic death rate is 4%, 48% if the true rate is 7%, and 79.2% if the true rate is 10%.

Since it is estimated that only about 13 patients on each arm will be >18 years of age at enrollment, separate stopping rules for this subset would not have much power (~74% at a true rate of 30%, or 13% power at a true rate of 10%). Instead of a formal monitoring rule for AYA patients, continuous monitoring will be done, such that any death occurring among the older patients, after the proposed supportive care changes are initiated, will trigger a study committee review and communication to the COG Data Safety Monitoring Committee.

With Amendment #8, more patients will be enrolled in the HR/IR cohort. The above safety monitoring rule on toxic deaths will be implemented until the originally planned sample size of 170 evaluable patients are enrolled and completed protocol treatment. If the toxic death rates are not concerning with the 170 patients, then no formal statistical monitoring rule on toxic deaths will be implemented for the remaining patients who will be enrolled in this cohort. However, informal continuous monitoring of occurrences of toxic deaths will continue to be conducted.

9.3.2 LR Randomization for LR relapse patients

9.3.2.1 Primary endpoint: intent-to-treat DFS from randomization

The original design (Activation Protocol)

The primary efficacy analysis for LR Randomization will be an intent-to-treat comparison of the DFS curves between the randomized arms based on the Log-rank test. All late B-ALL marrow and IEM relapse patients with end Block 1 MRD < 0.1% who are not deemed to be treatment failures at the end of Block 1 or Block 2 will be eligible for LR Randomization . For IEM patients, uninterpretable MRD (due to lack of diagnostic marker) will be considered to be MRD negative. The randomization will occur upon recovery from Block 2 of therapy, and will be stratified as described in Section 9.2. Data from past studies suggest that most events are to occur within 3 years, but events continue to occur in subsequent years, and hence an exponential distribution is considered more appropriate than a cure-rate model for comparing survival curves for this cohort of patients at the time of final analysis. An estimate of 206 evaluable patients will be randomized 1:1 (103 evaluable patients per arm) between randomized experimental (blinatumomab) and control (chemotherapy) arms. Assuming a minimum of 3-years of follow up, this sample size estimate is based on a goal of achieving a 11% improvement in 3-year DFS rate with blinatumomab over the expected 3-year DFS rate of 73% with chemotherapy backbone alone, with 80.4% power at a one-sided significance level of 5%, which represents a 44.6% reduction in the hazard rate. The power calculations are based on the assumption of proportional hazards and using the log rank test.

Interim analysis will be conducted to monitor for efficacy and futility. The efficacy stopping boundaries to be used will be based on the O' Brien-Fleming spending function. The futility boundaries are based on testing the alternative hypothesis at the 0.039 level.[62] This monitoring rule can be applied to any interim analysis schedule and maintains the overall significance level of 0.05. Assuming exponential distribution and the final analysis is performed at the 3 years after the completion of enrollment, the expected maximum number of events to be observed is estimated to be 75. The first interim analysis will be performed after 25 events have been observed. The cumulative power to detect a difference is approximately 80%. The sample of monitoring boundaries for efficacy and futility with 3 interim analyses are given in the table below.

Looks	# of events	Information	Efficacy Boundary	Futility Boundary
1	25	33%	3.202	-0.312
2	50	67%	2.140	0.288
3	75	100%	1.695	1.695

<u>Re-design for the LR cohort (Amendment #8)</u>

<u>Summary of the original design</u>

For the LR cohort, the study was originally designed to have approximately power of 0.80 to detect a hazard ratio of 0.55 using a one-sided logrank test with Type I error of 0.05. The hazard ratio of 0.55 corresponds to an increase in 3-year DFS rate from 73% in the control arm to 84% in the experimental arm, assuming exponential distribution in survival function. This cohort was originally planned to enroll a total of 206 randomized, evaluable patients. It was expected to accrue for 5.6 years, with 3 years of additional follow-up after completion of enrollment.

<u>Extended accrual duration and increased sample size</u>

With the extended accrual duration, the LR cohort will continue to enroll until 10/31/2019. Based on the observed accrual rate of 53 patients/year, this extended accrual duration will lead to a sample size of approximately

236 randomized patients in the LR cohort. As initially planned, the primary analysis on efficacy will be based on a one-sided logrank test, with one-sided Type I error of 0.05. The primary analysis will be conducted 3 years after completion of enrollment or when the expected total number of events is observed, whichever comes first. Assuming exponential distribution for the survival function, with 4.4 years of enrollment and 3 years of additional follow-up, the expected total number of events is 80. With the sample size of 236, the study will have approximately power of 0.83 to detect a HR of 0.55.

Amended statistical monitoring plan for DFS

With the extended accrual duration, the full information increases from the original 75 events to 80 events. The new interim monitoring plan, developed by an independent statistician, accounts for the alpha-spending that has already occurred.[63,64] Specifically, with the new monitoring plan, the overall alpha to be expended is the original significance level (0.05) minus the alpha expended with the first interim monitoring that has been conducted (0.00068).[63,64] That is, the remaining alpha of 0.04932 can be used for the new monitoring plan. A monitoring plan that includes two more looks (the second look and the final look) was developed using the O'Brien-Fleming monitoring boundaries,[65,66] with an overall significance level of 0.04932, scheduled at 66.25% and 100% of the total expected information. This way the cohort-wide significance level of 0.05 is maintained. The futility boundaries are based on testing the alternative hypothesis at the 0.039 level.[62] The boundaries are shown in the following table.

		New Efficacy Boundaries					Futility
Looks	**# of Events**	**Inf. Time Revised**	**Upper Boundary of Z value**	**Nominal Alpha**	**Cumu. Alpha**	**Overall alpha**	**Futility Boundary of Z value**
2	53	66.25%	2.151	0.01573	0.01573	0.01641	0.361
3	80	100%	1.702	0.04462	0.04932	0.05	1.702

9.3.2.2 Secondary Endpoint: Intent-to-treat OS

From past studies suggest that most events for LR patients are to occur within 4 years after randomization and the 4-year OS rate is estimated to be 77%. Therefore, a cure-rate model with exponential distribution assumed during the first 4 years followed by a flat curve is considered for OS analysis for LR randomized patients. An interim OS analysis will be conducted at the time of the final DFS analysis, i.e. when all the 206 randomized patients are followed up for 3 years. Assuming 10% improvement in 4-year OS rate with blinatumomab over the expected 4-year OS rate of 77% with chemotherapy backbone alone, approximate 36 deaths are to be observed by the time of the interim OS analysis. The power to detect such improvement at a one-sided significance level of 5% is approximate 60% based on the log-rank test.

If DFS analysis meets its target level of improvement (i.e. one-sided p-value < 0.05), the formal OS analysis will be performed at 1 year after the interim OS analysis, by which time approximate 37 deaths are to be observed. The power to detect the above desired improvement is approximately 61%.

Power of the analysis of OS with the extended accrual duration (Amendment #8)
With the accrual duration extended to 10/31/2019, the power of the analysis of OS for the LR cohrt will be approximately 0.63 if conducted at 3 years after completion of accrual, and will be approximately 0.64 if conducted at 4 years after completion of accrual.

9.3.2.3 Monitoring for severe toxicities and toxic deaths

According to the past study of ALLR3, the cumulative toxic death rate of Block 3, Continuation and Maintenance chemotherapy was estimated to be 4% (2.7% for Block 3 and 1.5% for Continuation and Maintenance). The toxic death rate is expected to be lower in the experimental arm than the control arm because the myelosuppressive Block 3 is replaced with targeted immunotherapy. Therefore, toxic deaths will be closely monitored on all patients enrolled on to each arm of LR Randomization separately from the start of Block 3 of therapy to the completion of protocol therapy. LR Randomization will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths in either arm is greater than or equal to that specified in the table below. The boundary of toxic death was computed based on Pocock-type spending function at one-sided 20% significant level.

Looks	**# evaluable patients**	**Information**	**Pocock boundary of excessive toxic death**	**Excessive toxic death rate**
1	34	33%	4	11.76%
2	69	67%	6	8.70%
3	103	100%	7	6.80%

Either arm of LR Randomization will be rejected for excessive toxicity if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring an arm too toxic are approximately 98.7%, 90.9%, 61.5% and 14.4% when the true toxic death rate is 13%, 10%, 7% and 4%, respectively.

In addition, during Block 3, Continuation 2 (Week 1 - 5) and Maintenance (Week 6 - 10) the toxic deaths and all toxicities of all grades between the two arms will also be monitored/compared. If the toxic death rate or the rate for any specific toxicity is significantly higher on the blinatumomab arm compared to the control arm, the data will be reviewed for possible suspension of the randomization and modification of therapy.

The potential for late adverse effects due to long term depletion of $CD19^+$ normal lymphocytes following blinatumomab treatment is unknown. We will monitor for lymphocyte recovery and late events related to delayed recovery. Since HR/IR/TF patients go to HSCT soon after blinatumomab, it would be difficult to make sense of lymphocyte recovery/late events after blinatumomab for them. However, the LR patients that are randomized to +/- blinatumomab and do not proceed to HSCT serve as an excellent population to monitor for these delayed adverse effects. For all LR patients, we will collect absolute lymphocyte counts (ALC)/lymphocyte subset counts (total T and B cells) and data regarding late infections and progressive multifocal leukoencephalopathy (PML) after each 12-week maintenance cycle and every 3 months after completion of therapy for 1 year. The peripheral B-cell recovery rates and rates of late events by randomized arms will be monitored and compared descriptively between the two randomized arms every 6 months in the biannual study progress report and DSMC report.

With Amendment #8, more patients will be enrolled in the LR cohort. The above safety monitoring rules on severe toxicities and toxic deaths will be implemented until the originally planned sample size of 206 evaluable patients are enrolled and completed protocol treatment. If the toxic death rates are not concerning with the 206 patients, then no formal statistical monitoring rule on severe toxicities and toxic deaths will be implemented for the remaining patients who will be enrolled in this cohort. However, informal continuous monitoring of occurrences of toxic deaths will continue to be conducted.

9.3.3 Pilot intervention for very high risk subset of HSCT recipients based on MRD and aGVHD

9.3.3.1 Primary endpoint

The primary endpoint of this non-randomized exploratory pilot intervention (accelerated taper of immune suppression) is feasibility and safety, with “success” defined as < 25% rate of Grade III-IV aGVHD and < 5% rate of treatment-related mortality (TRM) associated with the accelerated taper. We anticipate that 36 patients will meet the criteria to receive the intervention. We will calculate the observed rates of Grade III – IV aGVHD and TRM among this subset with 95% confidence intervals and compare descriptively to our target rates.

9.3.3.2 Exploratory endpoint

As secondary endpoints, we will calculate the percent of patients able to wean off immunosuppression without significant aGVHD (future intervention group), DFS of intervention group (vs. similar pts in ASCT0431 historical controls), rate of conversion from MRD+ to MRD- among preMRD-/postMRD+ subset (correlated with DFS), aGVHD rates post-intervention (correlated with DFS). These data will be analyzed descriptively.

9.3.3.3 Safety monitoring

The toxic death and Grade 3+ GVHD rates will be closely monitored for the subset of HSCT patients with MRD ≥ 0.01% pre- and/or post-HSCT with no acute graft versus host disease (aGVHD) who undergo accelerated taper of immune suppression during the study. According to past studies, the cumulative toxic death rate was estimated to be 5% and the cumulative incidence rate of Grade 3+ GVDH was approximately 25%.

The safety stopping boundaries to be used for toxic death and Grade 3+ GVHD, respectively, will be based on the Pocock-type spending function at one-sided 20% significance level. Assuming 85% of evaluable HR/IR patients will proceed to HSCT study and approximately 25% of them will have MRD ≥ 0.01% pre- and/or post-HSCT with no evidence of aGVHD, an estimate of 36 patients will be monitored in this subset. The intervention (accelerated taper of immune suppression) will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths or the number of Grade 3+ GVHD is greater than or equal to that specified in the corresponding table below.

Table for toxic death monitoring boundary:

Looks	**# evaluable patients**	**Information**	**Pocock boundary of excessive toxic deaths**	**Excessive toxic death rate**
1	12	33%	3	25.00%
2	24	67%	4	16.67%
3	36	100%	4	11.110%

The intervention will be rejected for excessive toxicity death if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring the intervention too toxic are approximately 88.5%, 71.1%, 41.6% and 10.9% when the true toxic death rate is 17%, 13%, 9% and 5%, respectively.

Table for Grade 3+ GVHD monitoring boundary:

Looks	**# evaluable patients**	**Information**	**Pocock boundary of excessive toxicity**	**Excessive toxicity rate**
1	12	33%	6	50.00%
2	24	67%	10	41.67%
3	36	100%	13	36.11%

The intervention will be rejected for excessive Grade 3+ GVHD if the number of observed Grade 3+ GVHD is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring the intervention too toxic are approximately 96.4%, 80.5%, 45.9% and 13.2% when the true rate of Grade 3+ GVHD is 49%, 41%, 33% and 25%, respectively.

See Appendix XII for guidelines for establishing organ stage and overall grade of acute GVHD.

With Amendment #8, the above monitoring of toxic deaths and Grade 3+ GVHD in the subset of HSCT patients with MRD ≥ 0.01% pre- and/or post-HSCT with no aGVHD who undergo accelerated taper of immune suppression during the study will continue to be conducted until the HR/IR cohort meet the original planned accrual target of 170 evaluable patients. After that, no formal monitoring of toxic deaths or Grade 3+ GVHD will be conducted in this subset of patients. However, informal continuous monitoring of occurrences of toxic deaths will continue to be conducted.

9.3.4 Treatment Failure (TF) patients who are non-randomly assigned to blinatumomab

Point estimate and the corresponding exact 95% confidence interval based on Clopper-Pearson's method will be provided to estimate the hematologic CR , the rate of MRD < 0.01%, and the proportion treatment failure patients able to proceed to hematopoietic stem cell transplant (HSCT).

The toxic death will be closely monitored for TF patients who are non-randomly assigned to blinatumomab. According to past studies, an approximate 60 (10%) of enrolled patients will be deemed as TF, and the cumulative toxic death rate is estimated to be 6%. The safety stopping boundaries to be used for toxic death will be based on the Pocock-type spending function at one-sided 20% significance level. The intervention for TF patients will be temporarily closed for detailed review and possible therapy modifications if the number of toxic deaths is greater than or equal to that specified in the corresponding table below.

Table for toxic death monitoring boundary:

Looks	**# evaluable patients**	**Information**	**Pocock boundary of excessive toxicities**	**Excessive toxic death rate**
1	12	20%	3	25.00%
2	24	40%	4	16.67%
3	36	60%	5	13.89%
4	48	80%	6	12.50%
5	60	100%	7	11.67%

The intervention will be rejected for excessive toxicity death if the number of observed toxic deaths is greater than or equal to the corresponding boundary at any interim analysis. The actual power (based on exact binomial test) of declaring the intervention too toxic are approximately 85.9%, 67.1%, 39.1% and 12.9% when the true toxic death rate is 15%, 12%, 9% and 6%, respectively.

With Amendment #8, after monitoring toxic death rates in 60 evaluable TF patients, no further formal monitoring of toxic deaths among TF patients will be conducted. However, informal continuous monitoring of occurrences of toxic deaths will continue to be conducted.

9.3.5 Blinatumomab related reportable adverse event (RAE)

A reportable adverse event (RAE) with respect to blinatumomab is defined in Section 5.2. The reporting period case report form (CRF) for each blinatumomab course will specifically collect data regarding blinatumomab RAEs. Due to limited experience with blinatumomab, very little information is available estimate the expected incidence of blinatumomab RAEs. We will prospectively monitor the blinatumomab RAE rate on monthly study committee calls, and will report the blinatumomab RAE rate every 6 months in the biannual study progress report and DSMC report. RAE rates ≥ 10% will be of particular concern and will prompt discussion with the DSMC.

9.3.6 Monitoring for infection rate of 96-hour bag changes in Blinatumomab administration (Amendment #2)

The rate of Grade 3 or higher relevant infections (defined as sepsis, bacteremia, device or catheter-related infection) will be monitored among patients who received blinatumomab with the infusion bag changed up to 96 hours. We will consider 96 hour bag change acceptable if the infection rate is 5% or less. All Grade 3 or higher relevant infections will be evaluated every six months and the infection rate will be tested to determine whether the true rate is greater than 5% using exact one-sided one-sample binomial test, and the results will be presented to DSMC. If at one of scheduled analyses, the one-sided p-value of the test is less than 0.05, the 96 hour bag change would be considered unacceptable and the DSMC will be consulted regarding whether the bag change frequency should be changed back to 48 hours. The two-sided 90% confidence interval for the infection rate will also be provided.

9.3.7 Monitoring for infection rate of 7-day bag changes in Blinatumomab administration (Amendment #8)

Amendment #8 incorporates the allowance of a 7-day (168 hours) bag change schedule for Blinatumomab. This infusion schedule is added as an additional option to the existent 24-hour, 48-hour, and 96-hour infusion schedules.

To ensure safety of using the 7-day bag change schedule, after the activation of this amended protocol, the rate of grade 3 or higher relevant infections (defined as sepsis, bacteremia, device or catheter-related infection) will be monitored among patients weighing ≥ 22 Kg who are enrolled after activation of the amended protocol and randomized to receive blinatumomab.

We will conduct monthly monitoring of rate of relevant infections of grade 3+ using a Bayesian safety monitoring approach. Based on the observed accrual rate, we expect that every month we will have approximately 4 to 5 patients randomized to the blinatumomab arms (LR and HR/IR cohorts combined), and that the majority of them will be using 7-day bag change schedule. For this monitoring we will assume that from the date of the activation of this amended protocol, every patient weighing ≥ 22 Kg who are enrolled and randomized to receive blinatumomab will be using 7-day bag change schedule. We expect that the rate of grade 3+ infections related to the use of 7-day bag change schedule is 5% or less.

We assume that the number of patients experiencing relevant grade 3+ infections among those who use 7-day bag change schedule follows a binomial distribution, and that the probability for a patient to have relevant infections has a prior distribution of Beta(0.05,0.95). The first interim monitoring of infections for 7-day bag change will be undertaken after an initial 6 patients have received at least 1 cycle of blinatumomab using 7-day bag change schedule and have AE data reported in Medidata RAVE, which is expected to occur 3 to 4 months after the activation of the amended protocol. After that, we will conduct monthly interim monitoring of the infection rate.

At each interim monitoring, the posterior distribution of the probability for a patient to experience relevant grade 3+ infection ($p_{infection}$) will be calculated. If it is >95% likely that $p_{infection}$ > 5%, the study committee will conduct toxicity review related to 7-day bag change, consider the necessity of changing the bag change frequency back to 96 hours, and report the analysis results to DSMC. A simulation study showed that the probability for the rule to be triggered is approximately 0.97, 0.84, 0.50 and 0.10 when the true rate of relevant grade 3+ infection is 20%, 15%, 10% and 5%, respectively.

9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be (Activation Protocol):

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	85	79	164
Not Hispanic or Latino	225	209	434
Ethnic Category: Total of All Participants	310	288	598
Racial Category			
American Indian/Alaska Native	5	3	8
Asian	12	14	26
Black or African American	35	22	57
Native Hawaiian or Other Pacific Island	2	1	3
White	256	248	504
Racial Categories: Total of All Subjects	310	288	598

* These totals must agree

This distribution was derived from past studies on AALL01P2, AALL02P2, ADVL04P2 and AALL0433.

The gender and minority distribution of the study population is expected to be (Amendment #8):

Accrual Targets	
	Sex/Gender

Ethnic Category	Females	Males	Total
Hispanic or Latino	99	93	192
Not Hispanic or Latino	263	245	508
Ethnic Category: Total of All Participants	363	337	700
Racial Category			
American Indian/Alaska Native	5	4	9
Asian	14	16	30
Black or African American	41	26	67
Native Hawaiian or Other Pacific Island	3	1	4
White	300	290	590
Racial Categories: Total of All Subjects	363	337	700

This distribution was derived from past studies on AALL01P2, AALL02P2, ADVL04P2 and AALL0433.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (i.e., v4.02 and all subsequent iterations prior to version 5.0).

10.2 Response Criteria

See definitions in Section 3.3.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

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

An <u>investigational agent</u> 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.

<u>Commercial agents</u> 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 that occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as *Grade 5 "Disease progression: in the system organ class (SOC) "General disorders and administration site conditions."* Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

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

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.4.5 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, **pregnancy in partners of men on study needs be reported and followed in the same manner as a patient pregnancy**.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero.*" Any Pregnancy loss should be reported expeditiously, as **Grade 4 "*Pregnancy loss" under the "Pregnancy, puerperium and perinatal conditions"* SOC.** Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"Newborn death occurring during the first 28 days after birth*", should be reported expeditiously as **Grade 4 *"Death neonatal"* under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897–7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (e.g., H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (301) 897-7404.

Also: Fax or email supporting documentation to COG for **all** IND studies (fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG CTEP-AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A
Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[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

11.10 **Protocol Specific Additional Instructions and Reporting Exceptions**

- **Grades 1 - 4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.**
- **Any blinatumomab-related AE that results in interruption of dosing as described in Section 5.2 requires expedited reporting.**
- **Any Grade 3 or higher infection (defined as sepsis, bacteremia, device or catheter-related infection) that occurs more than 30 days after the last administration of blinatumomab and has an attribution of possible, probable, or definite must also be reported via CTEP-AERS.**

11.11 **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 that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.12 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting is split into three categories:

1. During all blinatumomab cycles as well as parallel control arm cycles, routine reporting will include **all toxicities of all grades (see table)**.
2. HSCT routine reporting will include All toxicities reported via CTEP-AERS and all Grade 4 and higher non-hematological Adverse Events
3. During all other blocks of therapy, routine reporting will include **all toxicities reported via CTEP-AERS and all Grade 3 and higher non-hematological Adverse Events (see table).**

<table>
<tr><th colspan="3">ADVERSE EVENT REPORTING BY TREATMENT PHASE</th></tr>
<tr><th colspan="2">ALL PATIENTS</th><th>REPORTING REQUIREMENT</th></tr>
<tr><td colspan="2">Block 1</td><td>Grade 3 and higher non-hematological Adverse Events and all toxicities reported via CTEP-AERS</td></tr>
<tr><th colspan="2">HR/IR</th><th></th></tr>
<tr><th>Arm A
(Control)</th><th>Arm B
(Experimental)</th><th></th></tr>
<tr><td>Block 2</td><td>Blinatumomab: Cycle 1</td><td>Grade 1-5 hematological and non-hematological Adverse Events</td></tr>
<tr><td>Block 3</td><td>Blinatumomab: Cycle 2</td><td>Grade 1-5 hematological and non-hematological Adverse Events</td></tr>
<tr><td colspan="2">Bridging Therapy</td><td>Grade 3 and higher non-hematological Adverse Events and all toxicities reported via CTEP-AERS</td></tr>
<tr><td>HSCT</td><td>HSCT</td><td>Grade 4 and higher non-hematological Adverse Events and all toxicities reported via CTEP-AERS</td></tr>
<tr><th colspan="2">LR</th><th></th></tr>
<tr><th>Arm C
(control)</th><th>Arm D (Experimental)</th><th></th></tr>
<tr><td>Block 2</td><td>Block 2</td><td>Grade 3 and higher non-hematological Adverse Events and all toxicities reported via CTEP-AERS</td></tr>
<tr><td>Block 3</td><td>Blinatumomab cycle 1</td><td>Grade 1-5 hematological and non-hematological Adverse Events</td></tr>
<tr><td>Continuation 1</td><td>Continuation 1</td><td>Grade 3 and higher non-hematological Adverse Events and all toxicities reported via CTEP-AERS</td></tr>
<tr><td>Continuation 2
(first 5 weeks – days 1-35)</td><td>Blinatumomab cycle 2</td><td>Grade 1-5 hematological and non-hematological Adverse Events</td></tr>
<tr><td>Continuation 2
(last 3 weeks – days 36-53)</td><td rowspan="2">Continuation 2</td><td rowspan="2">Grade 3 and higher non-hematological Adverse Events and all toxicities reported via CTEP-AERS</td></tr>
<tr><td>Maintenance
(first 5 weeks – days 1-35)</td></tr>
<tr><td>Maintenance
(second 5 weeks – days 36-70)</td><td>Blinatumomab cycle 3</td><td>Grade 1-5 hematological and non-hematological Adverse Events</td></tr>
</table>

Maintenance (remainder)	Maintenance (all)	Grade 3 and higher non-hematological Adverse Events and all toxicities reported via CTEP-AERS
TF-Salvage Therapy		
Blinatumomab-S 1		Grade 1-5 hematological and non-hematological Adverse Events
Blinatumomab-S 2		

12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

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

12.2 CTA/CRADA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

12.2.1 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.

12.2.2 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.

12.2.3 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.

12.2.4 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.

12.2.5 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.

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

Email: ncicteppubs@mail.nih.gov

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

13.0 SPECIAL STUDIES AND SPECIMEN REQUIREMENTS

NOTE: Enrollment APEC14B1 is ENCOURAGED, but NOT REQUIRED. APEC14B1 only require a single cell bank specimen (i.e. not separate AALL1331 and APEC14B1 specimens).

13.1 Banking for Future Research (optional)

For cases with a limited amount of tissue available for analysis, please prioritize specimen for tissue banking. Samples will be collected at different time points. See Section 7.2 for time points.

This study is designed to provide material for banking for the purpose of performing retrospective studies to refine risk stratification, identify new targets for therapy, identify biomarkers to predict response, and to link host polymorphisms with various disease characteristics and toxicities. See Appendix VI for details.

Sample Collection Procedures

A Specimen Transmittal Form should accompany every shipment of specimen(s) to the COG Reference Laboratory. Please complete one form per patient per shipment.

Please note: The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Shipping Media (SM)

Samples for the Reference Laboratories are to be collected in shipping media (SM) in special 15 mL conical tubes. The SM contains RPMI with EDTA as the anticoagulant. These tubes will be prepared in the Molecular Reference Laboratory and shipped in batches to each participating institution, where they can be stored frozen at -20°C until use. Tubes are stable for 3 months if refrigerated and stable for 1 year if frozen. To request prepared and pre-packaged sample shipping tubes, order tubes through the Biopathology Center kit management system https://ricapps.nationwidechildrens.org/KitManagement/.

Please note: The receiving institutions are strongly encouraged to make requests for sample tubes well in advance of their first patient registration on AALL1331; it will not be possible to expedite shipping because of prohibitive costs.

Bone Marrow/Peripheral Blood Collection Procedures for Reference Laboratories:

a. Collect BM/PB into a syringe and transfer the specimen immediately into the SM tube with RPMI/EDTA.
b. Mix well. At least 2 mL and up to 5 mL of BM/PB can be placed in 1 SM tube. If you don't have SM tubes, you can place the BM/PB into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is greatly enhanced in the SM tubes.
c. For BM, use multiple syringes and tubes as necessary. Reposition the BM aspirate needle at least once during the diagnostic procedure to ensure the maximum quality of BM. DO NOT SHIP SYRINGES.
d. Label each tube with COG registration number, patient name and date of birth, collection date, institution and type of specimen (bone marrow).
e. Samples are to be shipped at room temperature except for international samples that are expected to be delayed for more than 48 hours – place a cold pack (not ice pack) in shipment.

NOTE: For patients who are not having a BM for medical reasons at diagnosis or other time points and have an absolute blast count of at least 1,000/µL, PB may be submitted to the Reference Laboratories instead of BM. Submit 2 mL of PB for each 1 mL of required marrow.

Reference Laboratory – Shipping Address (including Saturday delivery):

COG Leukemia Biospecimen Bank
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

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.
Notify Laboratory of each Saturday delivery (email or phone) and remember to mark "For Saturday Delivery" on the FedEx paperwork.

13.2 **Local Bone Marrow: Central review of cytogenetics/FISH**

Bone marrow aspiration to confirm relapse (and/or to detect potential marrow disease in presumed isolated extramedullary relapse patients) is required for **study entry**. Morphologic, immunophenotypic, & cytogenetic/FISH analysis should be performed by the local institution. Cytogenetic analysis should include FISH for any cytogenetic abnormalities known from the patient's original leukemia if applicable. All FISH should be performed on uncultured, directly-harvested cells or unstimulated overnight cultured cells if the former is not possible. FISH for abnormalities shown by cytogenetics to be unique to the relapse specimen should also be done on directly harvested cells or unstimulated overnight cultured cells if the former is not possible. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively by the COG Cytogenetics Committee.

Please see the following link for a list of COG approved cytogenetics labs:
https://www.cogmembers.org/site/admin/default.aspx

Required Material:

a) Two **original** karyotypes of different cells from each abnormal clone or of two normal cells when no abnormalities are found; full-size metaphase images of the karyotypes cells.
b) A completed COG Cytogenetics Reporting Form and FISH Form (if done). These reporting forms are available on the AALL1331 protocol web page. Electronic submission of the karyotypes/FISH images is required.

Shipping: The review materials on each case should be sent to the COG ALL Cytogenetic Coordinators within 4 weeks of study entry. If the institution is west of the Mississippi River, send these materials to Dr. Andrew Carroll (University of Alabama). If the institution is east of Mississippi River (except Minnesota and Wisconsin, which go to Dr. Carroll), send all materials to Dr. Nyla Heerema (The Ohio State University).

Western Laboratory – Shipping Address:
Dr. Andrew Carroll, Ph.D.
Ph.D. Department of Genetics
University of Alabama at Birmingham
720 20th St. So. Kaul Bldg. Room 314B
Birmingham, AL 35294
Phone: 205-934-0665
Fax: 205-934-1078
Email: acarroll@ uab.edu

Eastern Laboratory – Shipping Address:
Dr. Nyla Heerema, Ph.D.
Professor and Director of Cytogenetics
The Ohio State University
Division of Clinical Pathology
Hamilton Hall, Room 167
1645 Neil Ave. Columbus, OH 43210
Phone: 614-292-7815
Fax: 614-292-7072
Email: Nyla.Heerema@osumc.edu

13.3 **Bone Marrow for Central Flow-Immunophenotyping and MRD (required)**
Immunophenotyping will be done on fresh bone marrow specimens collected **at study entry** (see Section 7.1). Minimal residual disease will be detected using 6 color flow cytometry (Dr. Michael Borowitz, Johns Hopkins University) on fresh bone marrow specimens collected **during therapy at various designated time points** (see Section 7.1).
Sample Collection Procedures
A Specimen Transmittal Form should accompany every shipment of specimen(s) to the COG Reference Laboratory. Please complete one form per patient per shipment.

Please note: The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Shipping Media (SM)
Samples for the Reference Laboratories are to be collected in shipping media (SM) in special 15 mL conical tubes. The SM contains RPMI with EDTA as the anticoagulant. These tubes will be prepared in the Molecular Reference Laboratory and shipped in batches to each participating institution, where they can be stored frozen at -20°C until use. Tubes are stable for 3 months if refrigerated and stable for 1 year if frozen. To request prepared and pre-packaged sample shipping tubes, order tubes through the Biopathology Center kit management system https://ricapps.nationwidechildrens.org/KitManagement/.

Please note: The receiving institutions are strongly encouraged to make requests for sample tubes well in advance of their first patient registration on AALL1331; it will NOT be possible to expedite shipping because of prohibitive costs.

Bone Marrow Collection Procedures for Reference Laboratories:

a. Collect BM into a syringe and transfer the specimen immediately into the SM tube with RPMI/EDTA.
b. Mix well. At least 2 mL and up to 5 mL of BM can be placed in 1 SM tube. If you don't have SM tubes, you can place the BM into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is greatly enhanced in the SM tubes.
c. Use multiple syringes and tubes as necessary. Reposition the BM aspirate needle at least once during the diagnostic procedure to ensure the maximum quality of BM. DO NOT SHIP SYRINGES.
d. Label each tube with COG registration number/Biopathology number, patient name and date of birth, date, institution and type of specimen (bone marrow).
e. Samples are to be shipped at room temperature except for international samples that are expected to be delayed for more than 48 hours – place a cold pack (not ice pack) in shipment.

NOTE: For patients who are not having a BM for medical reasons at diagnosis or other time points and have an absolute blast count of at least 1,000/µL, PB maybe submitted to the Reference Laboratories instead of BM. Submit 2 mL of PB for each 1 mL of BM required.

Please note: Specimens will be shipped to the COG Reference Laboratory at Johns Hopkins (Eastern) ONLY.

Reference Laboratory – Shipping Address (including Saturday delivery):
Michael Borowitz, MD, PhD
Flow Cytometry Laboratory, Johns Hopkins Medical Institutions
Weinberg Building – Room 2300
401 N. Broadway
Baltimore, MD 21287
Phone: 410-614-2968
Fax: 410-502-1493
Email: mborowit@jhmi.edu

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.
Notify Laboratory of each Saturday delivery at 410-614-2968 or via email at kbowles3@jhmi.edu

13.4 **Bone Marrow for CRLF2 expression (optional)**
We will quantify surface CRLF2 expression by flow cytometry and correlate with outcome. This assay will be done in conjunction with the immunophenotyping performed at study entry in Dr. Mike Borowitz's lab at Johns Hopkins University (see Section 13.3). For details, refer to Appendix IX.

Sample Collection Procedures
NOTE: A separate specimen is NOT REQUIRED. Please note on the specimen transmittal forms that accompany the required immunophenotyping specimen whether the patient has consented for the optional CRLF2 expression assay.

13.5 Blinatumomab Pharmacodynamics (PD) (optional)

Immunopharmacologic testing will be performed using blood and bone marrow specimens in consenting patients treated with blinatumomab during the first exposure to blinatumomab in an effort to identify biomarkers of blinatumomab response. For details, refer to Appendix X.

NOTE: All patients will be offered participation in this study at Block 1, prior to treatment assignment/randomization. Bone marrow samples will be drawn on all consenting patients at end Block 1. If the patient is subsequently randomized or assigned to treatment with blinatumomab (Arm B, Arm D, or Salvage Therapy), the Block 1 bone marrow sample will be analyzed and subsequent blood samples should be obtained. If the patient is randomized to treatment on the control arm (Arm A or Arm C), the Block 1 bone marrow sample will be destroyed and no further samples will be collected.

Sample Collection Procedures
A Specimen Transmittal Form should accompany every shipment of specimen(s) to the Brown Laboratory. Please complete one form per patient per shipment.

In the event that the infusion is interrupted, the peripheral blood collection should likewise be delayed to account for the interruption. i.e. collect the timed sample after X days of infusion rather than X days from start of infusion.

Please note: The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Blood and marrow collection schedule (see Section 7.2)

- Bone Marrow (1 sample, 5-10mL in sodium heparin tube)
    - End Block 1 (All patients)
    - End Block 2 (LR patients on Arm D only)

- Blood during first blinatumomab cycle (7 samples, 3mL each in sodium heparin tubes)
    - Day 1
        - 0 hr (just prior to start of blinatumomab infusion)
        - 6 hr
        - 12 hr
    - Day 2
    - Day 7
    - Day 14
    - Day 21

Samples should be shipped at room temperature.

Brown Laboratory – Shipping Address (including Saturday delivery):
Dr. Patrick Brown
Johns Hopkins Oncology
Cancer Research Building I, Room 262
1650 Orleans Street
Baltimore, MD 21231

Laboratory phone: 410-955-8688
Pager no: 410-434-0732
E-mail: pbrown2@jhmi.edu

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.

Saturday deliveries are permissible. If a Saturday delivery is required, please notify Dr. Brown of the planned shipment via email (pbrown2@jhmi.edu) PRIOR to the time of shipment and clearly mark the package "For Saturday Delivery".

13.6 **Protein Cell Stress Pathways (optional)**

Note: Isolated extramedullary relapse patients are **not eligible** for this sub-study**.**

This study is designed to analyze two specific aims: 1) To determine if specific protein expression profiles, as determined by reverse-phase protein lysate array (RPPA) analysis and phospho-flow analysis, correlate with therapy response and 2) To determine if alterations in specific cell stress proteins (such as the UPR) during chemotherapy can identify low risk patients with "high risk" protein signatures. For details, refer to Appendix XI.

Consenting patients will have peripheral blood samples (5mL for those ≥ 10kg, 3 mL for those < 10 kg) collected at 0 hours (prior to start of Block 1 systemic chemotherapy), and at 2 time points after the initiation of therapy (6 hours and 24 hours after the first dose of Block 1 systemic chemotherapy) to examine for changes in protein expression patterns. Blood samples for RPPA using sucrose centrifugation and (if necessary) the lymphoblast population will be isolated by either bead technology or flow cytometry. Sample collected for phospho-flow will be analyzed directly from whole blood. Sorted lymphoblasts will be made into lysates for RPPA analysis prior to freezing. Remaining samples will be frozen as pellets for protein analysis.

Eligible samples:

Sample should be sent to the Horton lab only if the patient has an initial absolute blast count of **at least 1,000 lymphoblasts/µL**. To calculate the absolute blast percentage, multiply the total WBC by the % peripheral blasts:

$$(\text{WBC})(\%\ \text{blast})(1000) = \text{absolute blast count}/\mu\text{L}$$

Example: If the patient has a WBC of 10 and 50% blasts, the absolute blast count is: $(10)(.5)(1000) = 5000/\mu L$

If the initial % blasts is unknown, send samples only if the total WBC is more than 10,000 and notify the Horton lab of the % blast as soon as available (contact info provided below).

Sample Collection Procedures

A Specimen Transmittal Form should accompany every shipment of specimen(s) to the Horton Laboratory. Please complete one form per patient per shipment. **Please note:** The AALL1331 Specimen Transmittal Form should be used. This is a protocol specific form.

Sample collection time points:

	Day 1, Hour 0 (before start of systemic chemotherapy)	Day 1, Hour 6-8	Day 1, Hour 24
Peripheral Blood (Block 1 only)	• 3 – 5 mL# in CellSave Preservative Tube* • 3mL in heparin tube	• 3mL in CellSave Preservative Tube* • 3mL in heparin tube	• 3mL in CellSave Preservative Tube* • 3mL in heparin tube

5 mL for those ≥ 10kg, 3 mL for those < 10kg

* CellSave tubes will be provided by the Horton lab to each institution upon IRB approval. To obtain more CellSave tubes, contact the Horton lab at the numbers provided below. If the CellSave tubes are not available, submit entire 6 mL sample in 2 heparin tubes. Note that the **sample integrity is greatly enhanced by the use of CellSave tubes.**

Store samples in refrigerator until shipment, and use Thermosafe with ice pack (or similar Styrofoam shipping containers with sufficient ice packs if these are not available at your site.) These containers maintain biology samples at a constant temperature and are strongly recommended for biology sample shipment, particularly in warm weather months.

Horton Laboratory – Shipping Address (including Saturday delivery):
Dr. Terzah Horton c/o Gaye Jenkins
Feigin Center, Room 760.01
1102 Bates St.
Baylor College of Medicine
Houston, TX 77030
Phone: (832) 824-4676 or (832) 824-4269
Email tmhorton@txccc.org

All samples should be mailed by overnight carrier (Federal Express) PRIORITY (delivery before 10 am). Use the COG FedEx account number, which may be found at: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf.

The Horton lab can accept Saturday shipments if we are contacted ahead of time. Please contact Gaye Jenkins or Dr. Horton (832-824-4676 or 832-824-4269) for alternative address and shipping information for Saturday delivery.

13.7 Blinatumomab Immunogenicity Assessment (Required)
(See lab manual on protocol webpage for sample collection and shipping details)

Blinatumomab is a novel protein therapeutic under clinical development. As outlined in the Draft Guidance: Immunogenicity Assessment for Therapeutic Protein Products (Feb 2013) pre-specified immunogenicity sampling will be performed to evaluate and mitigate risk (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf).

Blood samples for the assessment of blinatumomab immunogenicity will be collected to determine whether anti-idiotype antibodies directed against blinatumomab have been developed. Screening for these antibodies will be done by ELISA assay on ECL Basis (electrochemiluminescence), and binding will be confirmed with a Biacore assay to measure protein-protein interaction and binding affinity.

In a tiered approach patient samples are initially tested in a screening assay. Samples that produce signals above a certain screening cut point (classified as "positive") may be subjected to a confirmatory assay. The screening assay is designed to minimize false negatives, so positive screening assays need to be confirmed as positive. These are performed using the same format as the screening assay. A comparison of patient serum in the presence and absence of excess blinatumomab is used to confirm or deny the existence of anti blinatumomab antibodies. The screening and confirmation assay in the context of blinatumomab clinical studies will be performed according to an internal standardized protocol using a validated assay.

Immunoassay-positive samples will be analyzed in a third step using a cell based blinatumomab-mediated cytotoxicity assay to determine if the detected antibodies have neutralizing properties. Detection of neutralizing anti-blinatumomab antibodies relies on a validated bioassay measuring changes in the biologic activity of blinatumomab triggered by the presence of the antibody.

Blood Serum samples for antibody testing are being collected on all patients randomized to receiving blinatumomab for the measurement screening of anti-blinatumomab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. The 'cell-based assay' for neutralizing antibody detection tests patient sera in a model cell based system. This does not require patient cells or additional serum to be collected. Both the screening and the neutralizing assays are well-established at the Amgen Research Munich laboratory.

COG will be notified of any positive neutralizing antibody results to blinatumomab. If results are not provided, no neutralizing antibodies to blinatumomab have been detected.
Patients who test positive for neutralizing antibodies to blinatumomab at the final scheduled study visit will be asked to return for additional follow-up testing. This testing is to occur approximately every three months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least one year (± 4 weeks) post administration of blinatumomab. All follow-up results, both positive and negative will be communicated to COG. More frequent testing (e.g. every month) or testing for a longer period of time may be requested in the event of safety-related concerns. Follow-up testing is not required where it is established that the subject did not receive blinatumomab. Patients who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-blinatumomab antibody response may also be asked to return for additional follow-up testing.

13.8 Blinatumomab PK (required)

Please see the Lab Manual posted on the protocol web page for sample collection and shipping details.

14.0 RADIATION THERAPY GUIDELINES FOR ALL PATIENTS

Radiation therapy (RT) for patients on COG protocols can only be delivered at approved COG RT facilities (per COG administrative policy: Other Membership: Radiation Oncology Paritipcation Requirements).

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).

14.1 General Guidelines

The objective of this protocol is to compare the benefits and risks of Blinatumomab in the treatment of first relapse B-ALL. Patients eligible for this study will undergo risk classification after an initial block of chemotherapy (Block 1). Risk classification and the indications for irradiation will be based on site of first relapse, time to first relapse, MRD status following Block1 chemotherapy and clinical response to chemotherapy (when testicular leukemia is present at protocol entry).

Patients determined to be low risk (LR) after Block 1, will receive additional chemotherapy (Block 2) post randomization to a control arm or an experimental arm. The experimental arm includes blinatumomab. Both the control and experimental arms include maintenance chemotherapy to complete the respective regimens. LR patients with testicular leukemia at protocol entry will receive testicular irradiation (2400cGy) during Block2 if they do not have a clinical complete response after Block1. LR patients with CNS leukemia at protocol entry will receive cranial irradiation (1800cGy) during maintenance chemotherapy.

Intermediate Risk (IR) and High Risk (HR) patients will proceed to protocol-specified hematopoietic stem cell transplant (HSCT). Selected patients that do not respond to Block1 and HR and IR patients that do not respond to the control arm will receive blinatumomab in a separate treatment arm and may proceed to HSCT depending on their response to Blinatumomab provided they do not have a history of CNS leukemia (CNS3) at or after protocol entry. IR/HR patients with testicular leukemia at protocol entry will receive testicular irradiation (2400cGy) during the first cycle of Blinatumomab (experimental arm) if they do not have a complete response after Block1. IR/HR patients with testicular leukemia who have a complete clinical response to Block 1 will receive *supplemental* testicular irradiation (600cGy) sequentially with total body irradiation (TBI). IR/HR patients with CNS leukemia at protocol entry will receive *supplemental* cranial irradiation (600cGy) sequentially with TBI. <u>*Supplemental* irradiation refers to irradiation of any site performed sequentially with TBI.</u>

Treatment failure (TF) patients are select patients that do not respond to Block1 and HR and IR patients that do not respond to the control arm. They will receive Blinatumomab in a separate treatment arm and may proceed to HSCT depending on their response to Blinatumomab provided they do not have a history of CNS leukemia (CNS3) at or after protocol entry. They may also receive testicular or cranial irradiation therapy when indicated. TF patients after block1 will receive testicular irradiation (2400cGy) during their first course of Blinatumomab. TF patients with testicular leukemia who have a complete clinical response to Block1 will receive supplemental testicular irradiation (600cGy) sequentially with total body irradiation (TBI). TF patients after block2 with CNS leukemia at protocol entry will receive supplemental cranial irradiation (600cGy) sequentially with TBI.

Because there is no consensus on fractionated TBI or supplemental irradiation regimens, the radiation therapy guidelines for this study were designed to promote protocol participation and match guidelines used at the majority of approved transplant institutions and evolved from guidelines developed for other COG protocols. Questions about these guidelines should be directed to the radiation therapy coordinator or principal investigator. *Complete clinical response* refers only to the testes. *Supplemental irradiation* refers to irradiation of any site performed sequentially with TBI.

14.1.1 Required Benchmark and Questionnaires

Radiation therapy will be administered using photons or electrons according to treatment site. All centers administering TBI must have completed the TBI benchmark for the specific TBI technique to be used for patients treated on this study. Benchmark instructions are available at the IROC Rhode Island website: https://www.qarc.org/.

The calibration of therapy units used in this protocol must be verified by IROC Houston (RPC) (http://irochouston.mdanderson.org).

14.2 Indications for Radiation Therapy

14.2.1 Total Body Irradiation

TBI is indicated as part of the preparative regimen for IR/HR patients undergoing HSCT.

14.2.1.1 Supplemental cranial irradiation is indicated for HSCT patients with a history of CNS leukemia at protocol entry and shall be given sequentially.

14.2.1.2 Supplemental testicular irradiation is indicated for HSCT patients with the diagnosis of testicular leukemia and complete response after Block1 and shall be given sequentially. Those with testicular leukemia and without complete response after Block1 will not require supplemental testicular irradiation because they will have already received 2400cGy earlier in the regimen.

14.2.1.3 Patients who require irradiation to extra-medullary sites other than brain and testes should contact the Study Chair.

14.2.2 Cranial Irradiation

LR patients with a history of CNS leukemia at protocol entry should receive cranial irradiation. Cranial irradiation will be given between the first and second 12 week blocks of Maintenance chemotherapy. This corresponds to Week 40 for LR patients treated on the control arm and Week 54 for LR patients treated on the experimental arm. IR/HR patients will receive supplemental cranial irradiation sequentially with TBI prior to HSCT. Exceptions to the use of cranial irradiation include concerns about additional effects due to patient age, history of prior cranial irradiation and history or imaging evidence of CNS toxicity including leukoencephalopathy, stroke and necrosis.

14.2.3 Testicular Irradiation

Patients with persistent testicular leukemia at the end of Block 1 will receive 2400 cGy of testicular radiation during either Block 2 chemotherapy (for LR patients and HR/IR patients randomized to the control arm) or during blinatumomab (for HR/IR patients randomized to the experimental arm and TF patients after Block 1). Prior testicular irradiation will not be a contraindication to supplemental testicular irradiation on this protocol.

14.3 Timing

14.3.1 All patients who might require irradiation should be seen in consultation by a radiation oncologist in advance of treatment. The purpose of the consultation is to participate in planning the sequence of treatment and to determine the need for extra medullary (cranial, testicular and other) and supplemental irradiation in conjunction with HSCT.

14.3.2 The timing of TBI and supplemental irradiation will be determined in part by the TBI fractionation regimen. Supplemental irradiation should precede TBI and be performed during weekdays.

14.4 Emergency Irradiation

There may be instances when radiation therapy has been administered prior to enrollment on this protocol because of potentially life-threatening or function-threatening extramedullary involvement. Although it is not expected that prior treatment would make total body irradiation contraindicated, it should be considered when describing to the patient or parent the potential complications of treatment on this protocol.

14.5 Equipment and Methods of Delivery

Treatment Site	Photons	Electrons
TBI	Any Energy	
Cranial Irradiation	4 or 6MV	
Testicular Irradiation	Any Energy	Any Energy

Any energy for photons or electrons can be used as long as the skin and target dose requirements are met.

14.6 Treatment Volumes

14.6.1 Total Body Irradiation

The entire body will be treated including the head and feet in one field. Care should be taken to insure that the patient is entirely within the 90% isodose line of the beam and not in the penumbra region.

14.6.2 Cranial Irradiation

The treatment site consists of the entire brain and intracranial subarachnoid volume as well as the optic nerves and the posterior halves of the optic globes. The caudal border shall be the C2/3 vertebral interspace.

14.6.3 Testicular Irradiation

The treatment site consists of the testes in the scrotal sac.

14.7 Target Dose

14.7.1 Dose Definition

Photon and electron dose is to be specified in centigray (cGy)-to-muscle.

14.7.2 Prescribed Dose, Fractionation and Dose Rate for TBI

TBI may be administered with either of the following two regimens:

- 1200 cGy administered over 3 consecutive treatment days (Days -7, - 6, - 5) at 200cGy BID
- 1200 cGy administered over 4 consecutive treatment days (Days -8, -7, - 6, -5) at 150cGy BID

Allowable but not preferred TBI regimen:

- 1320 cGy given over 4 consecutive treatment days (Days -8, -7, -6, -5) at 165 cGy BID

Important considerations for TBI:

- Effort should be made to avoid interruptions in TBI administration
- The inter-fraction interval shall be no less than 5 hours between treatments (start to start)
- A mid-plane dose rate of between 6 and 15 cGy per minute is required

14.7.3 Prescribed Dose and Fractionation for Cranial Irradiation

14.7.3.1 LR patients will receive 1,800 cGy administered in 10 daily fractions of 180 cGy during Maintenance chemotherapy.

14.7.3.2 IR/HR patients will receive 600 cGy administered in 3 daily fractions of 200 cGy immediately before TBI

14.7.4 Prescribed Dose and Fractionation for Testicular Irradiation (testicular leukemia at protocol entry)

14.7.4.1 LR patients will not receive testicular irradiation if a complete clinical response is observed after Block1.

14.7.4.2 LR patients will receive 2400 cGy testicular irradiation administered in 12 daily fractions of 200 cGy during Block 2 if a complete clinical response is not observed after Block 1.

14.7.4.3 IR/HR patients will receive 600 cGy administered in 3 daily fractions of 200 cGy immediately before TBI if complete clinical response is observed after Block 1.

14.7.4.4 IR/HR patients will receive 2400 cGy testicular irradiation administered in 12 daily fractions of 200 cGy During Block 2 if a complete clinical response is not observed after Block 1.

14.7.5 Prescribed dose and fractionation for testicular irradiation (testicular leukemia not present at protocol entry)

14.7.5.1 Supplemental testicular irradiation of 400 cGy in 1 or 2 daily fractions prior to or during TBI may be administered according to institutional preference but is not required.

14.8 Treatment Technique

14.8.1 TBI

Supine and prone, lateral decubitus, upright seated and standing positions are allowed. Treatment will be delivered with equally weighted parallel opposed portals. Each treatment will include both fields. All treatment techniques and patient positions should meet the criteria on dose, dose rate, and dose uniformity. Beam spoilers or other equally effective devices may be used to increase skin dose to meet the dose uniformity requirements. Changes in patient positioning after the patient has started TBI must be documented. Changes in lung blocking and dose recalculation should be reported.

14.8.2 TBI - Lung Shielding

Lung shielding is mandated to restrict the lung dose (see Section 14.9.1). Lung shielding to achieve dose reduction should conform to the following guidelines:

- The lateral edges will be 1.0 – 1.5 cm inside the inner border of the ribs;
- The inferior edges will be 1.0 – 1.5 cm superior from the dome of the apex of the diaphragm;
- The superior borders will be 1.0 – 1.5 cm below the clavicles;
- The medial border 2.0 – 2.5 cm lateral to edges of the thoracic vertebral bodies.
- No contouring of the lung shields will be done around the hilum unless there is residual hilar adenopathy in which case the margins around the hilar abnormality will be 1.0 – 1.5 cm. When utilized, lung blocks should be employed for sequential treatments starting with the first treatment.
- Compensatory electron boost of the portion of the chest wall shielded by the lung blocks is not required.

14.8.3 Cranial Irradiation

Supine treatment is recommended with immobilization appropriate for the age of the child. Two opposed lateral equally weighted photon beams are preferred. The fields shall extend at least 1 cm beyond the periphery of the scalp. Customized field-shaping is required with blocks that are at least 5 HVL thick. Alternatively, a multi-leaf collimator may be used provided the leaf width is less than or equal to 5 mm.

Lens sparing techniques are encouraged with 1 of 2 techniques:

- Angling of the 2 lateral fields in the anterior direction (RAO/LAO) using the lateral canthus markers to "flatten" the beam edge. Shielding blocks are used to block the anterior halves of the eyes, the nose, and mouth.
- Set the central axes of the horizontal cranial beams so that they are aligned to the lateral canthi (half-beam blocking technique). 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.

14.8.4 Testicular Irradiation

The patient shall be treated in the supine position. Field shaping for photons and electrons will be done with either customized cerrobend blocking or multi-leaf collimation. The testes may be supported posteriorly and, if possible, extended caudally in order to minimize perineal irradiation. The penis should be excluded from the field.

14.9 Organs at Risk

14.9.1 Normal tissue sparing for TBI

Restricting the lung dose to ≤ 800 cGy is required on this protocol. This requirement applies to both AP/PA and lateral treatments.. Institutions are allowed to use their preferred method of beam attenuation to achieve the dose reduction to lungs. The lung dose shall be reported as reference point C for lateral treatments and reference point D for AP/PA treatments (see Section 14.10.1.2). It should be reported on the TBI Summary form.

14.9.2 Normal tissue sparing for cranial irradiation

- Lens sparing techniques, as outlined in Section 14.8.3, are encouraged.

14.9.3 Normal tissue sparing for testicular irradiation

- Techniques for sparing perineum and penis are outlined in Section 14.8.4.

14.10 Dose Calculation and Reporting

14.10.1 Dose calculations for TBI

14.10.1.1 Suggested Methods for Dose Calculations for TBI

The TBI percent depth dose (PDD) or Tissue Maximum Ratio (TMR) and output factors may be measured under TBI treatment conditions for a range of phantom sizes to establish the database for TBI beam-on time calculations and to validate the calculation method. Measurements of entrance and exit dose at the center of a phantom equivalent to the size of the typical patient are performed and compared to the calculated dose. If differences are found, additional correction factors should be introduced to the calculation method. The prescription point is defined as the point along the longitudinal axis of the patient at the mid-plane at the level of the umbilicus (Point E below). Tissue inhomogeneity correction is not required in the calculation of dose to the prescription point.

14.10.1.2 Dose Calculations and Measurements to Selected Anatomical Reference Points for TBI

Prescription Point:

The following reference points will be determined:

The calculated and measured doses to selected anatomical points must be submitted to IROC RI as part of the quality assurance documentation:

(Point A - Head) This reference point is defined along the longitudinal axis of the skull at the greatest mid-separation (immediately superior to the nasal bridge). The depth should be taken as midway between the entrance and exit points of the opposed radiation beams.

(Point B – Neck) This reference point is defined along the patient’s longitudinal axis at the level of C3/C4 (approximate mid-neck, but chosen for the thinnest mid-separation of the neck). The point is taken to be midway between the entrance and exit point of the beam.

(Point C - Mid-mediastinum) For APPA: The point is in the center of the chest along the sagittal plane midway between the anterior and posterior surfaces (Usually at the level of the carina). For opposed laterals: this point is located midway between the entrance and exit points of the beams at the level of the carina. Calculations at this reference point should include lung shielding if present.

(Point D – Mid-Lung) APPA only: This reference point is centered in the middle of the right or left lung (both medial/lateral and cephalocaudad directions). The depth should be taken as midway between the entrance and exit points of the opposed radiation beams. Calculations at this reference point should include lung shielding if present.

(Point E – Umbilicus) This is the PRESCRIPTION POINT. This point is located along the patient’s longitudinal axis at the level of the umbilicus and midway between the entrance and exit points of the opposed beams.

(Point F – Hip or Pelvis) This reference point is defined at the level approximately 1 cm superior to pubic symphysis midway between the entrance and exit points of the beam.

(Point G - Knee) This reference point is defined along the midline in the mid-plane of the knee at the level of the patella.

(Point H -Ankle) This reference point is defined along the midline at the mid-plane of the ankle at the level of the lateral malleolus.

14.10.1.3 Lung Dose Calculation

Tissue heterogeneity must be accounted for in the calculation of dose to lung. The preferred method is use of CT to enable use of CT numbers in the calculation. Alternatively, other methods as developed by the participating institution may be used. Lung density value estimates, based on methods adopted by treating institutions, may be incorporated into the dose calculation. The methodology used by each participating institution for lung dose determination will be evaluated as part of the benchmark approval process.

14.10.2 Dose Uniformity and Treatment Site Coverage

14.10.2.1 TBI Dose Uniformity and Treatment Site Coverage

The TBI fields should be set up to cover the patient's entire body without any part of the patient extending into the penumbra region. The dose difference between the prescription point and each reference point (see separate guidance for lung dose in Section 14.9.1) shall be within ± 10% of the prescribed dose. The calculated dose to the lung shall be in accordance with the lung dose requirements specified in Section 14.9. To limit overall total lung dose to ≤ 800 cGy, partial transmission lung blocks can be used. For AP/PA treatments the lung blocks may be placed in both AP and PA fields or alternatively in just the AP or PA field alone.

14.10.2.2 Cranial Irradiation Dose Uniformity and Treatment Site Coverage

The prescription point for the cranial treatment is at or near the center of the field. Regardless of the location of the central axis, the dose should be prescribed at the center of the cranial volume –midway between the points of maximum separation. The variations of dose within the treatment site shall be within +7%, -5% of the dose to the prescription point.

14.10.2.3 Testicular Irradiation Dose Uniformity and Treatment Site Coverage

The scrotum should be treated with en face electrons with the prescription depth covered by the 90% isodose. If electron beam is used for testicular irradiation, the prescription should include the beam energy and the dose coverage. Photon irradiation is allowed.

14.10.3 Tissue heterogeneity

There shall be no required correction for tissue heterogeneity for the cranial and testicular treatment.

14.10.4 Interruption of therapy

Excluding weekends and holidays, supplemental cranial irradiation, testicular irradiation and fractionated TBI should be continuous. All efforts should be made not to have treatment delay or interruption. Once patients have begun testicular treatment, they should immediately proceed to TBI for transplantation. If interruptions occur, the radiation therapy coordinator should be notified.

14.11 Quality Assurance Documentation and Review

There are no on-treatment review or image submission requirements for this study. A post-treatment review will be conducted by IROC RI.

Within 1 week of the completion of radiotherapy, the following data shall be submitted for TBI and/or cranial and testicular irradiation:

- TBI Summary Form for Total Body Irradiation.
- Measured and/or calculated doses for the TBI reference points.
- A copy of the radiotherapy record including the prescription, and daily and cumulative doses for all treated sites including TBI and supplemental sites (cranial, testicular).
- The "RT-2 Radiotherapy Total Dose Record" forms must be completed for cranial and testicular irradiation.
- If the treatment technique differs from an approved benchmark, a new benchmark must be completed and approved (see Section 14.1.1).

Data should be sent by email to the IROC Rhode Island QA Center:
datasubmission@qarc.org

Questions regarding the dose calculations or documentation should be directed to the COG Protocol Dosimetrist at the IROC Rhode Island QA Center.
Email: physics@qarc.org
Phone: (401) 753-7600

14.12 Definitions of Deviation in Protocol Performance

14.12.1 TBI

14.12.1.1 Deviations for prescription dose
Deviations for TBI Dose
Variation Acceptable:

- The dose to the prescription point and to any of the reference points (except points C and D lung dose points) differs from the protocol specified dose by >10% or <15%.

Deviation Unacceptable:

- The dose to the prescription point and to any of the reference points (except points C and D lung dose points) differs from the protocol specified dose by >15%.

14.12.1.2 Deviations for TBI Dose Rate

- A dose rate exceeding 15cGy/min will be considered as an unacceptable deviation.

14.12.1.3 Deviations for Lung Dose

- The dose to the lungs (reference points C and D) that is < 700 cGy or > 900 cGy will be considered an unacceptable deviation.

14.12.2 <u>Deviations for Cranial Irradiation Dose</u>

Variation Acceptable:

- The dose to the prescription point differs from the protocol specified dose by > 6 but ≤ 10%.

Deviation Unacceptable:

- The dose to the prescription point differs from the protocol specified dose by >10%.

14.12.3 <u>Deviations for Testicular Irradiation Dose</u>

Variation Acceptable:

- The dose to the prescription point differs from the protocol specified dose by > 6% but ≤ 10%.

Deviation Unacceptable:

- The dose to the prescription point differs from the protocol specified dose by > 10%.

APPENDIX I: SUPPORTIVE CARE

NOTE: For blinatumomab-specific supportive care guidelines, please refer to Section 5.2.

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://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

Blood Components

Blood products should be irradiated following current FDA guidelines.
Investigators in Canadian institutions need to follow the CSA standards for Blood and Blood Components.

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.

Special Guidelines During Induction (Block 1)

Patients may experience profound myelosuppression and immune suppression during this time. Since steroids may mask fever as well as other components of the inflammatory response, sepsis during Induction 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 may have an intestinal component. Patients with subtle GI symptoms should be monitored very closely. ***Taken together, the risks of significant morbidity and mortality, including sudden death in patients with relapsed leukemia, are sufficient to strongly recommend hospitalization during remission Induction, until patients show consistent neutrophil recovery and transfusion needs that are deemed to be manageable in the outpatient setting.***

Tumor Lysis Syndrome

In this population with ALL, rapidly assess patients clinically and by appropriate laboratory parameters for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Suggested studies to be obtained prior to initiating antileukemia therapy include complete blood count (CBC), prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes, including creatinine, BUN, uric acid, phosphorous, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated. 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 situations it may be appropriate to use rasburicase. Hydrate at 2,400 – 3,000 mL/m²/day (potassium should not be added to hydration fluids) to maintain urine output > 100 mL/m²/hour until peripheral blasts and extramedullary disease are reduced.

Infection Prophylaxis

Patients undergoing transplantation for ALL on this protocol are at high risk for infection. This risk may be increased due to infections that occur during the intensive chemotherapy most patients will receive prior to stem cell transplant on this protocol. Centers should be especially mindful of this as they choose anti-bacterial, anti-fungal, anti-viral, and PCP prophylactic regimens. Aside from well established screening approaches for CMV, centers may wish to consider routine screening for other viral pathogens such as Adenovirus or HHV-6. Any prophylaxis regimen chosen must be the same for patients on both arms of the protocol. Special considerations should be given for antifungal prophylaxis (see below).

Supportive Care for Patients Age 15 Years and Older

It is recommended that adolescent and young adult (AYA) patients enrolled on this protocol (defined as patients between the ages of 15 and 31 years) be monitored in the hospital during Block 1, Block 2 and Block 3 of chemotherapy until they show signs of bone marrow recovery (specifically evidence that the absolute neutrophil count (ANC) is rising for 2 successive days) and the patient is afebrile and clinically stable. If a patient should experience profound myelosuppression at any other time, there should also be a very low threshold to hospitalize AYA patients with inpatient management continued until there is evidence of bone marrow recovery. Antibiotic prophylaxis against Gram-positive and Gram-negative organisms (e.g. levofloxacin) may be considered during these hospitalizations until patients meet the criteria for discharge. If the patient should develop febrile neutropenia while on antibiotic prophylaxis, the patient should be started on broad-spectrum intravenous antibiotics per institutional guidelines. Antifungal prophylaxis may also be considered during periods of myelosuppression. Options include an echinocandin such as caspofungin or micafungin, or an azole. Azole antifungal agents (i.e., fluconazole, itraconazole, posaconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Investigator caution is advised if azole antifungals are used. If antibiotic and/or antifungal prophylaxis is utilized, consultation with Infectious Disease may be considered.

Pneumocystis jiroveci

All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 2.5 mg/kg/dose (maximum dose 160 mg/dose) by mouth twice daily on 2 or 3 sequential days per week. For patients allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone (2 mg/kg/day by mouth, maximum dose 100 mg/day), aerosolized pentamidine (300 mg/q month ≥ 5 years of age), or atovaquone (4 - 24 month: 45 mg/kg/day; > 24 months: 30 mg/kg/day) by mouth may be considered. For children in whom TMP/SMX, dapsone, atovaquone, and inhaled pentamidine cannot be administered, IV pentamidine (4 mg/kg/dose IV every 2 to 4 weeks) should be given. (REF: Centers for Disease Control and Prevention. Guidelines for preventing infectious complications among hematopoietic stem cell transplant recipients: a global perspective. (https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm)

Varicella Vaccine

May be given to the siblings of patients in remission and stable at the physician's discretion. Varicella vaccination is not recommended for ALL patients during therapy.

Gamma globulin

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

Antifungals

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

Fluconazole and other azoles are expected to increase serum tacrolimus and sirolimus levels. Therefore, dosages of sirolimus and tacrolimus should be adjusted accordingly. Due to extreme interactions with sirolimus, voriconazole is contraindicated during sirolimus. Patients on voriconazole prior to transplant should have another drug substituted for voriconazole prior to starting sirolimus therapy.

Hospitalization after High-Dose Cytarabine
Empiric hospitalization after Day 8 of Induction 3 (intensively-timed Capizzi-II) until there is evidence of marrow recovery should be considered due to the risk of neutropenic sepsis; patients not hospitalized should be monitored very closely.

Treatment of Established or Presumed Infections

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. 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_Dec_2017.pdf

Use of filgrastim (G-CSF)
Filgrastim may be used for severe infections with neutropenia, but routine use is discouraged.

Filgrastim at a dose of 5 micrograms/kg/day given IV or subcutaneously is required for recipients of cord blood starting at Day +1 and continuing until patients are fully engrafted. Filgrastim is generally not necessary for BM/PBSC recipients and is not recommended, unless engraftment is delayed.

Primary Varicella Infection (Chickenpox)
Patients should be treated promptly with acyclovir 1500 mg/m²/day intravenously divided q8 hours, and monitored closely for the development of invasive systemic disease.

Empiric Management of Pulmonary Infiltrates
Pulmonary infiltrates should be evaluated with bronchoscopy and biopsy, lavage or open lung biopsy. If a procedure cannot be tolerated, begin empiric antifungal therapy given the high likelihood of fungal disease during Induction, Re-induction and periods of intensive chemotherapy (HDAraC). Empiric coverage should include treatment for gram-negative and positive bacteria, Legionella (erythromycin), Pneumocystis (TMP/SMX), and fungi (amphotericin) pending culture results. If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis and brain are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician. Azole antifungal agents (i.e. fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase the risk of neurotoxicity. Investigator caution is advised if azole antifungals are used.

Management of Mucositis/Perirectal Cellulitis

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

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, as an antiemetic is discouraged but may be appropriate in select patients with demonstrated intolerance to higher-dose chemotherapeutic agents.

Gastrointestinal (GI) Protection

While patients are on steroid therapy, consider using an H2 receptor antagonist (e.g., ranitidine, famotidine).

Constipation

As vincristine may cause severe constipation, prophylactic stool softeners/laxatives (per investigator's discretion) are recommended during all phases in which VCR is given.

APPENDIX II: THERAPY DELIVERY MAPS

APPENDIX II-A **Block 1 (All patients)** Block 1 therapy is common to all patients on study	Patient COG ID number DOB

Block 1 lasts 4 weeks (28 days). Please see Section 4.2 for treatment details. This therapy delivery map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Intrathecal Methotrexate (IT MTX)	IT	Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥9 15 mg	1	**ALL PATIENTS** Note age-based dosing	a. Hx, PE [VS/Wt (BSA)] b. CBC/diff/platelets c. Local BM evaluation[%] d. BM for Immunophenotyping e. CSF cell count, cytospin[1] f. Bilirubin, ALT & creatinine, BUN g. Echocardiogram h. Pregnancy test i. Testicular Exam & Testicular biopsy, if indicated[®] [1] Obtain with each IT/ITT See Section 7.0 for details. **Optional studies** j Banking for future research k Protein cell stress pathways l. CRLF2 expression m. BM sample for Blinatumomab PD See Section 7.2 for details. **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	8	**CNS1/2 ONLY** ***For CNS2: Continue weekly until 2 clear csf samples are obtained i.e. CNS1** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX)/ Hydrocortisone (HC)/Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	8, 15, 22	**CNS3 ONLY** Note age-based dosing	
MitoXANTRONE (MITOX)	IV over 15-30 minutes	10 mg/m²/dose	1, 2	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	
Dexamethasone (DEX)	PO	10 mg/m²/dose BID	1-5, 15-19	Total Daily Dose 20 mg/m²/day divided BID **Cap dose at 40 mg per day**.	
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²	1, 8, 15, 22	+Or infusion via minibag as per institutional policy. **Maximum dose: 2mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	3, 17	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	

APPENDIX II-A **Block 1 (All patients)** Block 1 therapy is common to all patients on study	 Patient COG ID number DOB

Ht ________cm **Wt ________kg** **BSA ________m^2**

Date Due	Date Given	Day	IT MTX **ALL PATIENTS** ____mg	IT MTX **CNS1/2 ONLY*** ____mg	ITT **CNS3 ONLY** ____mg	MITOX ____mg	DEX ___mg	VCR ____mg	PEG-ASP ____IU	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below						a, b, c[%] d-i, l[$],j[+]	
		1	_____mg			____mg	____mg ↓	____mg		k[¥]	
		2				____mg					
		3							____IU		
		4									
		5									
		--									
		8		_____mg	_____mg			____mg		b, e, f	
		--									
		15		_____mg*	_____mg		____mg ↓	____mg		b, e*, f	
		--									
		17							____IU		

		19									
		22		_____mg*	_____mg			____mg		b, e*, f	
		--									
		29								b, c, e^, f, i[®],j[+], m	
				Begin next course based on Day 29 risk assignment and treatment randomization. IR/HR patients are not eligible for post-Induction treatment and will be removed from protocol therapy at the end of Induction. **LR patients** will be randomized to Arm C (control arm) or Arm D (experimental arm). All LR patients (**Arm C and Arm D**) receive Block 2 therapy (Section 4.3, APPENDIX II-B). Treatment failures post-Block 1 with M3 marrow without residual CNS disease (CNS1) are eligible for treatment with at least 2 blocks of Salvage Therapy (Blinatumomab-S) (Section 4.7, APPENDIX II-F); treatment failures with residual CNS disease (CNS2/3), irrespective of marrow status will be off protocol therapy. See Section 4.3 for further details on time frame for end-Block 1 evaluations and criteria to fulfill prior to subsequent therapy.							

***For CNS2 patients, continue weekly until 2 clear CSF (CNS1) samples are obtained; can be a max of 4 (Days 1, 8, 15 and 22). If still unclear, patients are treatment failures and will be off protocol therapy regardless of marrow status.**

^ A diagnostic LP should be performed on Day 29 for CNS2 or CNS3 patients for whom clearance of CSF blasts has not yet been documented.

® Testicular biopsy is only done in the setting of persistent testicular enlargement. Patients with persistent testicular leukemia at the end of Block 1 who are deemed treatment failure (TF) will receive 2400 cGy of testicular radiation during Blinatumomab.

$ No separate specimen needed-cell pellet from required central flow MRD assays will be used (see Section 13.4 for complete details).

¥ PB before and after chemotherapy on Day 1 of Block 1 (see Section 13.6) for complete details).

% BM evaluation to confirm relapse and/or detect marrow disease in presumed isolated extramedullary relapse patients should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab and cases will be reviewed retrospectively

\+ **Bone marrow:** at Baseline and End Block 1. **Peripheral blood:** At Baseline and End Block 1. (See Section 13.1 for complete details)

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-B **Block 2** Block 2 therapy is for all LR patients post Block-1 (**Arm C and Arm D**)	Patient COG ID number DOB

Block 2 lasts 4 weeks (28 days). Block 2 should begin after receipt of risk assignment according to timing outlined in Section 4.2.7. All patients can proceed with Day 1 of Block 2 without awaiting count recovery (must be no later than 5 calendar days after callback). Patients with M1 marrow after Block 1 should await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 8 ID MTX; Patients with M2 marrow after Block 1 should not await recovery prior to beginning Day 8 ID MTX. All patients should await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 15 cyclophosphamide and etoposide. Please see Section 4.3 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	3 mg/m^2/dose BID	1-5	Total Daily Dose: 6 mg/m^2/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Local BM evaluation d BM for MRD evaluation e CSF cell count, cytospin[1] f Bilirubin, ALT & creatinine, BUN g Testicular Exam **Optional studies** h Banking for future research i Bone Marrow for Blinatumomab PD (Arm D ONLY) [1] Obtain with each IT/ITT See Section 7.0 for details. See Section 7.2 for details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m^2/dose	1	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
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	8	**CNS 1/2 ONLY** 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).	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) / Dose 1-1.99: MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99: MTX: 10mg, HC: 10 mg, ARAC: 20 mg 3-8.99: MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥9: MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	8, 22	**CNS3 ONLY.** Note age-based dosing.	
Intermediate Dose Methotrexate (ID MTX)	IV over 36 hours	1000 mg/m^2/dose	8	See Section 5.8 for admin guidelines.	
Leucovorin (LCV)	PO/IV	15 mg/m^2/dose Q6H	10, 11	48 hours after the start of ID MTX infusion. See Section 5.8 for admin guidelines	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m^2/dose	9 or 10*	*Administer 4 hours after completion of Day 8 IV MTX.	
Cyclophosphamide (CPM)	IV over 15-30 mins.	440 mg/m^2/dose	15-19		
Etoposide (ETOP)	IV over 60-120 mins.	100 mg/m^2/dose	15-19		
Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation during Block 2 therapy. See Section 14.2 for details of TRT.					

APPENDIX II-B **Block 2** Block 2 therapy is for all LR patients post Block-1 (**Arm C and Arm D**)	Patient COG ID number DOB

Ht _________cm **Wt _________kg** **BSA _________m^2**

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	IT MTX **CNS1/2 ONLY** _____mg	ITT **CNS3 ONLY** _____mg	ID MTX ___mg	LCV ___mg	PEG-ASP ___IU	CPM ___mg	ETOP ___mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below										
		1	____mg	____mg								a, b, f	
		5	↓										
		8			____mg	____mg	____mg^					b, e, f	
		9							____IU*				
		10						____mg					
		11						____mg					
		15								____mg$^{\&}$	____mg$^{\&}$	b, f	
		19								↓	↓		
		22				____mg						b, e$^{\#}$, f	
		29										b,c,d,f,g,h^{+},i	
			Following count recovery, **LR patients randomized to Arm C** receive Block 3 therapy (Section 4.4, APPENDIX II-C), and **LR patients randomized to Arm D** rece Blinatumomab Block 1: Cycle 1 therapy (Section 4.15, APPENDIX II-M.										

^ All patients with M1 marrow are recommended to await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 8 ID MTX. Day 8 treatment must begin no later than 14 calendar days after giving the Day 1 vincristine and dexamethasone to continue to receive protocol therapy.

& Await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 15 cyclophosphamide and etoposide.

+ **Peripheral blood:** End Block 2 (See Section 13.1 for complete details)

*Administer 4 hours after completion of Day 8 IV MTX. (Day 9 or 10)

CNS3 ONLY

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-C **Block 3** Block 3 therapy is for all LR patients randomized to the control arm (**Arm C**).	Patient COG ID number DOB

Block 3 lasts 4 weeks (28 days) and starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL. Await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 22 ID MTX. See Section 4.4 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Dexamethasone (DEX)	PO (May be given IV)	3 mg/m²/dose BID	1-5	Total Daily Dose: 6 mg/m²/day, divided BID.
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**
Cytarabine (ARAC)	IV over 3 hours	3000 mg/m²/dose Q12H	1, 2, 8, 9	
Asparaginase (Erwinia)	IM or IV over 1 hour	25, 000 International units/m²/dose	2, 4, 9, 11, 23	See Section 4.4 for administration guidelines. • On Days 2 and 9, Erwinia should be given 4 hours after last cytarabine infusions. • On Day 23, Erwinia is to be given 4 hours after the completion of the Day 22 MTX infusion.
Intermediate Dose Methotrexate (ID MTX)	IV over 36 hours	1000 mg/m²/dose	22	See Section 5.8 for admin guidelines.
Leucovorin (LCV)	PO/IV	15 mg/m²/dose	24, 25	48 hours after the start of ID MTX infusion. See Section 5.8 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	1 **All Patients** 22 **CNS 1/2 ONLY**	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). Note age-based dosing
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) / Dose 1-1.99: MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99: MTX: 10mg, HC: 10 mg, ARAC: 20 mg 3-8.99: MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥9: MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	22	**CNS3 ONLY** When ITT therapy and ID MTX are scheduled for the same day, deliver the ITT 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). Note age-based dosing

OBSERVATIONS

a Hx, PE [VS/Wt (BSA)]
b CBC/diff/platelets
c Local BM evaluation
d BM for MRD evaluation
e CSF cell count, cytospin[1]
f Bilirubin, ALT & creatinine, BUN

[1] Obtain with each IT/ITT

See Section 7.0 for further details.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

APPENDIX II-C **Block 3** Block 3 therapy is for all LR patients randomized to the control arm (**Arm C**).	Patient COG ID number DOB

Ht ________cm Wt ________kg BSA ________m²

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	ASP ERWINIA ____IU	ID MTX ____mg	LCV ____mg	ARAC ____mg ____mg	IT MTX **All Patients** ______mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below										
		1	____mg	____mg				____mg ____mg	____mg			a, b, e, f	
		2	↓		____IU			____mg ____mg					
		3											
		4			____IU								
		5											

		8						____mg ____mg				b, f	
		9			____IU			____mg ____mg					

		11			____IU								

		15										b, f	

		22				____mg^				____mg	____mg	b, e, f	
		23			____IU								
		24					____mg						
		25					____mg						

		29										b, (c, d)* f	
		Following count recovery ANC ≥ 500/µL and platelets ≥ 50,000/µL. **HR/IR Treatment Failures** post-Block 3 have the option of receiving 2 blocks of Salvage Therapy – Blinatumomab-S (Sections 4.7, 4.8, APPENDIX II-F, II-G). **LR patients randomized to Arm C** receive Continuation 1 therapy (Section 4.11, Appendix II-I).											

^ Await count recovery until ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 22 ID MTX.

***HR/IR Patients ONLY.**

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-D **Blinatumomab Block - Cycle 1** (HR/IR Patients in **Arm B**) This therapy is the 1st cycle of therapy with blinatumomab for the HR/IR patients assigned to the experimental arm (Arm B)	Patient COG ID number DOB

Blinatumomab Block-Cycle 1 lasts 5 weeks (35 Days). For patients with M1 marrow, treatment begins when ANC ≥ 500/µL and platelets ≥ 50,000/µL and must begin no later than 14 calendar days after risk assignment for patient to continue to receive protocol therapy. For patients with M2 marrow, treatment begins without awaiting count recovery, and must be no later than 5 calendar days after callback. See Section 4.5 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN) (IND#117467) **Do not use commercial supply**	IV	15 micrograms/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c BM (Local evaluation & MRD)
Dexamethasone (DEX)	PO or IV	5 mg/m^2 (max 20 mg) 30 to 60 minutes prior to the start of the Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	d CSF cell count, cytospin[1] e Bilirubin, ALT & creatinine, BUN
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	15, 29	**CNS1/2 ONLY** Note age-based dosing	f Peripheral blood for PK g Peripheral blood for Immunogenicity **Optional studies**
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	15, 29	**CNS3 ONLY** Note age-based dosing	h Blinatumomab PD [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation during Blinatumomab Block – Cycle 1. See Section 14.2 for details of TRT.					

APPENDIX II-D **Blinatumomab Block - Cycle 1** (HR/IR Patients in **Arm B**) This therapy is the 1st cycle of therapy with blinatumomab for the HR/IR patients assigned to the experimental arm (Arm B)	Patient COG ID number DOB

Ht _________cm Wt _________kg BSA _________m²

Date Due	Date Given	Day	BLIN ____mcg	DEX ____mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	____mcg	____mg			a*, b, e, h+,g$	
		2	↓				f&,h+	

		7					h+	
		8					b, e,	

		14					f&, h+	
		15			____mg	____mg	b, d, e	

		21					h+	
		22					b, e,	

		28						
		29			____mg	____mg	b, c, d, e	
		30-35	**Rest Period**					
			Following count recovery, start next cycle, Blinatumomab Block Cycle 2 (Section 4.6, APPENDIX II-E). Treatment failures will be taken off protocol therapy.					

+Peripheral blood: Prior to (Hour 0) and during (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion (see Section 13.5 for complete details).

$ Prior to (Hour 0) first blinatumomab infusion (see Section 13.7 & lab manual for details)
& See lab manual for collection and shipping details
*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-E **Blinatumomab Block - Cycle 2** (HR/IR Patients in **Arm B**) This therapy is the 2nd cycle of therapy with blinatumomab for the HR/IR patients assigned to the experimental arm (Arm B)	Patient COG ID number DOB

Blinatumomab Block-Cycle 2 lasts 5 weeks (35 Days) and begins when ANC ≥ 500/µL and platelets ≥ 50,000/µL. See Section 4.6 for treatment details. This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN) (IND#117467) **Do not use commercial supply**	IV	15 micrograms/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c BM (Local evaluation & MRD)
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	8, 29	**CNS1/2 ONLY** Note age-based dosing	d CSF cell count, cytospin[1] e Bilirubin, ALT & creatinine, BUN f Peripheral blood for Immunogenicity
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	8, 29	**CNS3 ONLY** Note age-based dosing	[1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht _________**cm** **Wt** _________**kg** **BSA** _________**m²**

Date Due	Date Given	Day	BLIN ____mcg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	____mcg ↓			a*, b, e	
		8		____mg	____mg	b, d, e	
		15					
		22				b, e	
		28					
		29		____mg	____mg	b, c, d, e,f$	
		30-35	**Rest Period**				
			Following count recovery, patients will proceed to HSCT (Section 4.9). See Section 4.10, Appendix II-H for suggested bridging therapy in the event that HSCT is delayed. Treatment failures will be taken off protocol therapy.				

$ In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1. See Section 13.7 and lab manual for details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

& See lab manual for collection and shipping details

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-F **Blinatumomab-S: Cycle 1 (Treatment Failure)** This therapy is the 1st cycle of therapy with Salvage Therapy (Blinatumomab-S) for the HR/IR patients classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Blinatumomab-S: Cycle 1 lasts 5 weeks (35 Days). See Section 4.7 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN) (IND#117467) **Do not use commercial supply**	IV	5 micrograms/m²/day 15 micrograms/m²/day	1-7 8-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & creatinine, BUN e Local BM evaluation f BM for MRD- pre HSCT g Peripheral blood for PK h Peripheral blood for Immunogenicity **<u>Optional studies</u>** i Blinatumomab PD [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Dexamethasone (DEX)	PO or IV	5 mg/m² (max 20 mg) 30 to 60 minutes prior to the start of the Blinatumomab infusion	1, 8	**Start prior to blinatumomab therapy on Day 1 and prior to step dose on Day 8.**	
Intrathecal Methotrexate (IT MTX)	IT	<u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥9 15 mg	15	Note age-based dosing	

Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation during the 1st cycle of Blinatumomab-S therapy. See Section 14.2 for details of TRT.

APPENDIX II-F **Blinatumomab-S: Cycle 1 (Treatment Failure)** This therapy is the 1st cycle of therapy with Salvage Therapy (Blinatumomab-S) for the HR/IR patients classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Ht _________cm **Wt _________kg** **BSA _________m²**

Date Due	Date Given	Day	BLIN ____mcg days 1-7 ____mcg days 8-28	DEX ____mg	IT MTX ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	____mcg days 1-7	____mg		a*, b, d, i⁺,h$	
		2	↓			g&	
		3					
		4					
		5					
		6					
		7				i⁺	
		8	____mcg days 8-28	____mg		b, d	
		9	↓				
		10					
		14				b, c, d, g&, i⁺	
		15			____mg		
		16					
		21				b, d, i⁺	
		22					
		28					
		29				b, d, e, f⁺⁺⁺	
		30-35	**Rest Period**				
			See Section 4.7.6 for criteria for proceeding to HSCT (Section 4.9) or to Blinatumomab-S: Cycle 2 (Section 4.8, APPENDIX II-G)				

⁺ **Peripheral blood:** Prior to (Hour 0) and during (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion (see Section 13.5 for complete details).

$ Prior to (Hour 0) first blinatumomab infusion. In cases where blinatumomab treatment will not continue to Cycle 2, collect additional sample at end of Cycle 1. (see Section 13.7 and lab manual for details)

& See lab manual for collection and shipping details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

+++ Pre-HSCT evaluation

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-G **Blinatumomab-S: Cycle 2** (Treatment failure) This therapy is the 2nd cycle of therapy with Salvage Therapy (Blinatumomab-S) for the HR/IR patients classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Blinatumomab-S: Cycle 2 lasts 5 weeks (35 Days) and starts no earlier than Day 36 after the beginning of Blinatumomab-S: Cycle 1.. See Section 4.8 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN) (IND#117467) **Do not use commercial supply**	IV	15 micrograms/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Local BM evaluation d CSF cell count, cytospin[1] e Bilirubin, ALT & creatinine, BUN f BM for MRD- pre HSCT g Peripheral blood for Immunogenicity [1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Intrathecal Methotrexate (IT MTX)	IT	<u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥9 15 mg	8, 29	Note age-based dosing	

APPENDIX II-G **Blinatumomab-S: Cycle 2** (Treatment failure)	
This therapy is the 2nd cycle of therapy with Salvage Therapy (Blinatumomab-S) for the HR/IR patients classified as treatment failures who have not previously had blinatumomab on study.	Patient COG ID number DOB

Ht _________cm Wt _________kg BSA _________m²

Date Due	Date Given	Day	BLIN ______mcg	IT MTX ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below			
		1	_____mcg		a*, b, e	
		8	↓	_____mg	b, d, e	
		15	↓		b, e	
		22	↓		b, e	
		29		_____mg	b, c, d, e,g[$], f[+++]	
		30-35	**Rest Period**			
			See Section 4.8.5 for criteria for proceeding to HSCT (Section 4.9) or to Bridging Maintenance Therapy Section 4.10, Appendix II-H. Patients with M2/M3 marrow after Blinatumomab-S: Cycle 2 will be taken off protocol therapy.			

[$] In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1. See Section 13.7 and lab manual for details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

+++ Pre-HSCT evaluation

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

Appendix II-H **Bridging Maintenance Therapy: Optional (HR/IR patients and TF patients that are eligible for HSCT)** *This therapy is only for HR/IR patients awaiting stem cell transplant therapy due to stem cell source or facility scheduling issues causing a lag time > 2 weeks after count recovery. Bridging therapy can be given for a maximum of 6 weeks, but does not need to be given the full 6 weeks if patient is ready for HSCT earlier.*	Patient COG ID number DOB

This therapy lasts for a maximum of 6 weeks (42 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50 000/µL. See Section 4.10 for 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/m²/dose	1, 22	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	**a** Hx, PE [VS/Wt (BSA)] **b** CBC/diff/platelets **c** BM for MRD evaluation **d** BUN/creatinine e LFTs See Section 7.1c for Follow up observations.
Mercaptopurine (MP)	PO	75 mg/m²/dose	1-42		
Methotrexate (MTX)	PO	20 mg/m²/dose	1, 8, 15, 22, 29, 36		

Ht ________cm Wt ________kg BSA ________m²

Date Due	Date Given	Day	VCR ____mg	MP ___mg	PO MTX ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	_____mg	_____mg	_____mg	a, b, d,e	

		8			_____mg		

		15			_____mg		

		22	_____mg		_______mg		

		29			_____mg		

		36			_____mg		

		42					
		43				c[1]	

[1] Bone marrow for MRD evaluation must be repeated prior to the start of HSCT.

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-I **Continuation1/2 (All LR patients)** This therapy is for all LR patients and is the same for Continuation 1 and Continuation 2.	Patient COG ID number DOB

Continuation lasts 8 weeks and is given twice, for a total of 16 weeks. Begin when ANC ≥ 500/µL and platelets ≥ 50,000/µL. Await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 22 ID MTX. See Section 4.11 for treatment details. This therapy delivery map is for one cycle of Continuation and is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	1-5	Total Daily Dose: 6 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & creatinine, BUN [1] Obtain with each IT/ITT See Section 7.0 for further details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute[+]	1.5 mg/m²/dose	1	[+] Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Methotrexate (MTX)	PO	20 mg/m²/dose	8, 15, 29, 36		
Intermediate Dose Methotrexate (ID MTX)	IV over 36 hours	1000 mg/m²/dose	22	**CNS3 ONLY**	
Methotrexate (MTX)	PO	25 mg/m²/dose Q6H x 4 doses	22	**CNS1/2 ONLY**	
Mercaptopurine (MP)	PO	75 mg/m²/dose daily	1-42		
Leucovorin (LCV)	IV/PO	15 mg/m²/dose Q6H	24, 25	**CNS3 ONLY** Begin **48 hrs** after the **START** of ID MTX infusion.	
Leucovorin (LCV)	PO	10 mg/m²/dose Q6H x 2	24	**CNS1/2 ONLY** Begin **48 hrs** after the **START** of day 22 PO Methotrexate	
Cyclophosphamide (CPM)	IV over 15-30 minutes	300 mg/m²/dose	43, 50	See Section 4.11 and Appendix IV for administration guidelines.	
Etoposide (ETOP)	IV over 60-120 minutes	150 mg/m²/dose	43, 50		
Thioguanine (TG)	PO	40 mg/m²/dose	43-49		
Cytarabine (ARAC)	IV over 1 – 30 minutes or SQ	50 mg/m²/dose	44-47, 51-54		
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	1, 43	**CNS1/2 ONLY** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	1, 43	**CNS3 ONLY** Note age-based dosing	

APPENDIX II-I **Continuation1/2 (All LR patients)**
This therapy is for all LR patients and is the same for Continuation 1 and Continuation 2.

Patient COG ID number DOB

Enter Cycle #: _____ Ht _________cm Wt _________kg BSA _________m²

Date Due	Date Given	Day	DEX. __mg	MP __mg	VCR __mg	PO MTX __mg	PO MTX **CNS1/2 ONLY** ___mg	ID MTX **CNS3 ONLY** ____mg	LCV ____mg	ETOP __mg	CPM __mg	TG __mg	ARAC __mg	IT MTX **CNS1/2 ONLY** ___mg	ITT **CNS3 ONLY** ___mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below														
		1	___mg	___mg	__mg									___mg	___mg	a, b, c,d	
		2															
		3															
		4															
		5															

		8				___mg										b,d	

		15				___mg										b,d	

		22^					____mg ____mg ____mg ____mg	_____mg								b,d	

		24							____mg								
		25							____mg								

		29				___mg										b,d	

		36				___mg										b,d	

		42															
		43^								___mg	___mg	___mg		___mg	___mg	b, c,d	
		44											___mg				

		47															

		49															
		50								___mg	___mg					b, d	
		51											___mg				

		53															
		54															

		56														b,d	

Following Continuation 1, upon count recovery, **LR patients randomized to Arm C** will receive Continuation 2 therapy (Section 4.11, APPENDIX II-I), **LR patients randomized to Arm D** will receive Blinatumomab Block: Cycle 2 therapy (Section 4.16, APPENDIX II-N),
Following Continuation 2, upon count recovery, **LR patients randomized to Arm C** will receive Maintenance Cycle 1 therapy (Section 4.12, Appendix II-J), **LR patients randomized to Arm D** will receive Blinatumomab Block: Cycle 3 therapy (Section 4.16, APPENDIX II-N),

^ Await count recovery to ANC ≥ 500/µL and platelets ≥ 50,000/µL prior to beginning Day 22 and Day 43 therapy. See Section 4.11 for details
See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

Appendix II-J **Maintenance Cycle 1 (All LR patients)** This Maintenance therapy is for all LR patients (**Arm C** and **Arm D**)	Patient COG ID number DOB

Maintenance Cycle 1 lasts for 12 weeks (84 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50 000/µL. See Section 4.12 for treatment details. This therapy delivery map is for Maintenance and is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	1-5, 29-33, & 57-61	Total Daily Dose: 6 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & creatinine, BUN e Absolute lymphocyte count with T and B subset quantification.[2] f Peripheral blood for Immunogenicity [1] Obtain with each IT/ITT [2] To be done at the end of each 12 week maintenance cycle and every 3 months after completion of therapy for 1 year. See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CAR**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1, 29, 57	+ Or infusion via minibag as per institutional policy. **Maximum dose: 2 mg**	
Mercaptopurine (MP)	PO	75 mg/m²/dose daily	1-84		
Methotrexate (MTX)	PO	20 mg/m²/dose weekly	8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78		
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	1	**CNS1/2 ONLY** Note age-based dosing	
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	1	**CNS3 ONLY** Note age-based dosing	

Appendix II-J **Maintenance Cycle 1 (All LR patients)** This Maintenance therapy is for all LR patients (**Arm C** and **Arm D**)	____________________ Patient COG ID number DOB

Ht _________**cm** **Wt** _________**kg** **BSA** _________**m²**

Date Due	Date Given	Day	DEX. ____mg	VCR _____mg	MP ____mg	MTX ______mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below							
		1	_____mg	_____mg	_____mg		______mg	______mg	a, b, c, d, f$	
		2								
		3								
		4								
		5								
		8				______mg				
		15				______mg				
		22				______mg				
		29	_____mg	_____mg		______mg			a, b, d	
		30								
		31								
		32								
		33								
		36				______mg				
		43				______mg				
		50				______mg				
		57	_____mg	_____mg		______mg			a, b, d	
		58								
		58								
		60								
		61								
		64				______mg				
		71				______mg				
		78				______mg				
		84							a, b, d, e	
		85	Following Maintenance Cycle 1 therapy, **CNS3 patients ONLY** will receive CNS directed therapy with chemoradiation (Section 4.13, APPENDIX II-K). All other patients on Arm C and Arm D will continue with Maintenance Post-Cycle 1 therapy (Section 4.14, APPENDIX II-L)							

$ Arm D ONLY. Prior to start of Maintenance therapy for eligible patients (see Section 13.7 and lab manual for details)

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-K **Maintenance Chemoradiation-CNS Directed Therapy (LR Patients)** This therapy is for all CNS3 patients **ONLY** and is given between 1st and 2nd cycles of Maintenance therapy.	Patient COG ID number DOB

This CNS directed therapy lasts 3 weeks (21 days) and starts when ANC ≥ 500/µL and platelets ≥ 50,000/µL (whichever occurs later). See Section 4.13 for treatment details. This Therapy Delivery Map is on one (1) page

DRUG	**ROUTE**	**DOSAGE**	**DAYS**	**IMPORTANT NOTES**	**OBSERVATIONS**
Dexamethasone (DEX)	PO	5 mg/m²/dose BID	1-7, 15-21	Total Daily Dose: 10 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Bilirubin, ALT & creatinine, BUN
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1, 8, 15	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	1	Administer through the tubing of a freely infusing solution of D_5W or 0.9% NaCl	See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cranial Radiotherapy: Patients with CNS3 and isolated CNS relapse will receive cranial radiation during Maintenance, between Blocks 1 and 2. See Section 14.1 for details of cXRT.					

Enter Cycle #: _____ Ht _________cm Wt _________kg BSA _________m²

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	PEG-ASP ____IU	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	________mg	________mg	_______IU	a, b, c	
		2	↓				
		3					
		4					
		5					
		6					
		7					
		8		________mg			
		...					
		15	________mg	________mg			
		16	↓				
		17					
		18					
		19					
		20					
		21					
		22	Following chemoradiation, patients will receive Maintenance Post-Cycle 1 therapy (Section 4.14, APPENDIX II-L) when count parameters are met.				

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-L **Maintenance Post Cycle 1 (All LR patients)** This therapy is for all LR patients (**Arm C** and **Arm D**)	Patient COG ID number DOB

Maintenance Post Cycle 1 is given in 12 week cycles based on dose modifications for low counts and platelets. See Section 4.14 and Section 5.9 for details. This therapy delivery map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dexamethasone (DEX)	PO	3 mg/m²/dose BID	1-5, 29-33, & 57-61	Total Daily Dose: 6 mg/m²/day, divided BID.	a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1] d Bilirubin, ALT & Creatinine, BUN e Absolute lymphocyte count with T and B subset quantification[2] [1] Obtain with each IT/ITT [2] To be done at the end of each 12 week maintenance cycle and every 3 months after completion of therapy for 1 year. See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV push over 1 minute+	1.5 mg/m²/dose	1, 29, 57	+ Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**	
Methotrexate (MTX)	PO	20 mg/m²/dose	1	**CNS3 ONLY**	
Mercaptopurine (MP)	PO	75 mg/m²/dose daily	1-84		
Methotrexate (MTX)	PO	20 mg/m²/dose weekly	8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78		
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	1	**CNS1/2 ONLY** Note age-based dosing	

APPENDIX II-L **Maintenance Post Cycle 1 (All LR patients)** This therapy is for all LR patients (**Arm C** and **Arm D)**	Patient COG ID number DOB

Cycle # ____   **Ht _________cm**   **Wt _________kg**   **BSA _________m^2**

Date Due	Date Given	Day	DEX. ____mg	VCR ____mg	MTX (PO) **CNS3 ONLY** ____mg	MTX (PO) _____mg	MP _____mg	IT MTX **CNS1/2 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below							
		1	____mg	_____mg	______mg		_____mg	______mg	a, b, c, d	
		2								
		3								
		4								
		5								
		8				______mg				
		15				______mg				
		22				______mg				
		29	____mg	_____mg		______mg			a, b, d	
		30								
		31								
		32								
		33								
		36				______mg				
		43				______mg				
		50				______mg				
		57	____mg	_____mg		______mg			a, b, d	
		58								
		59								
		60								
		61								
		64				______mg				
		71				______mg				
		78				______mg				
		84							a, b, d, e	
		85	Maintenance cycles are repeated in 12 week cycles based on dose modifications for low counts or low platelets until 2 yrs from start of Block 1 therapy for both male and female patients.							

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-M **Blinatumomab Block - Cycle 1** (LR Patients in **Arm D**) This therapy is the 1st cycle of therapy with blinatumomab for the LR patients randomized to Arm D	Patient COG ID number DOB

This cycle lasts 5 weeks (35 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50 000/µL.. See Section 4.15 for treatment details. This Therapy Delivery Map is on two (2) pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN) (IND#117467) **Do not use commercial supply**	IV	15 micrograms/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c CSF cell count, cytospin[1]
Dexamethasone (DEX)	PO or IV	5 mg/m² (max 20 mg) 30 to 60 minutes prior to the start of the Blinatumomab infusion	1	**Start prior to blinatumomab therapy**	d Bilirubin, ALT & creatinine, BUN e Peripheral blood for PK
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	8, 29	**CNS1/2 ONLY** Note age-based dosing	f Peripheral blood for Immunogenicity **Optional studies** g Blinatumomab PD
Intrathecal Triple Therapy (ITT): Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	IT	Age (yrs) Dose 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	8, 29	**CNS3 ONLY** Note age-based dosing	[1] Obtain with each IT/ITT See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Testicular Radiotherapy: Patients with persistent testicular disease will receive testicular radiation. See Section 14.2 for details of TRT.					

APPENDIX II-M **Blinatumomab Block - Cycle 1** (LR Patients in **Arm D**) This therapy is the 1st cycle of therapy with blinatumomab for the LR patients randomized to Arm D	Patient COG ID number DOB

Ht ________cm **Wt ________kg** **BSA ________m^2**

Date Due	Date Given	Day	BLIN ______mcg	DEX ______mg	IT MTX **CNS1/2 ONLY** ______mg	ITT **CNS3 ONLY** ______mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	____mcg ↓	_____mg			a*, b, d, g+,f$	
		2					e& g+	
		7					g+	
		8			____mg	____mg	b, c, d,	
		14					e& g+	
		15					b, d	
		21					g+	
		22					b, d	
		28	↓					
		29			____mg	____mg	b, c, d	
		30-35	**Rest Period**					
		36	Following Blinatumomab Block: Cycle 1, patients receive Continuation 1 therapy (Section 4.11, APPENDIX II-I) when count parameters are met.					

+ **Peripheral blood:** Prior to (Hour 0) and during (Hour 6, Hour 12, Day 2, Day 7, Day 14, Day 21) first blinatumomab infusion (see Section 13.5 for complete details).

$ Prior to (Hour 0) first blinatumomab infusion (see Section 13.7 and lab manual for details)

& See lab manual for details

*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX II-N **Blinatumomab Block - Cycle 2 and 3** (LR Patients in **Arm D**) This therapy is Cycles 2 and 3 of therapy with blinatumomab for the LR patients randomized to Arm D	Patient COG ID number DOB

Blinatumomab Block: Cycles 2 & 3; each last 5 weeks (35 days) and starts when peripheral counts recover to ANC ≥ 500/µL and platelets ≥ 50,000/µL. See Section 4.16 for treatment details.
This Therapy Delivery Map is on one (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Blinatumomab (BLIN) (IND#117467) **Do not use commercial supply**	IV	15 micrograms/m²/day	1-28		a Hx, PE [VS/Wt (BSA)] b CBC/diff/platelets c Bilirubin, ALT & creatinine, BUN d Peripheral blood for Immunogenicity See Section 7.0 for further details. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Enter Cycle #_________ Ht _________cm Wt _________kg BSA _________m²

Date Due	Date Given	Day	BLIN ____mcg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below		
		1	____mcg	a*, b, c	
		...	↓		
		8		b, c	
		...			
		15		b, c	
		...			
		22		b, c	
		...			
		28			
		29		b, c,d$	
		30-35	**Rest Period**		
		36	Following Blinatumomab Block Cycle 2: LR B-ALL patients randomized to **Arm D** will receive Continuation 2 (Section 4.11, APPENDIX II-I) when count parameters are met. Following Blinatumomab Block Cycle 3: LR B-ALL patients randomized to **Arm D** will receive Maintenance Cycle 1 therapy-(Section 4.12, Appendix II-J) when count parameters are met.		

$Obtain at End Cycle 2. In cases where blinatumomab treatment will not continue to Cycle 2, collect sample at end of Cycle 1. See Section 13.7 and lab manual for details
*See recommended vital sign monitoring for Blinatumomab blocks in Section 7.1e

See Section 5.0 for Dose Modifications for Toxicities and Appendix I for Supportive Care Guidelines.

APPENDIX III: MERCAPTOPURINE DOSING GUIDELINES

MERCAPTOPURINE 75 mg/m^2

Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

Body Surface Area (m^2)*	Daily Dose (d) for 7 days (1 tablet = 50 mg)	Cumulative Weekly Dose
0.36 - 0.40	½ tab / d x 6; 1 tab / d x 1	200 mg/wk
0.41 - 0.45	½ tab / d x 5; 1 tab / d x 2	225 mg/wk
0.46 - 0.49	½ tab / d x 4; 1 tab / d x 3	250 mg/wk
0.50 - 0.54	1 tab / d x 4; ½ tab / d x 3	275 mg/wk
0.55 - 0.59	1 tab / d x 5; ½ tab / d x 2	300 mg/wk
0.60 - 0.64	1 tab / d x 6; ½ tab / d x 1	325 mg/wk
0.65 - 0.69	1 tab / day	350 mg/wk
0.70 - 0.73	1 tab / d x 6; 1½ tab / d x 1	375 mg/wk
0.74 - 0.78	1 tab / d x 5; 1½ tab / d x 2	400 mg/wk
0.79 - 0.83	1 tab / d x 4; 1½ tab / d x 3	425 mg/wk
0.84 - 0.88	1½ tab / d x 4; 1 tab / d x 3	450 mg/wk
0.89 - 0.92	1½ tab / d x 5; 1 tab / d x 2	475 mg/wk
0.93 - 0.97	1½ tab / d x 6; 1 tab /d x 1	500 mg/wk
0.98 - 1.02	1½ tab / day	525 mg/wk
1.03 - 1.07	1½ tab / d x 6; 2 tab / d x 1	550 mg/wk
1.08 - 1.11	1½ tab / d x 5; 2 tab / d x 2	575 mg/wk
1.12 - 1.16	1½ tab / d x 4; 2 tab / d x 3	600 mg/wk
1.17 - 1.21	2 tab / d x 4; 1½ tab / d x 3	625 mg/wk
1.22 - 1.26	2 tab / d x 5; 1½ tab / d x 2	650 mg/wk
1.27 - 1.30	2 tab / d x 6; 1½ tab / d x 1	675 mg/wk
1.31 - 1.35	2 tab / day	700 mg/wk
1.36 - 1.40	2 tab / d x 6; 2½ tab / d x 1	725 mg/wk
1.41 - 1.45	2 tab / d x 5; 2½ tab / d x 2	750 mg/wk
1.46 – 1.49	2 tab / d x 4; 2½ tab / d x 3	775 mg/wk
1.50 – 1.54	2½ tab/ d x 4; 2 tab / d x 3	800 mg/wk
1.55 – 1.59	2½ tab/ d x 5; 2 tab / d x 2	825 mg/wk
1.60 – 1.64	2½ tab/ d x 6; 2 tab / d x 1	850 mg/wk
1.65 – 1.69	2½ tab/ d	875 mg/wk
1.70 – 1.73	2½ tab/ d x 6; 3 tab / d x 1	900 mg/wk
1.74 – 1.78	2½ tab/ d x 5; 3 tab / d x 2	925 mg/wk
1.79 – 1.83	2½ tab/ d x 4; 3 tab / d x 3	950 mg/wk
1.84 – 1.88	3 tab/ d x 4; 2½ tab / d x 3	975 mg/wk
1.89 – 1.92	3 tab/ d x 5; 2½ tab / d x 2	1000 mg/wk
1.93 – 1.97	3 tab/ d x 6; 2½ tab / d x 1	1025 mg/wk
1.98 – 2.02	3 tab/ d x 7	1050 mg/wk

2.03 – 2.07	3 tab/ d x 6; 3½ tab / d x 1	1075 mg/wk
2.08 – 2.11	3 tab/ d x 5; 3½ tab / d x 2	1100 mg/wk
2.12 – 2.16	3 tab/ d x 4; 3½ tab / d x 3	1125 mg/wk
2.17 – 2.21	3½ tab/ d x 4; 3 tab / d x 3	1150 mg/wk
2.22 – 2.26	3½ tab/ d x 5; 3 tab / d x 2	1175 mg/wk
2.27 – 2.30	3½ tab/ d x 6; 3 tab / d x 1	1200 mg/wk
2.31 – 2.35	3½ tab/ d x 7	1225 mg/wk
2.36 – 2.40	3½ tab/ d x 6; 4 tab / d x 1	1250 mg/wk
2.41 – 2.45	3½ tab/ d x 5; 4 tab / d x 2	1275 mg/wk
2.46 – 2.49	3½ tab/ d x 4; 4 tab / d x 3	1300 mg/wk
2.50 – 2.54	4 tab/ d x 4; 3½ tab / d x 3	1325 mg/wk
2.55 – 2.59	4 tab/ d x 5; 3½ tab / d x 2	1350 mg/wk
2.60 – 2.64	4 tab/ d x 6; 3½ tab / d x 1	1375 mg/wk
2.65 – 2.69	4 tab/ d x 7	1400 mg/wk
2.70 – 2.73	4 tab/ d x 6; 4½ tab / d x 1	1425 mg/wk
2.74 – 2.78	4 tab/ d x 5; 4½ tab / d x 2	1450 mg/wk
2.79 – 2.83	4 tab/ d x 4; 4½ tab / d x 3	1475 mg/wk
2.84 – 2.88	4½ tab/ d x 4; 4 tab / d x 3	1500 mg/wk
2.89 – 2.92	4½ tab/ d x 5; 4 tab / d x 2	1525 mg/wk
2.93 – 2.97	4½ tab/ d x 6; 4 tab / d x 1	1550 mg/wk
2.98 – 3.00	4½ tab/ d x 7	1575 mg/wk

Patients exceeding a BSA of 3.00 m^2 should have their MP doses calculated on actual BSA with no maximum dose.

APPENDIX IV: THIOGUANINE DOSING GUIDELINES

THIOGUANINE 40 mg/m²

*****Patients exceeding a BSA of 3 m² should have their TG doses calculated on actual BSA with no maximum dose.*

Body Surface Area (m²)*	Daily Dose (d) for 7 days (1 tablet = 40 mg)	Cumulative Weekly Dose
0.27 – 0.3	Use oral compounded suspension	
0.31 – 0.34	Use oral compounded suspension	
0.35 – 0.38	Use oral compounded suspension	
0.39 – 0.41	Use oral compounded suspension	
0.42 – 0.45	Use oral compounded suspension	
0.46 – 0.48	Use oral compounded suspension	
0.49 – 0.54	½ tab / d x 7	140 mg/wk
0.55 – 0.61	½ tab / d x 6; 1 tab / d x 1	160 mg/wk
0.62 – 0.68	½ tab / d x 5; 1 tab / d x 2	180 mg/wk
0.69 – 0.75	½ tab / d x 4; 1 tab / d x 3	200 mg/wk
0.76 – 0.82	1 tab / d x 4; ½ tab / d x 3	220 mg/wk
0.83 – 0.89	1 tab / d x 5; ½ tab / d x 2	240 mg/wk
0.9 – 0.96	1 tab / d x 6; ½ tab / d x 1	260 mg/wk
0.97 – 1.04	1 tab / d x 7	280 mg/wk
1.05 – 1.11	1 tab / d x 6; 1½ tab / d x 1	300 mg/wk
1.12 – 1.18	1 tab / d x 5; 1½ tab / d x 2	320 mg/wk
1.19 – 1.25	1 tab/ d x 4; 1½ tab / d x 3	340 mg/wk
1.26 – 1.32	1½ tab / d x 4; 1 tab / d x 3	360 mg/wk
1.33 – 1.39	1½ tab / d x 5; 1 tab /d x 2	380 mg/wk
1.4 – 1.46	1½ tab / d x 6; 1 tab / d x 1	400 mg/wk
1.47 – 1.54	1½ tab /day	420 mg/wk
1.55 – 1.61	1½ tab / d x 6; 2 tab / d x 1	440 mg/wk
1.62 – 1.68	1½ tab / d x 5; 2 tab / d x 2	460 mg/wk
1.69 – 1.75	1½ tab / d x 4; 2 tab / d x 3	480 mg/wk
1.76 – 1.82	2 tab / d x 4; 1½ tab / d x 3	500 mg/wk
1.83 – 1.89	2 tab / d x 5; 1½ tab / d x 2	520 mg/wk
1.9 – 1.96	2 tab / d x 6; 1½ tab / d x 1	540 mg/wk
1.97 – 2.04	2 tab / day	560 mg/wk
2.05 – 2.11	2 tab / d x 6; 2½ tab / d x 1	580 mg/wk
2.12 – 2.18	2 tab / d x 5; 2½ tab / d x 2	600 mg/wk
2.19 – 2.25	2 tab / d x 4; 2½ tab / d x 3	620 mg/wk
2.26 – 2.32	2½ tab / d x 4; 2 tab / d x 3	640 mg/wk
2.33 – 2.39	2½ tab / d x 5; 2 tab / d x 2	660 mg/wk
2.4 – 2.46	2½ tab / d x 6; 2 tab / d x 1	680 mg/wk
2.47 – 2.54	2½ tab / d	700 mg/wk
2.55 – 2.61	2½ tab / d x 6; 3 tab / d x 1	720 mg/wk
2.62 – 2.68	2½ tab / d x 5; 3 tab / d x 2	740 mg/wk
2.69 – 2.75	2½ tab / d x 4; 3 tab / d x 3	760 mg/wk
2.76 – 2.82	3 tab / d x 4; 2½ tab / d x 3	780 mg/wk
2.83 – 2.89	3 tab / d x 5; 2½ tab / d x 2	800 mg/wk
2.9 – 2.96	3 tab / d x 6; 2½ tab / d x 1	820 mg/wk
2.97 – 3	3 tab / d x 7	840 mg/wk

APPENDIX V: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY
(for children from 7 through 12 years of age)

A trial to compare 2 ways to treat children with B-Lymphoblastic Leukemia (B-ALL) that has come back (relapsed) after the first treatment

1. We have been talking with you about your illness, B-ALL. You have received treatment for this B-ALL before. After doing tests, we have found that the cancer has come back in your bone marrow, brain or spinal cord, or testes. B-ALL that has come back after the first treatment is called relapse.

2. We are asking you to take part in a research study because you have B-ALL that has relapsed. A research study is when doctors work together to try out new ways to help people who are sick. In this study we are trying to learn more about how to treat B-ALL when it has come back after the first time it was treated. During this study, we want to test whether the relapsed B-ALL responds better to combination chemotherapy or a new drug called blinatumomab. The treatment that you get will depend on a process called random assignment. Random assignment is a lot like flipping a coin and you will have an equal chance of getting both treatment options.

3. Children and teens who are part of this study will be treated with either combination chemotherapy or a new drug called blinatumomab. It is possible that some children will get radiation to their brain or testes, depending on where the leukemia is found. Some children will also get a stem cell transplant.

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 having the leukemia go away for as long as possible. But we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you might experience more side effects from the combination chemotherapy or blinatumomab. Another risk is that the therapy on this study might not be as effective as other options. 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 blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard tests are being performed, so there would be no extra procedures. You can still be treated on this study even if you don't allow us to collect the extra blood samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY
(for teens from 13 through 17 years of age)

A trial to compare 2 ways to treat children with B-Lymphoblastic Leukemia (B-ALL) that has come back (relapsed) after the first treatment

1. We have been talking with you about your illness, B-ALL. You have received treatment for this B-ALL before. After doing tests, we have found that the cancer has come back in your bone marrow, brain or spinal cord, or testes. B-ALL that has come back after the first treatment is called relapse.

2. We are asking you to take part in a research study because you have B-ALL that has relapsed. A research study is when doctors work together to try out new ways to help people who are sick. In this study we are trying to learn more about how to treat B-ALL when it has come back after the first time it was treated. During this study, we want to test whether the relapsed B-ALL responds better to combination chemotherapy or a new drug called blinatumomab. The treatment that you get will depend on a process called random assignment. Random assignment is a lot like flipping a coin and you will have an equal chance of getting both treatment options.

3. Children and teens who are part of this study will be treated with either combination chemotherapy or a new drug called blinatumomab. It is possible that some children will get radiation to their brain or testes, depending on where the leukemia is found. Some children will also get a stem cell transplant.

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 having the leukemia go away for as long as possible. But we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that you might experience more side effects from the combination chemotherapy or blinatumomab. Another risk is that the therapy on this study might not be as effective as other options. 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 blood and bone marrow. We want to see if there are ways to tell how the cancer will respond to treatment. These samples would be taken when other standard tests are being performed, so there would be no extra procedures. You can still be treated on this study even if you don't allow us to collect the extra samples for research.

APPENDIX VI: ADDITIONAL INFORMATION FOR BANKING FOR FUTURE RESEARCH CORRELATIVE BIOLOGY STUDY

a) Rationale

The ability to collect leukemic and normal tissue samples for future research, and to link these samples to patient characteristics and outcomes, has been critical to recent seminal discoveries regarding the molecular basis of de novo ALL and relapsed ALL, and the relationship of specific molecular lesions with outcomes and response to targeted therapies. In the context of this protocol, we will seek consent from participants to provide material for banking for the purpose of performing retrospective studies to refine risk stratification, identify new targets for therapy, identify biomarkers to predict response, and to link host polymorphisms with various disease characteristics and toxicities.

b) Aims and methods

These studies will be performed as stand-alone biology studies subject to review and approval in accordance with the NCTN policies. The following are general descriptions of the types of studies planned.

- Leukemia genomic studies

  Modern genomic studies of high risk ALL have identified novel genetic alterations in ALL that are associated with treatment failure. In particular, high frequencies of mutations have been described in genes involved in B lymphocyte development (*EBF1*, *IKZF1*, *PAX5*) and signaling (*BTLA*, *CD200*, *RAS*) and in cell cycle regulation (*CDKN2A/B*, *RB*, *TP53*).[67] Limited genomic analyses of paired diagnosis and relapse ALL samples have also shed light upon the early origin and clonal nature of such leukemia-associated mutations.[68,69] Other yet-undiscovered mutations likely contribute the pathogenesis of this heterogeneous group of malignancies, and comprehensive prospective evaluation of the genetic landscape of relapsed ALL has not been performed. We hypothesize that integration of genomic profiling data will provide important insights regarding the molecular pathogenesis of relapsed ALL and may identify potential therapeutic targets or identify novel mechanisms of resistance within the context of the agents employed.[70-72]

  We hypothesize that high-throughput genome-wide profiling via multiple non-overlapping techniques provide a comprehensive genetic and epigenetic "fingerprint" and will identify key alterations that contribute to the pathogenesis and progression of relapsed ALL. We further hypothesize that integration of these approaches will allow discovery of alterations that may also be present in *de novo* ALL and could ultimately be used for initial risk stratification and new treatment approaches.

  Consenting patients will submit bone marrow and/or peripheral blood samples at study entry and, if applicable, at second relapse to the central COG Tissue Bank at Nationwide Children's Hospital for storage of viably cryopreserved cells and for isolation nucleic acids, including DNA and RNA. Nucleic acids isolated from relapse specimens will be stored for potential use for genomic profiling, which will include single nucleotide polymorphism (SNP) arrays, array-based gene expression profiles and/or quantitative RT-PCR-based gene expression analyses, methylation arrays, and/or comprehensive sequencing approaches (e.g., RNA-seq, whole exome sequencing), depending on currently available technologies and funding sources. Banked specimens subsequently will be distributed from the reference laboratories to the laboratories performing the individual correlative biology studies. Results from these correlative biology studies may ultimately facilitate (a) enhanced refinement of risk stratification for patients with relapsed ALL, (b) detection of previously-unsuspected subset specificity of blinatumomab, and (c) generation of additional hypotheses with respect to the underlying biology of relapsed ALL.

- Host polymorphism studies

  There is substantial evidence that both inherited germline constitutional and somatically-acquired ALL-specific genomic variation may contribute to variations in response.[73-82] Blood samples obtained during remission are requested specifically for the purpose of providing constitutional (germline) DNA from each patient. Several efforts are anticipated for study of how genomic variation (SNPs, copy number variations, DNA methylation and insertions/deletions) in the constitutional DNA may be associated with phenotypes in ALL. The phenotypes could include those related to probability of cure, response, adverse events or classification. Techniques for interrogation of DNA variation are constantly evolving, and thus these techniques vary but may include candidate polymorphism testing (eg, via Taqman, GoldenGate, or PCR/RFLP assays), candidate gene sequencing (eg, via next-generation technologies coupled with exon capture) or whole-genome sequencing (eg, via next-generation technologies, with or without capture).

- MRD by next generation sequencing (NGS)

  Next-generation sequencing (NGS) offers the potential for highly sensitive and standardized detection of minimal residual disease (MRD) in ALL. In comparison to current PCR methods, NGS assays do not require the laborious generation and validation of patient-specific primers, resulting in improved turn-around time and reduced cost, and may provide improved specificity by direct enumeration of leukemia-derived sequences. Current flow cytometric methods for MRD detection rely on relatively subjective assessments by trained interpreters and are about 1 log less sensitive than PCR-based methods. To determine the suitability of NGS methods for routine MRD assessment in a clinical trial setting, we will sequence the variable regions of IGH in pretreatment and post-treatment samples. Both the presence and the frequency of the MRD clone relative to the total IGH repertoire will be noted.

APPENDIX VII-A: CLINICAL SITE MANAGEMENT OF OUT-PATIENT TREATMENT USING CTEP-SUPPLIED BLINATUMOMAB

- PREPARED IV INFUSION BAGS MAY NOT BE CHANGED BY THE STUDY SUBJECT
- PREPARED INFUSION BAGS OR INTACT VIALS MUST NOT BE TRANSPORTED TO ANOTHER LOCATION BY THE STUDY SUBJECT

AGENT PREPARATION AND ADMINISTRATION OPTIONS

- Prepare all out-patient infusion bags at the registering/treating NCTN Network institution. Study subjects should return to the registering/treating institution for all infusion bag changes.

- For study subjects that cannot return to the registering/treating institution for infusion bag exchanges, the next preference would be for **another NCTN Network institution that is participating on the trial and is closer to the subject's home take over** responsibility for the study subject's protocol participation. In such cases, transfer of the subject's protocol registration to another participating investigator and institution should be considered.

- If transferring the subject's protocol registration to another participating investigator and trial site within the NCTN Network is not feasible, use of **a local outpatient infusion center** could be considered.

    a. First preference would be for all infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container to the local out-patient infusion center.

    b. The prepared infusion bags are stored at the local outpatient infusion center. The infusion center would perform each infusion bag change.

    c. If the local outpatient infusion center will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the local outpatient infusion center, with infusion bags prepared and administered by the local outpatient infusion center staff.

    d. In either case, the local outpatient infusion center would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

    e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the local infusion center by registering/treating institution or local infusion center staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the local infusion center via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container.

- If an outpatient infusion center is not an option, use of a **home health care service** provider can be considered.

    Note: If a home health care agency is being considered to prepare and change the blinatumomab infusion bag, the drug company that provides blinatumomab will cover the costs associated with a home health care agency providing these services.

a. The first preference would be for all outpatient infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container to the servicing home health care agency.

b. The prepared infusion bags are stored by the home health care agency and each individual infusion bag transported to the subject's home by the home health care service nursing staff under refrigerated storage conditions for each infusion bag change.

c. If home health care agency will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the home health care agency, with infusion bags prepared and administered by the home health care agency staff.

d. In either case, the home health care agency would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the home health care agency by registering/treating institution or home health care agency staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the home health care agency via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container.

5. If all options above are not feasible, shipping the prepared infusion bags directly to patient's home via overnight courier delivery service for administration by home healthcare agency staff is acceptable.

   a. The prepared infusion bags are to be shipped in a 2º to 8ºC pre-qualified shipping container containing one infusion bag per box. Example 1, if you are making 2 x 48 hour infusion bags, each infusion bag will be shipped in a separate 2º to 8ºC pre-qualified shipping container. Example 2, if you are making a 2 x 96 hour infusion bags, each infusion bag will be shipped in a separate 2º to 8ºC pre-qualified shipping container. The infusion of the 2nd 96 hour bag must be completed within 8 days (192 hrs) of preparation to avoid exceeding the expiration date. The number of infusion bags that may be prepared and shipped is dependent on the duration the shipping container used is qualified to maintain 2º to 8ºC temperature.

   b. Patients should NOT open the shipping container upon arrival. Shipping containers are to be stored in a secured area away from reach of children or pets.

   c. Shipping containers must only be opened by the home health care service staff at the time of the infusion bag change. Only one shipping container should be opened at a time. If cold-chain management of the prepared infusion bag has been interrupted by opening of the shipping container or storage of the prepared infusion bag in the shipping container exceeds the duration of the qualified time the container will maintain 2º to 8ºC temperature, the infusion bag should not be used.

The home health care service staff should immediately contact the registering/treating institution site pharmacy as indicated on the shipment form. Within 1 business day, the registering/treating institution site should send an email to the COG Industry Sponsored Trials office at istprogram@childrensoncologygroup.org with a copy to PMB/CTEP at PMBafterhours@mail.nih.gov to report all such occurrences of prepared, unusable infusion bags shipped to a patient's home.

d. Form documenting the time of packaging in the shipping container, duration of time the container will maintain 2° to 8°C temperature and verification that cold-chain management was maintained prior to administration must be included in each shipping container and returned to registering/treating institution for documentation purposes. (See Appendix VII-B)

e. Home health care service staff is to use GCP guidelines.

EVALUATION OF POTENTIAL SATELLITE PHARMACY SITES

When the registering/treating institution is considering use of a local infusion center or home health care agency as a satellite pharmacy, the following must be assessed by the registering/treating institution in relation to the suitability of the local infusion center or home health care agency:

- Ability to appropriately store (temperature and security) the intact agent vials and/or prepared infusion bags.
- Ability to provide documentation of controlled and monitored temperature storage conditions while the IND agent is in the local infusion center or home health care agency possession.
- Availability of appropriately trained staff to prepare doses in compliance with USP <797> guidelines and the protocol, to label infusion bags according to the protocol instructions and to store agent doses under appropriate controlled temperature conditions.
- For home health care agency services, the ability to transport each prepared dose individually to the subject's home under appropriate controlled storage conditions or the ability to assess and confirm that cold-chain management of prepared infusion bags shipped to the subject's home is maintained prior to administration.
- Availability of appropriately trained staff to administer the prepared doses and perform the infusion bag changes according to the protocol.
- Methods for proper disposal of the waste, empty vials, IV bags, etc. are in place.
- Plan for return of unused intact vials to the registering/treating institution is in place.
- Source documentation to confirm agent administration must be maintained by the local infusion center or home health care agency and must be provided to the registering/treating institution for incorporation into the patient's medical/research records and for audit purposes.
- Plan for handling missed doses is in place.
- Agent accountability must be maintained via use of the NCI Drug Accountability Record Form (DARF). The originating site must keep a Control DARF and the local infusion center or home health care agency would be required to maintain a Satellite DARF if receiving and storing supplies of intact vials or receiving and storing infusion bags prepared by the registering/treating institution. Maintenance of a Satellite DARF is not required by home health care agency staff for prepared infusions bags shipped to the subject's home.
- The DARF must be provided to the registering/treating institution for record keeping purposes and audits.

- Documentation of IRB coverage for the protocol must be maintained. The IRB of record for the site must be informed that the study subject may receive therapy administered by a non-research site (i.e., the local infusion center or home health care agency).

TRAINING FOR ALL PARTICIPATING SITES

The Lead Network Group for the trial must work with participating sites to:

a. Implement a training process for participating NCTN Network sites regarding blinatumomab preparation and administration. Documentation of participating site training must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial.

b. Develop a plan for participating NCTN Network sites to assess and train local outpatient infusion centers or home health care agency for patient treatment if required and document training of such sites.

c. Have a training manual available for local outpatient infusion centers or home health care agencies on the clinical trial, appropriate agent preparation, handling and administration requirements and appropriate record keeping requirements.

d. Create a definitive written communication plan for use between registering/treating institution and the local outpatient infusion centers or home health care agency on an ongoing basis during subject's treatment regimen, including emergency contact information for the registering/treating institution and investigator.

APPENDIX VII-B: SHIPMENT OF BLINATUMOMAB IV BAG FROM SITE/PHARMACY TO PATIENT'S HOME

To be completed by Site/Pharmacy:

From: (Investigator Name, Address)	**To Patient:** (Patient Initials, Study ID No) ______________ ; ______ __ __ __ Patient Initials Study ID Number	**Protocol No.:**

Prepare shipment of IV bag at 2°C to 8°C in validated/pre-qualified insulated shipper as per manufacturer instructions (see shipping container instructions). Please take care to use the applicable instructions for summer or winter package preparation, respectively.

Date of packaging [DD/MMM/YYYY]	**Time of packaging** [hh:mm]	**packed by** (initials)

Please tick the boxes and fill in the information below when preparing the IV bag shipment!

- ☐ Validated/pre-qualified shipping container duration of time 2°C to 8°C temperature is maintained: ____________________________ hours
- ☐ Cooling elements for provided box used according to manufacturer's instruction

Confirmed by: ____ ____________________
(print name, signature) (date)

To be completed by Ambulant/Home Care Service Provider:

Shipment box unopened and content intact? **YES** ☐

NO ☐

IF NO, please comment_

____

Date and time shipment box opened:____
(date) (time)

Confirmed by: ____ ____________________
(print name, signature) Amb. Care Service (date)

<u>Note</u>: **If content is not intact, please do not use IV bag and inform site immediately!**
If time box opened minus time of packaging exceeds the time duration the shipping container maintains 2°C to 8°C, please do not use IV bag and <u>inform site immediately!</u>

APPENDIX VIII: ADDITIONAL INFORMATION FOR MRD CORRELATIVE BIOLOGY STUDY

a) Rationale

Minimal residual disease is known to be a powerful prognostic factor in childhood ALL.[1-5,12,20-22] Although the majority of work has been done in newly diagnosed ALL patients, several studies using both polymerase chain reaction methods[13,14,16-18] and flow cytometry[19,23] have shown that MRD is highly predictive of second marrow relapse.

Flow cytometric MRD results will be used for the following purposes in this study:

- For late B-ALL marrow and late B-ALL IEM patients, we will use end-Block 1 flow cytometric MRD levels of < 0.1% vs. ≥ 0.1% to define low risk group vs. intermediate risk group, respectively. The low risk group will be eligible for LR randomization. The intermediate risk group will be eligible for HR/IR Randomization.
- For the LR patients participating in LR randomization, we will use end-Block 2 MRD levels of < 0.01% vs. ≥ 0.01% as a randomization stratification criteria to ensure balanced randomization.
- For the IR and HR patients participating in HR/IR Randomization, we will use end-Block 1 MRD levels of <0.1% vs. ≥ 0.1% as a randomization stratification criteria to ensure balanced randomization.
- For HR/IR Randomization patients proceeding to HSCT, we will use the end-Block 3/pre-HSCT MRD level, the peri-engraftment MRD level and the day +100 MRD level to determine eligibility for rapid tapering of immunosuppression.
- In HR/IR Randomization, we will use flow cytometric MRD+ rates at the end of Blocks 2 and 3 as a secondary efficacy objective.

Amendment #10 incorporates the High Risk/Intermediate Risk randomization closure. Effective September 18, 2019, accrual and randomization on the HR/IR arms closed. At completion of Block 1, if patient is found to be HR/IR the patient comes off protocol therapy .

b) Technique

Aliquots of fresh bone marrow specimens **at study entry and during therapy at various designated time points** (see study schema and TDMs) will be adjusted to suitable cell concentrations and stained with the following combinations of monoclonal antibodies in 6-color immunofluorescence:

Tube 1: CD20-FITC/CD10-PE/CD38-PerCP-Cy5.5/CD58-APC/CD19-PE-Cy7/CD45-APC-Cy7
Tube 2: CD9-FITC/CD13-PE+CD33-PE/CD34-PerCP-Cy5.5/CD10-APC/CD19-PE-Cy7/CD45-APC-Cy7

After incubation, samples will be lysed with ammonium chloride, fixed with 0.25% ultra pure formaldehyde, and washed once before analysis. Samples will be run on a Becton Dickinson FACSCanto. A minimum of 750,000 events will be collected, and data will be analyzed by software developed by Dr. Brent Wood, University of Washington that facilitates the hierarchical gating strategy useful for identifying phenotypically aberrant cells. In cases in which the above panels are not informative for detecting abnormal cells, additional markers including but not limited to CD15 and TdT will be added to the panel to help identify MRD populations. In addition, if the administration of blinatumomab creates difficulties in identifying leukemic cells by virtue of CD19 expression, cytoplasmic CD79a and/or CD22 will be used to aid gating.

APPENDIX IX: ADDITIONAL INFORMATION FOR CRLF2 CORRELATIVE BIOLOGY STUDY

a) Rationale

Recent genomic studies of ALL have identified genomic alterations of CRLF2, which encodes the thymic lymphopoietin receptor (TSLPR) and which results in upregulation of CRLF2 as an important contributor to leukemic pathogenesis.[3-5,7] Upregulation may occur by gene alterations, most often fusing CRLF2 to either P2RY8 or IGH@, as well as rarely, a CRLF2 point mutation (F232C),[3-5,7] though there may also be as yet unrecognized mechanisms. In addition, patients with whose blasts show upregulated CRLF2 typically also have simultaneous activating mutations in kinase genes including IKZF1, JAK1 and JAK2, and as a result have abnormalities in signal transduction networks.[3,4,7] Our results suggested high risk children with overexpressed CRLF2 as detected by PCR have very poor outcome irrespective of whether structural rearrangements can be identified,[8] while other studies have suggested that this is only true of patients with P2RY8-CRLF2 translocations.[2,9] Moreover, in our studies CRLF2 did not appear to be prognostically significant in standard risk patients.[8] However, virtually nothing is known about CRLF2 overexpression in the relapse setting, and whether its expression has continued prognostic significance in this already poor-risk group of patients. In addition, because of the underlying kinase abnormalities in this patient population, these patients are potentially ideal candidates for treatment with novel signal transduction inhibitors. Assessing CRLF2 expression may help to identify patients who might be candidates for specific therapy in trials that may be developed as these agents mature.

b) Technique

In conjunction with the immunophenotyping performed at study entry as a baseline for flow cytometric MRD testing, we will also quantify surface TSLPR expression and correlate with outcome.

c) Specific Aims

Aims:

1) To determine if the frequency of high CRLF2 expression (which correlates with CRLF2 genomic lesions) is higher in the first marrow relapse B-ALL patient population than in the initial diagnosis B-ALL patient population.

2) To determine if first marrow relapse B-ALL patients with high CRLF2 expression have an inferior outcome to those without high CRLF2 expression.

d) Power calculations

Aim 1: Comparison of the frequency of CRLF2 expression among B-ALL patients in first marrow relapse to that in newly diagnosed B-ALL patients.

From past COG studies for newly diagnosed B-ALL, it is estimated that 10% of standard risk (SR) and 21% of high risk (HR) patients will relapse. Assuming there are 2/3 SR and 1/3 HR newly diagnosed patients, it is estimated that around 49% and 51% of patients in first relapse will be NCI SR and HR, respectively. Given that about 7% and 12% of the SR and HR patients have high level CRLF2 expression via flow cytometery, the overall rate of high CRLF2 expression (which correlates with genomic lesions) in newly diagnosed B-ALL patients is about 10%.

The following table provides the power to detect a difference in rates of high CRLF2 expression between newly diagnosed and 1st relapse B-ALL patients when the rate of high CRLF2 expression of the 1st relapse patients is 13%, 15%, 18% and 20% (i.e. RR=1.3, 1.5, 1.8 and 2.0), respectively. The power calculations are based on a one-sample exact test at 5% significance levels (one-sided). A total of 426 B-ALL marrow relapse ALL patients [180 early (CR1<36 months) and 246 late (CR1 ≥36 months)] were considered in this power calculation.

Significance Level	Rate of high CRLF2 expression in relapse B-ALL pts (baseline rate = 10% among newly diagnosed pts)	Power (%)
5%	13%	60.0
	15%	92.4
	18%	99.9
	20%	100.0

Aim 2: Comparison of EFS in first marrow relapse B-ALL patients with high level CRLF2 expression vs. those without high level CRLF2 expression.

It is anticipated that a total of 180 early (CR1<36 months) and 246 late (CR1 ≥36 months) marrow B-ALL patients will be enrolled to AALL1331. According to past studies, the 3-year EFS of early and late marrow relapse patients are approximately 26% and 65%, respectively, giving an overall 3-year EFS of about 48%. Assuming the above rates of high-level CRLF2 expression and minimum 2 years of follow-up, the table gives powers for comparing EFS between patient groups with and without high level CRLF2 expression. The power calculations are based on the one-sided log-rank test at the 5% significance level.

Significance Level	CRLF2 high rate for 1st relapsed pre-B pts	Sample Size		3-year EFS rates		Power
		CRLF2 +	CRLF2-	CRLF2+	CRLF2-	
0.05	0.13	55	371	0.18	0.52	100.0
	0.13	55	371	0.20	0.52	99.9
	0.13	55	371	0.23	0.52	99.8
	0.13	55	371	0.26	0.51	99.0
	0.13	55	371	0.30	0.51	96.3
	0.13	55	371	0.33	0.50	88.8
	0.13	55	371	0.36	0.50	77.7
	0.13	55	371	0.39	0.49	55.1
	0.15	64	362	0.18	0.53	100.0
	0.15	64	362	0.20	0.53	100.0
	0.15	64	362	0.23	0.52	99.9
	0.15	64	362	0.26	0.52	99.6
	0.15	64	362	0.30	0.51	97.5
	0.15	64	362	0.33	0.51	93.5
	0.15	64	362	0.36	0.50	81.2
	0.15	64	362	0.39	0.50	65.0
	0.18	77	349	0.18	0.55	100.0
	0.18	77	349	0.20	0.54	100.0
	0.18	77	349	0.23	0.53	100.0
	0.18	77	349	0.26	0.53	99.9
	0.18	77	349	0.30	0.52	99.1
	0.18	77	349	0.33	0.51	95.7
	0.18	77	349	0.36	0.51	88.8

	0.18	77	349	0.39	0.50	69.6
	0.20	85	341	0.18	0.56	100.0
	0.20	85	341	0.20	0.55	100.0
	0.20	85	341	0.23	0.54	100.0
	0.20	85	341	0.26	0.54	100.0
	0.20	85	341	0.30	0.53	99.6
	0.20	85	341	0.33	0.52	97.8
	0.20	85	341	0.36	0.51	90.6
	0.20	85	341	0.39	0.50	72.1

APPENDIX X: ADDITIONAL INFORMATION FOR BLINATUMOMAB PHARMACODYNAMICS CORRELATIVE BIOLOGY STUDY

a) Rationale

For patients with relapsed/refractory ALL, response patterns to blinatumomab are essentially binary. Some patients have a striking response, with a systemic cytokine release syndrome (CRS, most notably IL-6) accompanying clearance of leukemic blasts and culminating in an MRD-negative remission, and others do not respond.[10,11,83] For patients that have received blinatumomab in the setting of MRD positivity (i.e., with very low tumor burden), response rates are generally higher and significantly less likely to be associated with CRS.[4,5] Attempts to correlate responses with various peripheral blood parameters (such as ALC and T-cell subset quantitation) have been largely unsuccessful in either setting, although the patient numbers have been limited.[3]

The bone marrow microenvironment contains various immunologic components that have been shown to either enhance or suppress cytotoxic T-cell effector response to tumor antigens. The bone marrow serves as a reservoir of memory T-cells with heightened antigen specificity compared to peripheral blood memory T-cells, and the bone marrow microenvironment is capable of effectively priming naïve T-cell responses.[84-86] However, the bone marrow is also a reservoir for suppressive regulatory CD4/CD25/FOXP3+ T-cells (T regs).[87] Comparative studies of bone marrow vs. peripheral blood in patients with myeloma have shown that marrow-infiltrating lymphocytes (MILs) are more effectively activated and expanded and are more capable of tumor-specific cytotoxicity than peripheral blood lymphocytes (PBLs).[88] In addition, bone marrow contains myeloid-derived suppressor cells (MDSCs) that have been shown to preferentially capture and present tumor associated antigens to T regs, resulting in tumor tolerance, and preventing the capture and presentation of these antigens by dendritic cells to activate tumor-specific cytotoxic effector T-cells.[89] IL-6 is among the key mediators that skews the marrow T-cell repertoire from T regs to cytotoxic effector T-cells.[90]

As has been suggested by previous studies, lymphocyte populations and cytokine profiles in the peripheral blood may also provide insight into responses[3] and adverse effects[11]. Since our study will include more patients than any blinatumomab trial to date, our study may be particularly well-suited to detect these associations.

b) Hypotheses and specific aims

The overall objective of this correlative study is to generate new knowledge regarding the mechanisms that determine the observed heterogeneity of clinical responses to blinatumomab in relapsed ALL, for which there are currently no biomarkers. While this study is preliminary and will not by itself establish biomarkers of blinatumomab response, it may identify putative biomarkers that can then be evaluated for validation in future studies.

We hypothesize that the balance of enhancing vs. suppressive components of the cytotoxic T-cell effector response in the bone marrow microenvironment (which we will directly measure using flow cytometry and single-cell RNA sequencing, and infer functionally using ex-vivo response assays) may be playing a particularly important role in determining the presence or absence of clinical response to blinatumomab. Specifically, we hypothesize that the bone marrow of patients that respond to blinatumomab (i.e., achieve complete continuous remission after treatment with blinatumomab) will be characterized by a relative predominance of cytotoxic memory/effector T-cells over T regs and MDSCs, , and ex-vivo induction of apoptosis and cytokine production, while the opposite pattern will be characteristic of the bone marrow of non-responders (i.e., those that relapse after treatment with blinatumomab).

- **Specific Aim 1**: To determine if the balance of enhancing vs. suppressive components of the cytotoxic T-cell effector response in the bone marrow microenvironment at baseline correlates with disease free survival (DFS) in relapsed ALL patients treated with blinatumomab.

We further hypothesize that lymphocyte populations and cytokine profiles in the peripheral blood at baseline and at post-treatment time points (hours 6 and 12 on day 1, and once on days 2, 7, 14 and 21) may also provide insight into adverse effects and clinical response, and so we will collect peripheral blood for flow cytometric characterization of lymphocyte subsets (including T-cell subsets as above, as well as circulating normal B-cells) and isolate plasma for multiplex cytokine profiling (including IL-6, IL-2R, IL-8, IL-10, MCP-1, MIP-1B, and INF-γ).

- **Specific aim 2**: To determine if peripheral blood patterns of lymphocyte subsets and cytokines, both at baseline and at post-treatment time points, correlates with incidence of blinatumomab-related reportable adverse events (see Section 5.2), and DFS in relapsed ALL patients treated with blinatumomab.

c) Methods

- Processing, cryopreservation and quality control

Refer to Section 13.5 for specimen collection and shipment. All blood and marrow samples will first be centrifuged to allow isolation of plasma. Plasma will be stored in 250 uL aliquots and stored at -80 C for subsequent batched assays. Cell pellets will be diluted in HBSS and centrifuged over Lymphocyte Separation Medium (LSM) to isolate mononuclear cells, then suspended in cryoprotectant solution and viably cryopreserved in liquid nitrogen in aliquots of 10e6 cells for subsequent batched assays. Assays will be performed as cohorts of five patients have provided a complete set of samples.

The Brown laboratory routinely processes blood and marrow specimens from cooperative group clinical trials and performs a wide variety of assays using plasma and viably cryopreserved cells. Samples are generally received in the laboratory within 48 hours of collection and processed immediately. Plasma and cells are sufficiently stable in transport under these conditions for the proposed assays. The flow cytometric assays are routinely performed in the Pardoll laboratory, which is collaborating on this project and has provided the processing protocol described above.

- Multiparameter flow cytometric measurement of lymphocyte subsets and MDSCs

Vials of viably cryopreserved marrow and blood cells will be thawed and washed and viable cells counted by trypan blue exclusion. Cells will then be stained with isotype controls and the following antibody panels, and analyzed in triplicate by flow cytometry
  - For lymphocyte subsets: CD3, CD4, CD8, CD19, CD20, CD45RO, CD45RA, HLADR, CD27, CD62L, CD25, CD28 and CD127.
  - For MDSCs (marrow only): Lin, HLA-DR, CD33, CD11b, CD14, CD15

The **endpoint** for this assay will be the relative percentage and absolute number (in cells/uL) and of each of the following:
  - T regs
  - Naïve T-cells
  - Memory T-cells (central vs. effector)
  - Activated T-cells
  - B-cells
  - Monocytic MDSC (marrow only)
  - Granulocytic MDSC (marrow only)

- Cytokine profiling in marrow and blood plasma

Vials of frozen plasma will be thawed and a panel of cytokines will be quantitated in triplicate using a custom cytometric bead array kit (custom BD CBA) designed to measure the following: IL-6, IL-2R, IL-8, IL-10, MCP-1, MIP-1B, and INF-γ. Isotype controls will serve as negative controls, and standard curves will be generated using control cytokine solutions.

The **endpoint** for this assay will be levels of each cytokine in pg/mL.

- Single cell RNA-seq

We will use the 10X Genomics scRNASeq platform, which allows mRNA expression profiling of up to ~12,000 individual cells per sample, as an unbiased approach to decompose the cellular composition of the BM microenvironment.

The **endpoint** for this assay will be the relative percentage of each of the following:
  - T regs
  - Naïve T-cells
  - Memory T-cells (central vs. effector)
  - Activated T-cells
  - B-cells
  - Monocytic MDSC (marrow only)
  - Granulocytic MDSC (marrow only)

- Functional ex vivo cytotoxic response assays to mimic in vivo response

We will co-incubate:
  - Thawed cryopreserved patient BM samples, initially enriched for mononuclear cells by centrifugation over lymphocyte separation medium (with healthy donor BM, available through institutional banking protocols, as control);
  - Human B-ALL CD19+ cell lines (REH, NALM6) as leukemia stimulation (with CD19- AML cellline HL60 as control); and
  - Blinatumomab (AMG 103) (with control BiTE MEC14 as control)

Co-culture for up to 24 hrs to allow for optimal T-cell activation and blinatumomab-mediated B-ALL killing. Harvest cells and measure cytotoxic effect of blinatumomab on the leukemia cell line using Annexin V staining in conjunction with CD19 staining to isolate B-ALL cells. The **endpoint** for this assay will be proportion of apoptotic (Annexin V positive) B-ALL cells (relative to normal controls).

Also, harvest cell culture supernatant to measure soluble cytokine protein expression using bead-based custom assays as above. The **endpoint** for this assay will be levels of each cytokine in pg/mL (relative to negative controls).

- Dynamic T-cell clonal repertoire (ImmunoSEQ)

Genomic DNA will be isolated from a small amount of each PB sample. We will send DNA for sequencing using the ImmunoSeq platform developed by Adaptive Biotechnologies, which uses genomic DNA to generate an absolute count of every TcR sequence present.

- Rationale for selection of methods and laboratories

  The methods described above are performed routinely in the Brown laboratory, and are likely to optimize the chances that the proposed studies will be successful.

d) Analysis and Statistical Considerations

- **Specific Aim 1:**

For the flow and scRNASeq assays, we will calculate ratio (R) of enhancing to suppressive components in bone marrow microenvironment for each patient as follows:

R = (# Memory T-cells + # Activated T-cells)/(# T regs + # MDSC)

For the ex-vivo assays, we will calculate an apoptosis index (AI) as follows:

AI = (% apoptosis with blina)/(% apoptosis with control BiTE)

We will use logistic regression to model outcome (no relapse vs. relapse) as a function of R. The Benjamin-Hochberg procedure will be used to control for multiple comparisons.

The anticipated result is that R and AI are negatively correlated with risk of relapse (i.e., a higher ratio of enhancing to suppressive components, and higher ex-vivo apoptosis induction, will reduce risk of relapse). If this anticipated result is seen, multivariate analysis that includes known associations with relapse (duration of first remission, MRD, etc.) will be performed to determine whether the marrow microenvironment ratio adds anything independent to known predictors of relapse in blinatumomab-treated patients.

This analysis will be performed on the entire cohort of patients treated with blinatumomab, and also separately on the HR/IR cohort and on the LR cohort.

We anticipate that a total of 156 evaluable patients will be treated with blinatumomab on this study (Section 9.2), of which 72 will be HR/IR and 84 will be LR. We assume that we will have 90% compliance with submission of the marrow sample. We assume that about 10% of submitted samples will fail analysis for technical reasons. Thus, we expect that our sample size for R will be 127 (59 HR/IR and 68 LR).

Since we are proposing to use standard assays (flow cytometric and scRNASeq quantification of marrow cell subsets, and ex-vivo apoptosis) in a novel way (calculation of enhancing vs. suppressive components), we do not have *a priori* knowledge of the expected range of observed ratios. As such, these studies are exploratory and definitive power calculations are not possible. However, if we assume the log(R) and log(AI) follows a Gaussian distribution with a mean of 0 and standard deviation of 1 (i.e., a standard normal distribution), and assuming an overall relapse rate of 50% for the trial, a sample size of 127 will have 80% power to detect an effect size of 0.5, using a 2-sided significance level of 0.05. For example, if we assume patients who eventually relapse have a mean R/AI of 1 (log(R/AI) = 0), then we would be able to detect that patients who do not eventually relapse have a mean R/AI of >3.16 (log(R/AI) = 0.5) or a mean R/AI of < 0.316 (log(R/AI) = - 0.5). This effect size is not unreasonable to expect. These calculations are based on methods from Hsieh, et al. Statist. Med. 17, 1623-1634 (1998).

The relationships between the ratios and rates of relapse will be described, and subsequent studies will be designed to validate these findings prospectively in the context of future clinical trials.

- **Specific Aim 2:**

There are 12 variables to be determined for each blood sample (7 samples per patient):
1) Total T-cell number
2) CD4 count
3) CD8 count
4) Memory T-cell count
5) Activated T-cell count
6-12) Level of each of 7 individual cytokines

For each of the 12 variables, we will determine the baseline value (BV; hour 0) and the maximal change value (MCV; value at the post-treatment timepoint for which the variable has increased or decreased to the greatest degree). For the MCV, a landmark approach will be used in which all cases are followed for 21 days, and the maximal change observed up to that point will be used to predict outcome *from that point forward* for all patients who are still observable up to that landmark time point.

There are 2 outcomes of interest:
1) Presence or absence of blinatumomab-related reportable adverse event
2) No relapse vs. relapse

As a first level analysis, we will use logistic regression to model each of the 2 outcomes as a function of each of the 12 variable's BV, and each of the 12 variable's MCV. The Benjamin-Hochberg procedure will be used to control for multiple comparisons.

The anticipated results are:

1) BV of some subsets of T-cell counts (memory T-cells, e.g.) are positively correlated with the risk of blinatumomab-related reportable adverse events, and negatively correlated with risk of relapse.
2) MCV of a subset of cytokines (IL-6 and INF-γ, e.g.) is positively correlated with the risk of blinatumomab-related reportable adverse events, and negatively correlated with risk of relapse.

Subsequent levels of analysis will attempt to characterize combinations of T-cell subset counts and cytokine levels that may perform better than individual variables in modeling the outcomes of interest.

If any of the anticipated results are seen with respect to the relapse outcomes, multivariate analysis that includes known associations with relapse (duration of first remission, MRD, etc.) will be performed to determine whether any of the T-cell subset/cytokine variables adds anything independent to known predictors of relapse in blinatumomab-treated patients.

This analysis will be performed on the entire cohort of patients treated with blinatumomab, and also separately on the HR/IR cohort and on the LR cohort.

We anticipate that a total of 156 evaluable patients will be treated with blinatumomab on this study (Section 9.2), of which 72 will be HR/IR and 84 will be LR. We assume that we will have at least 90% compliance with submission of the blood samples, and that about 10% of submitted samples will fail analysis for technical reasons. Thus, we expect that our sample size will be 127 (59 HR/IR and 68 LR).

Since we are proposing to use standard assays (flow cytometric quantification of blood T-cell subsets and cytokines) in a novel way (combining variables to model risks of adverse events and relapse after treatment with blinatumomab), we do not have *a priori* knowledge of the expected ranges of values for most variables. As such, these studies are exploratory and definitive power calculations are not possible.

However, some estimates based on specific assumptions are possible. If we assume that the baseline value for memory T-cell count for the entire study population follows a Gaussian distribution with a mean of 500/uL and a standard deviation of 100/uL, and we assume an overall relapse rate of 50% for the trial, a sample size of 127 will have 80% power to detect an effect size of 50/uL, using a 2-sided significance level of 0.05. For example, if we assume patients who eventually relapse have a mean BV memory T-cell count of 500, then we would be able to detect that patients who do not eventually relapse have a mean BV T-cell count of > 550/uL, or a mean BV T-cell count of < 450/uL. This effect size is not unreasonable to expect. These calculations are based on methods from Hsieh, et al. Statist. Med. 17, 1623-1634 (1998).

The relationships between the variable(s) and rates of adverse events/relapse will be described, and subsequent studies will be designed to validate these finding prospectively in the context of future clinical trials.

For the ImmunoSEQ experiments, we will assay n=72 samples (pre- vs. day 14, n=36 patients, n=18 relapse, n=18 no relapse). We hypothesize that “no relapse” samples will selectively demonstrate oligoclonal expansion of specific TcR clones. We will analyze patterns of T-cell clonal repertoire at baseline and changes after therapy, and look for associations of identified patterns and relapse/no relapse outcome. For significant associations, baseline/post-treatment patterns will be assessed for diagnostic value (e.g., correlation of baseline TcR repertoire with response) to be subsequently tested as a predictive biomarker of response. These assays will be descriptive and hypothesis-generating.

APPENDIX XI: ADDITIONAL INFORMATION FOR PROTEIN CELL STRESS PATHWAYS CORRELATIVE BIOLOGY STUDY

a) Rationale

Many excellent studies have focused on gene expression profiles in ALL.[51,52] However, changes in protein cell stress pathways and deregulated signal transduction pathways, have been much less well studied in ALL. There is an unmet need to learn more about chemotherapy-induced proteins expression changes in order to determine if specific proteins or protein clusters can help predict response to therapy. Specific protein expression patterns are likely to correlate with disease-free survival (DFS) and will enable us to identify specific populations at risk for relapse. Since it is very difficult to salvage patients after second relapse, one of the **goals** of this study is to determine which patients classified as low risk based on timing and site of relapse (Section 9.2) would benefit from being risk stratified instead into the high risk group. This would improve DFS in all patients with relapsed ALL. Relevant protein expression profiles will be validated in future COG trial for patients with relapsed ALL and (if the increase in correct risk assignment increases to meets statistical specifications) will be used, in conjunction with molecular classification systems, as an adjunct for risk assignment.

b) Hypotheses and specific aims

We **hypothesize** that activation of cell stress pathways and signal transduction pathways deregulated in ALL will correlate with DFS, and that the expression of specific proteins or proteins clusters will identify patients classified as low risk patients that would benefit from more intensive therapy. We have two **specific aims** to address these hypotheses:

1. To determine if specific protein expression profiles, as determined by reverse-phase protein lysate array (RPPA) and phosphoflow cytometry, correlate with clinical outcome (DFS)
2. To determine if alterations in specific groups of cell stress proteins can be used to generate a "high-risk" protein expression signature that identifies patients stratified to the low-risk group (based on time and site of relapse) that would benefit from stratification into the high-risk group.

c) The contributions that the proposed study will make to the current knowledge base

Little is known about the changes in cell stress proteins during chemotherapy. This analysis will contribute greatly to our current knowledge base by 1) determining if specific proteins or protein clusters correlate with response therapy, 2) increasing our knowledge about lymphoblast response to standard relapse chemotherapy, 3) allowing a better understanding of the biology-defined ALL subgroups, aiding the development of targeted therapies, and 4) allowing for the development of protein expression risk-classifiers that could be validated and utilized, along with gene expression profiling, to aid in risk stratification in subsequent relapsed clinical trials.

d) Relevant preclinical data

1. RPPA The Kornblau lab has analyzed two cohorts of adult AML using RPPA. The first, with 539 samples from 258 patients, was probed with 51 antibodies. the second, with 747 samples from 539 patients, was probed with 194 antibodies [91,92] These samples demonstrated that there were recurrent patterns of protein expression that correlated with outcome. Recent studies have shown that the analysis of RPPA and single cell network profiling by phosphoflow to can be analyzed using recently developed computational methods to provide a combined protein expression predictor.[93]
2. Phosphoflow cytometry: Studies have demonstrated that phosphoflow analyses can be predictive of outcome in pediatric acute leukemia. As an example, Redell et al. identified that responsiveness to IL-6 in pediatric AML was associated with superior survival.[94]

e) Relevant data from previous clinical studies

1. RPPA: Our preliminary data shows that we can reliably assess post-chemotherapy protein activation. Using a test set of 32 validated RPPA antibodies, we assessed changes in protein

expression in 27 COG pediatric leukemia patients following induction chemotherapy. We have determined that 1) CellSave tubes preserve protein expression profiles post-treatment, as shown by the relative stability of actin expression, but a decrease in p-AKT; and 2) that we can detect the heterogeneous patterns of changes in protein expression over time, including changes in AKT, m-TOR, MAPkinase and the FOXO3 pathway following treatment (Horton, Kornblau, personal communication).

2. Phosphoflow: Based upon phosphoflow studies from phase 1 COG and adult trials using these assays,[81,95] we anticipate that we can reliably identify signaling upregulation at baseline and during therapy using shipped specimens. In an institutional study of adults with AML treated with sirolimus and chemotherapy, inhibition of phosphorylated S6 correlated with clinical responses (Perl 2012).

f) The comparability of the methods proposed to those previously used, and the likelihood that the resulting data will be able to be compared with existing data. Analysis of RPPA is currently being performed using the same methods in AAML1031, and so these results should be directly comparable. Analysis of signal transduction networks will use identical methods to those piloted in ADVL1011 and ADVL1114, and so these should be comparable as well.

g) The reason for selection of the assay methodology.

1. RPPA is a technique which can quantitate protein expression from over 1000 patient samples on a single slide using validated antibodies.[96] The sample requirements are quite small; analysis of protein panels can be accomplished with as little as 200,000 cells per patient. This is the only assay able to provide detailed analysis of protein expression with this number of cells. This technique is also relatively resistant to protein degradation during shipping time. Blood is collected into CellSave preservation tubes, which we have shown can stabilize protein expression for up to 72 hours (Horton et al manuscript in review).
2. Similarly, phosphoflow cytometry is a very sensitive and reproducible technique, analyzing signal transduction abnormalities and the level of the single cell. Phosphoflow can also be used to analyze samples both at baseline and following chemotherapy treatment.[95]

h) The stability of the samples used for analysis:

Although no formal studies have been performed to determine stability, samples collected locally over the past 15 years from the Horton laboratory were examined by RPPA. There were no statistically significant differences in expression patterns or protein intensity based on the age of the sample (Kornblau, personal communication).

i) Technical performance characteristics

1. <u>Antibody validation</u>: RPPA antibodies have gone through extensive testing prior to inclusion on the array,[88] including both analytic validation, and assay validation with clinically relevant samples.[94] Antibodies validated for RPPA demonstrate specificity of signal and, in the case of phosphorylation or cleavage sensitive antibodies, context-specific validation performed in baseline and stimulated samples.[87] Validation steps have included: 1) antibody specificity as determined by immunoblot, 2) appropriate induction of phosphorylation/cleavage in response to known inducing agents, 3) correlation of RPPA signal with immunoblot expression (R>0.5), 4) acceptable sigmoidal curve fit of signal with sample dilution (analyzed using Super-Curve), 5) variable slope normalization[97] and, in cases of high background, 6) topographical normalization. Slides with unacceptable variances will be redone. RPPA has acceptable intra-assay and inter-assay variability, with intra-assay coefficients of variation (COV) of 6-15% and established inter-assay reproducibility. We have established standard operating procedures (SOPs) for sample processing, cell sorting and RPPA, and laboratory staff in both the Horton and Kornblau labs are experienced with the procedure.

b. Minimizing sample variability: based on prior testing samples received within 72h of collection from the patient have very similar protein expression patterns. (Horton, manuscript in preparation). Samples for RPPA will be collected in CellSave preservation tubes and mailed by FedEx courier to maintain protein integrity.

j) A description of the positive and negative controls

Controls will include normal adult and pediatric bone marrow, ALL cell lines, and ALL cells stimulated with chemotherapy as described .[91,92,98]

k) The experience that the investigators have with the assay

1. The Horton Laboratory will be collaborating with Dr. Steve Kornblau who has extensive experience with RPPA analysis of leukemia samples.[91,92,98]
2. The Tasian laboratory has extensive experience with phosphoflow cytometry analyses of primary patient leukemia specimens and of xenografted pediatric ALL and AML specimens.[99-102]

l) The methods of scoring and plan for analysis

a. Overview: Statistical analyses will be performed in a stepwise manner. First, we will analyze dynamic changes in protein activations following chemotherapy in all patients. The purpose is to discover natural groupings based on proteomic data only and to analyze the response of different biologically relevant signal transduction pathways during treatment. Second, we will examine protein clustering stratified by risk group and genetic subtype using supervised clustering analysis. Third, once clinical outcome data become available, we will analyze differences between treatment groups as they relate to DFS. This analysis will include unsupervised clustering methods.[91,92,98] Finally, we will generate a classifier(s) that best correlates with clinical outcome for the group as whole. While the primary objective of the study is DFS, we will also examine classifiers stratified by CR and relapse after study completion.

b. Statistical analysis**:** *Supercurve* algorithms were used to generate a single value from the 5 serial dilutions.[1] Loading controls[2] and topographical normalization[3] procedures will account for protein concentration and background staining variations. Analysis using unbiased clustering, perturbation bootstrap clustering and principle component analysis was then performed as previously described.[4] We (SM Kornblau, KR Coombes (MDACC) and A. Qutub (Rice University) have developed a novel modification of the Gap statistic, named "stability Gap" for selecting the optimal number of patient clusters from the range of possible clusters[103] This will be utilized to select the optimal number of clusters for comparison in outcomes analysis. Analysis typically places samples into 3-7 clusters for further analysis.

Comparison of the protein levels between paired samples will be done by performing paired t-tests. Association between protein expression levels and categorical clinical variables will be assessed in R using standard t tests, linear regression or mixed-effects linear models. Association between continuous variable and protein levels will be assessed by using Pearson and Spearman correlation and linear regression. Bonferroni corrections were performed to account for multiple statistical parameters for calculating statistical significance. The Kaplan-Meier method was used to generate the survival curves. Univariate and multivariate Cox proportional hazard modeling will be performed to investigate association with survival with protein levels as categorized variables using Statistica version 10 software (StatSoft, Tulsa, OK).

Other methods of analysis may include: Hierarchical Clustering, Principal Component Analysis (PCA), Self-Organizing Maps (SOM) and other class discovery methods.[104] Cluster stability will be accessed using reproducibility measures, including GAP,[105] and Stability Gap (manuscript in preparation), as well as robustness and discrepancy indices.[106] Differentially expressed proteins will be found using paired t-test as well as repeated measures, mixed effect ANOVA and ANOVA with contrasts. To determine if dynamic changes in specific protein pathways predict chemoresistance, we will use different regression and classification methods: Self Organizing Maps(SOM) (when no outcome is used), class prediction methods such as logistic regression, Support Vector Machine,[107] Random Forest,[108] Binary Tree Prediction, Bayesian Compound Covariate Predictor, and Discriminant analysis (http://linus.nci.nih.gov/techreport/Manual32.pdf).

Correlation of protein data with clinical variables
For Specific Aim 1, we will determine if there is a protein classifier prognostic for clinical outcome. After assignment of each patient to a risk group (based on time and site of relapse, n=403 low-risk, n=195 high-risk), samples will be stratified based on risk group and supervised clustering analysis will be performed based on clinical outcome variables (DFS).

For Specific Aim 2, we will determine which patients classified as low-risk (based on time and site of relapse) that would benefit from the more intensive chemotherapy given to high-risk patients (*i.e.*, reassignment to the high risk group). Following the generation of a risk-based protein expression classifier from all low-risk patients, further testing of the putative classifier will be based on performance characteristics using predefined cutpoints using ROC curves. Comparisons will be made using the AUC of ROC curves between standard risk stratification (time and site of relapse), MRD response, and the putative protein expression classifiers. Model overfitting and biased assessment of model performance will be minimized using bootstrap clustering as previously described [91]ROC curves will be generated for each stratification group, as well as for combinations of groups. Since attainment of CR following subsequent relapse is suboptimal,[109,110] and DFS is guarded following subsequent relapse, protein expression classifiers that maximize specificity with adequate sensitivity will be prioritized for further characterization.

m) The sites performing the correlative studies.
RPPA analysis will be performed in the Kornblau laboratory (MD Anderson Cancer Center, Houston TX) in collaboration with Dr. Horton. Phosphoflow analysis will be performed in the Tasian laboratory (Children's Hospital of Philadelphia).

n) Maintenance of quality control/assurance
Quality control will be maintained as previously described (Section i).[91,92,98]

o) Marker prevalence:
Since the methods will analyze multiple proteins (RPPA) and signal transduction pathways (phosphoflow), the prevalence of each marker will vary.

p) Estimate what proportion of patients on a therapeutic trial will have available sample for correlative study analysis; discuss possible biases.
Based on prior samples obtained for RPPA analysis from patients enrolled on the Phase 3 COG AML trial AAML1031, we estimate 40% of enrollments will provide an evaluable sample. As the most common reasons for sample dropout include technical issues (20% sample dropout due to sample quality, 40% due to samples not being drawn at site, 10% due to delays in shipping), lack of consent (10-15%), and insufficient lymphoblasts in peripheral blood to qualify for the study (20%). The latter 20% will have a bias toward high-risk disease and early marrow relapse.

q) Specify how any cutpoints will be determined
Specific aim 1: Performance characteristics and cutpoints will be made by comparison of AUC for ROC curves of available classifiers including standard risk stratification (time to and site of relapse) and MRD status. Since the objective of this study is to improve DFS, and DFS are can be estimated by

both the hazard ratio and probability of relapse. These numbers will become available from AALL0433, AALL01P2, AALL04P2 and AALL07P1 prior to trial completion. In order to identify patients likely to relapse, without increasing the risk of overtreating patients that require minimal therapy to achieve DFS, we will choose classifiers that maximize the true positive rate (sensitivity) while maintaining adequate specificity using statistically meaningful and clinically relevant cutpoints.

Specific aim 2: To determine if alterations in specific cell stress proteins can be used to generate a "high-risk" protein expression signature that identifies patients stratified to the low-risk (based on time and site of relapse) group that would have benefited from stratification into the high-risk group. For analysis of clinical utility, assumptions are usually made based on prior clinical trials for a similar pediatric relapsed ALL cohort. However, previous relapsed ALL COG studies have used different risk assessments, making *a priori* cutpoint determination challenging. Therefore, we will present basic principles for determining cutpoints for protein expression classifiers.

To aid in determining specific cutpoints, data from the recently completed AALL0433 clinical trial will be used to determine the prevalence of relapse and DFS in a similar LR population.

Since our aim is to improve the detection of true high risk patients misclassified into the low-risk group, we are interested in both the sensitivity and specificity of a putative protein classifier. The clinical usefulness of a protein expression classifier is dependent the proportion of low-risk patients that relapse (which can be estimated from the AALL0433 trial), as well as the proportion of low-risk patients with the "high-risk" putative classifier (determined by this study). Depending on the change in DFS for those correctly identified as having a "high-risk" protein classifier, the relative risks that can be used to identify the clinical usefulness can be estimated. Once these estimates are known, we can estimate both absolute risk reduction and decrease in relative risk of a low-risk patient with a "high-risk" classifier. Our goal would be to identify a classification signature that outperforms the current method of risk stratification (time and site of relapse) and/or allowed for an absolute risk reduction of at least 5% in the low-risk group.

r) Specify the statistical power of the correlative study

Sample size for basis of power calculations:
Based on power size calculations (Section 9.2.2), we anticipate that the study will enroll 598 patients, including 195 high-risk and 403 low-risk patients (based on time and site of relapse). Based on sample retrieval rate of 36% (see Section p), we will have 215 patients for protein expression analysis. For specific aim 1, all evaluable patients with usable sample would be considered for analysis (n=215). For the second aim, patients in the low-risk group (n=403) would be eligible if we receive usable sample. Based on sample recruitment in AAML1031 (36%), we expect to collect usable sample for 145 of the 403 evaluable patients. Although all sample set are required to have a 0h sample, about 82% of samples have the full data set (i.e. sufficient material for RPPA (CellSave preservation tubes) and phospho-flow (heparin tubes) at 0h, 6h, and 24h). For measures of changes over time, we anticipate that we will have 176 patient sets for SA1 and 118 patients for SA2. If the unfolded protein response is of interest, we expect that 90% of patients will have sufficient material for transcript analysis (n=193 for SA1, n=130 for SA2).

A summary of sample size data is provided in Table XI-1:

In addition to determining the effect sizes (defined as the difference in the corresponding mean outcomes over a common standard deviation) of assays between treatment groups, we will also compare protein classifiers with clinical outcome (MRD status and EFS). For the analysis of data across time (0h, 6h and 24h) we do not know *a priori* the most relevant time points to compare. Short-term differences could have returned to baseline by 24h, and may be most accurately estimated by changes between 0h and 6h. Long-term differences would be best measured by 0h-24h comparison. Complex changes, such as increase at 6h and decreases by 24h (seen with NF-κB after chemotherapy) are best measured using all three time points as descriptors. However, for simplicity we have provided the affect sizes for changes from 0h to 24h in Table XI-1.

Table XI-1: Effect-size differences based on sample size for protein cell stress pathways		
1. RPPA and phospho-flow studies	**Samples size (max)**	**Effect size ***
Baseline and change at 24h by treatment arm (blinatumomab therapy vs non-blinatumomab therapy; randomized patients only)	135 (67/tx group) 110 (55/tx group)	0.488 0.539
Baseline and change at 24h by MRD response (rate of MRD >= 0.1%: 62% for high-risk, 28% for low-risk; 39% overall)	<u>All patients:</u> 215 (84 MRD >=0.1%/ 131 MRD < 0.1%) for baseline comparisons. 176 (69 MRD >=0.1%/107 MRD < 0.1%) for changes over time. <u>Low-risk:</u> 145 (41 MRD >=0.1%/ 104 MRD < 0.1%) for baseline comparisons. 118 (33 MRD >=0.1%/85 MRD < 0.1%) for changes over time.	0.393 0.435 0.520 0.579
Baseline and change at 24h by 3-year DFS for randomized patients (estimated 3-year DFS 64%)	135 (86 no event/ 49 with event) for baseline changes. 110 (70 no event/ 40 with event) For changes over time.	0.505 0.560
Assumptions: alpha = 0.05, beta = 0.2.Abbreviations: grp= group, tx = treatment * With this effect size, the study will have at least 80% power at 2-sided significance level of 0.05 to detect such difference given the corresponding sample size.		

s) Corrections for multiple comparisons

We will use the Benjamini-Hochberg correction to account for multiple comparisons.[111]

t) Discuss how the results will have an impact on future studies.

This contribution will significantly impact future studies because it will add protein cell stress markers to the armamentarium of genetic mutations currently used to assess relapse risk, increasing the power of risk stratification, and identifying patients most likely to relapse and those most likely to benefit from therapies that target deregulated cell signaling pathways in relapsed ALL.

APPENDIX XII: COG STEM CELL COMMITTEE CONSENSUS GUIDELINES FOR ESTABLISHING ORGAN STAGE AND OVERALL GRADE OF ACUTE GRAFT VERSUS HOST DISEASE (GVHD)

Reporting Requirements for Acute GVHD in COG Studies

In an attempt to standardize reporting of acute GVHD, the COG Stem Cell Transplantation Committee has adopted a modification of guidelines that were originally developed at the University of Michigan.

Table 1 outlines standard criteria for GVHD organ staging. However, confounding clinical syndromes (such as non-GVHD causes of hyperbilirubinemia) may make staging GVHD in a given organ difficult. In addition, timing of organ specific symptoms affects whether that symptom is more or less likely to be true GVHD. Please refer to ***Tables 2 and 3*** to assist you in deciding whether to attribute these clinical findings to GVHD, especially in situations where a biopsy is not possible. For additional help, please see the text which follows the tables. ***Table 4*** reviews the approach to assessing GVHD as acute, chronic, or the overlap between the two.

Finally, *engraftment syndrome* will be reported separately from the GVHD scoring presented below.

Engraftment Syndrome

A clinical syndrome of fever, rash, respiratory distress, and diarrhea has been described, just prior to engraftment in patients undergoing unrelated cord blood and mismatched transplantation. If, in the judgment of the local investigator, a patient experiences this syndrome, details of the event should be reported when requested in the study CRFs.

Modified Glucksberg Staging Criteria for Acute Graft versus Host Disease

Table 1 Organ Staging (See tables and text below for details)

Stage	Skin	Liver (bilirubin)	Gut (stool output/day)
0	No GVHD rash	< 2 mg/dL	Adult: < 500 mL/day Child: < 10 mL/kg/day
1	Maculopapular rash < 25% BSA	2 - 3 mg/dL	Adult: 500 – 999 mL/day Child: 10 - 19.9 mL/kg/day ***Or persistent nausea, vomiting, or anorexia, with a positive upper GI biopsy.***
2	Maculopapular rash 25 – 50% BSA	3.1 - 6 mg/dL	Adult: 1,000 – 1,500 mL/day Child: 20 – 30 mL/kg/day
3	Maculopapular rash > 50% BSA	6.1 - 15 mg/dL	Adult: > 1,500 mL/day Child: > 30 mL/kg/day
4	Generalized erythroderma plus bullous formation and desquamation > 5% BSA	> 15 mg/dL	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

For GI staging: The "adult" stool output values should be used for patients > 50 kg in weight. Use 3 day averages for GI staging based on stool output. If stool and urine are mixed, stool output is presumed to be 50% of total stool/urine mix (see Section 3.2).

For stage 4 GI: the term "severe abdominal pain" will be defined as:
(a) Pain control requiring institution of opioid use, or an increase in on-going opioid use, PLUS
(b) Pain that significantly impacts performance status, as determined by the treating MD.

If colon or rectal biopsy is +, but stool output is < 500 mL/day (< 10 mL/kg/day), then consider as GI stage 0.

There is no modification of liver staging for other causes of hyperbilirubinemia

Overall Clinical Grade (based on the highest stage obtained):
Grade 0: No Stage 1 - 4 of any organ
Grade I: Stage 1 - 2 skin and no liver or gut involvement
Grade II: Stage 3 skin, or Stage 1 liver involvement, or Stage 1 GI
Grade III: Stage 0 - 3 skin, with Stage 2 - 3 liver, or Stage 2 - 3 GI
Grade IV: Stage 4 skin, liver or GI involvement

Table 2 Evaluating Liver GVHD in the Absence of Biopsy Confirmation (See Table 3.0 below)

Establishing liver GVHD with no skin or GI GVHD

No Skin/GI GVHD Day 0 - 35	**Assume no liver GVHD,** unless proven by biopsy	
No Skin/GI GVHD Day 36 - 100	If NO other etiology identified, NO improvement with stopping hepatotoxic medications/TPN: **Stage as liver GVHD**	If other etiology identified or improves with stopping hepatotoxic drugs/TPN: **Do not stage as liver GVHD**

Establishing liver GVHD with skin or GI GVHD and other cause of hyperbilirubinemia

Skin and/or GI GVHD present	Worsening bilirubin level (includes worsening just prior to onset of skin or GI tract GVHD) OR stable elevated bilirubin despite resolution of non-GVHD cause of increased bilirubin: **Stage as liver GVHD**	Stable or improving bilirubin after diagnosis of skin or GI GVHD, irrespective of treatment: **Do not stage as liver GVHD**

Changing liver GVHD stage with other cause of hyperbilirubinemia

Skin and GI GVHD stable, improving, or absent	Liver GVHD staging is carried forward without increase in stage until other disease process resolves (e.g., if TTP is diagnosed in the presence of stage 2 liver GVHD, the liver GVHD stage 2 is carried forward despite rising bilirubin level until TTP is resolved. If there is no liver GVHD – stage 0 – and new onset TTP, the stage 0 is carried forward until TTP is resolved).

Skin and/or GI GVHD worsening	**Liver GVHD is staged according to the Glucksberg criteria. The elevated bili is attributed to GVHD alone.** Thus, when skin or GI GVHD is worsening, there is no downgrading of liver GVHD staging for other causes of hyperbilirubinemia. (e.g., if TTP is diagnosed in the presence of stage 2 liver GVHD and worsening skin or GI GVHD, the liver is staged according to the actual bilirubin level even if some of the rise in bilirubin is attributed to TTP). Similarly, even if there is no liver GVHD at onset of a new process, (such as TPN cholestasis), but skin or GI GVHD worsen during that process, then liver GVHD is diagnosed and staged according to the height of the bilirubin. **There is one exception to this**: the diagnosis of TTP, with high LDH and **unconjugated** bilirubin precludes the diagnosis and staging of new liver GVHD in the absence of a confirmatory liver biopsy.

Table 3 Evaluating GI GVHD in the Absence of Biopsy Confirmation (See Table 4.0 below)

Establishing GI GVHD with new onset diarrhea and no skin or liver GVHD

No Skin/liver GVHD Day 0 through engraftment	Assume no GI GVHD, unless proven by biopsy	
No Skin/liver GVHD Engraftment through day 100	NO other etiology of diarrhea identified: **Stage as GI GVHD**	Any other etiology of diarrhea identified: **Do not stage as GI GVHD**

Establishing GI GVHD with pre-existing diarrhea and skin or liver GVHD

Skin and/or liver GVHD present	Worsening diarrhea (includes worsening just prior to onset of skin or liver GVHD) OR persistent diarrhea despite resolution of non-GVHD cause: **Stage as GI GVHD**	Improving diarrhea after the diagnosis of skin or liver GVHD (irrespective of treatment) OR persistent diarrhea without resolution of underlying non-GVHD cause: **Do not stage as GI GVHD**

Differentiating Acute GVHD, Chronic GVHD, and Overlap Syndrome

There is often confusion differentiating acute from chronic GVHD, especially in the setting of reduced intensity transplants, DLI and new prophylactic treatments. The NIH Working Group recently published new classifications for GVHD:

Table 4 Acute GVHD, Chronic GVHD, and Overlap Syndrome

Category	Time of Symptoms after HCT or DLI	Presence of Acute GVHD features	Presence of Chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤100 d	Yes	No
Persistent, recurrent, or late-onset acute GVHD	>100 d	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

- Scoring of acute GVHD may need to occur past day 100. In particular, patients should continue to be scored for acute GVHD when classic acute GVHD symptoms (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea - particularly if bloody and ileus) persist past day 100 or if identical symptoms previously scored as acute GVHD resolve and then recur within 30 days during immunosuppression taper but past day 100.

- Those patients being scored as having acute GVHD should NOT have diagnostic or distinctive signs of chronic GVHD.

- **Patients with both acute and chronic symptoms should be diagnosed as having Overlap Syndrome and scored according to their <u>chronic</u> GVHD score**.

Further Explanation of Criteria presented in Tables 2 and 3

1.0 <u>Assessment of Skin GVHD</u>

1.1 Presence or Absence of Skin GVHD: Skin GVHD will be considered present if a rash characteristic of acute GVHD develops after allogeneic marrow transplantation involving more than 25% of the body surface not clearly attributable to causes such as drug administration or infection. The extent of the body surface area involved can be estimated by the "Rule of Nines". In estimating the extent of skin GVHD, the area involved is calculated for individual anatomic areas, such as the arm or leg, and then the total is derived from a simple summation. Areas that are non-blanching should not be considered involved regardless of the overlying color of the rash (red, brown, etc.). Limited distribution erythema (with the exception of palms and soles) in the absence of associated rash elsewhere on the body will not be considered GVHD.

2.0 <u>Assessment of Liver GVHD</u>

2.1 Assessing for the Presence or Absence of Liver GVHD

A. Hyperbilirubinemia (total bilirubin ≥ 2.0 mg/dL) in the **absence** of other signs of acute GVHD in the skin or GI tract:

i) Day 0-35: If hyperbilirubinemia alone is present with no other signs of acute GVHD in other organ systems, acute GVHD will not be diagnosed based solely on laboratory abnormalities. Acute GVHD will be diagnosed if findings on histopathology studies of liver from a biopsy or autopsy are confirmatory.

ii) Day 35-100: If hyperbilirubinemia (must be conjugated bilirubin) is not improving or is exacerbated (especially if serum alkaline phosphatase is increased), in the absence of acute GVHD in other organ systems, no other etiologies are identified, and does not improve with discontinuation of hepatotoxic drugs, acute GVHD will be diagnosed. However, it is distinctly unusual to develop ascites or a coagulopathy in the early stages of acute GVHD of the liver alone. In the absence of histopathology studies of liver from a biopsy or autopsy specimen, ascites or a coagulopathy secondary to liver dysfunction will be considered to indicate the presence of another disease process (e.g. veno-occlusive disease). Recommended non-invasive studies to define an etiology for hyperbilirubinemia are:

a. Imaging of liver (CT or ultrasound)
b. Hepatitis screen (only if ALT is elevated)
c. PT
d. Blood cultures
e. Review of medication list for potentially hepatotoxic drugs
f. Review of risk factors for viral liver infection (HSV, CMV, VZV, adenovirus, EBV, HBV, and HCV)
g. Hemolysis screen

B. Pre-existing hyperbilirubinemia clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems.
   i) If pre-existing non-GVHD liver disease (documented clinically, by lab assessment, or by imaging studies) is stable or improving at the onset of signs of acute GVHD in other organs, then acute GVHD of the liver will not be considered to be present unless proven by liver biopsy or autopsy.
   ii) If hyperbilirubinemia worsens several days before or at the time of onset of signs of acute GVHD in other organ systems, GVHD will be considered to be present unless histopathology studies of liver are available and negative on a biopsy during that time interval or autopsy results exclude GVHD.
   iii) If hyperbilirubinemia persists and is not improving after resolution of a pre-existing non-GVHD liver disease process (e.g. localized infection of liver, systemic sepsis, biliary tract obstruction) when signs of acute GVHD are present in other organ systems or no other intervening cause has been diagnosed, then acute GVHD will be considered to be present in the absence of a new, clearly identifiable cause of non-GVHD liver disease or unless a liver biopsy or autopsy specimen is negative.

C. Prior acute GVHD in liver with new onset of a disease process that exacerbates pre-existing or recently resolved hyperbilirubinemia:
   i) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia and acute liver GVHD has been diagnosed and has been stable, improving, or resolved, then the liver will not be restaged for acute GVHD until the resolution or stabilizing of the concurrent disease process (i.e., the liver stage prior to the onset of the new disease process will be carried forward until the new disease process resolves). Example: Acute GVHD of the liver and gut is diagnosed on Day 20. Treatment of acute GVHD results in falling bilirubin levels to liver Stage 1. Sepsis or TTP develops with transient worsening of the hyperbilirubinemia. The liver stage is not increased, despite a higher bilirubin level, because the cause of worsening hyperbilirubinemia is attributed to sepsis or TTP.
   ii) If an etiology other than acute GVHD is clearly identified as causing or exacerbating hyperbilirubinemia in the presence of already worsening acute liver GVHD **or** GVHD of the skin or GI tract is simultaneously worsening, then the liver GVHD will be staged according to the actual bilirubin level, even though another cause of hyperbilirubinemia is present.

3.0 Assessment of GVHD of the Gastrointestinal Tract

3.1 Assessing for the Presence or Absence of GVHD of the Gastrointestinal Tract

A. Diarrhea ($\geq$ 500 mL/day in adults or > 10 mL/kg in pediatric patients) in the absence of other signs of acute GVHD in other organ systems
   i) Day 0-engraftment: If diarrhea alone is present without other signs of acute GVHD in other

organ systems, acute GVHD will not be considered present. Diarrhea will be attributed to acute GVHD if histopathology studies of gastrointestinal tract from a biopsy or autopsy are diagnostic.

ii) Engraftment-day 100: If diarrhea persists and is not improving, is exacerbated, or develops de novo in the absence of acute GVHD in other organ systems, histopathology studies of gut biopsies or from autopsy specimens are not available, and no other etiologies are clearly identified, acute GVHD will be considered to be the cause. A stool specimen should be examined to rule out infectious causes (e.g. rotavirus, adenovirus, and C. difficile toxin). It is recommended, if at all possible, that biopsies be obtained for diagnostic purposes.

B. Pre-existing diarrhea clearly attributed to an etiology other than acute GVHD in the presence of signs of acute GVHD in other organ systems:
   i) If pre-existing diarrhea caused by a process other than GVHD has been documented clinically or by lab assessment and is stable or improving at the onset of signs of acute GVHD in the skin or liver, then acute GVHD of the intestine will not be considered to be present in the absence of biopsy confirmation or autopsy report.
   ii) If diarrhea or gastrointestinal symptoms are already present, but worsen significantly at the time of onset of signs of acute GVHD in the skin or liver, GVHD will be considered present, unless biopsy or autopsy are negative.
   iii) If diarrhea persists after resolution of a pre-existing disease process with signs of acute GVHD present in other organ systems, GVHD will be considered present, unless biopsy or autopsy are negative.

C. Prior or present acute GVHD in other organ systems with new onset of diarrhea:
   If diarrhea is **clearly** attributable to an etiology other than acute GVHD (e.g., infection) and a history of acute GVHD exists or acute GVHD is present in other organ systems and is stable, then the gastrointestinal tract will not be evaluable for acute GVHD until the resolution or stabilizing of the other disease process (e.g., infection) in the absence of biopsy or autopsy confirmation.

D. Persistent anorexia, nausea or vomiting in the absence of signs of acute GVHD in other organ systems:

   Persistent anorexia, nausea or vomiting in the absence of other known causes of these symptoms will be considered Stage 1 acute GVHD if confirmed by endoscopic biopsy.

   If a biopsy is not possible (e.g. secondary to thrombocytopenia) but the clinical findings are compatible with acute GVHD, then the patient will be treated and recorded as having acute GVHD.

3.2 Staging of the Gastrointestinal Tract for the Severity of Acute GVHD

The severity of gastrointestinal tract GVHD will be staged according to modified Glucksberg criteria. To minimize errors caused by large day-to-day variation, diarrhea volume is measured as an average over 3 days and reported as the volume in milliliters per day. When urinary mixing is noted the stool volume will be considered half of the total volume unless nursing staff is able to give a better estimate from direct observation. Abdominal cramps are considered significant for staging if the severity results in a clinical intervention (e.g. analgesia, fasting, etc.). Blood in the stools is considered significant if the blood is visible or hematochezia/ melena is present and not clearly attributed to a cause other than GVHD (e.g. epistaxis/ hemorrhoids).

APPENDIX XIII: CTEP AND CTSU 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).

Downloading Site Registration Documents:

Site registration forms may be downloaded from the [insert study number] protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the COG link to expand, then select trial protocol #[insert study number]

Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For AALL1331 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.

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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 3000
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 XIV: POSSIBLE DRUG INTERACTIONS

The lists below <u>do not</u> 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.

<u>Cyclophosphamide</u>

Drugs that may interact with cyclophosphamide
• Allopurinol • Amiodarone • Carbamazepine • Cyclosporine • Digoxin • Efavirenz • Etanercept • Hydrochlorothiazide • Lumacaftor • Mifepristone • Pentostatin • Rifampin • Ritonavir • Warfarin

Food and supplements that may interact with cyclophosphamide
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

<u>Cyclosporine</u>

Drugs that may interact with cyclosporine

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Aripiprazole, citalopram, clozapine, escitalopram, fluoxetine, fluvoxamine, lurasidone, nefazodone, paliperidone, quetiapine, thioridazine, ziprasidone
• Antifungals
  ○ Amphotericin, caspofungin, fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole
• Anti-inflammatory, arthritis, or pain medications
  ○ Aspirin, celecoxib, hydroxychloroquine, ibuprofen, indomethacin, ketorolac, leflunomide, naproxen, meloxicam, oxaprozin, sulindac, tofacitinib, tolmetin
• Anti-rejection medications
  ○ Mycophenolate, sirolimus, tacrolimus

- Antiretrovirals and antivirals
  - Atazanavir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, letermovir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
- Anti-seizure medications
  - Carbamazepine, phenobarbital, phenytoin, primidone
- Cholesterol medications
  - Atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, ezetimibe, fenofibrate, gemfibrozil, colesevelam, griseofulvin
- Heart medications
  - Aliskiren, amiodarone, dronedarone, carvedilol, digoxin, diltiazem, eplerenone, verapamil, captopril, enalapril, lisinopril, ramipril
- Kidney medications
  - Acetazolamide, amiloride, spironolactone, triamterene
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Ambrisentan, bosentan, sitaxentan, aprepitant, allopurinol, colchicine, danazol, fluoxymesterone, modafinil, methyltestosterone, omeprazole, oxandrolone, mifepristone, natalizumab, pimozide, butabarbital, secobarbital, ivacaftor, octreotide

Food and supplements that may interact with cyclosporine
• Alfalfa • Black cohosh • Echinacea • Grapefruit, grapefruit juice, Seville oranges, star fruit • Red Yeast Rice • St. John's Wort

<u>Cytarabine (by vein)</u>

Drugs that may interact with cytarabine
• Clozapine, flucytosine, leflunomide, natalizumab

Food and supplements that may interact with cytarabine
• Echinacea

<u>Dexamethasone</u>

Drugs that may interact with dexamethasone

- Antibiotics
  - Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
- Antidepressants and antipsychotics
  - Aripiprazole, buproprion, citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, quetiapine
- Antifungals

- Caspofungin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- Arthritis medications
  - Leflunomide, tofacitinib
- Anti-rejection medications
  - Cyclosporine, sirolimus, tacrolimus
- Antiretrovirals and antivirals
  - Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
- Anti-seizure medications
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, amlodipine, dronedenarone, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Some oral contraceptives or birth control medications
- Many other drugs, including the following:
  - Aprepitant, artemether/lumefantine, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone

- Echinacea
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

Etoposide

Drugs that may interact with etoposide

- Antibiotics
  - Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
- Antidepressants and antipsychotics
  - Clozapine, nefazodone
- Antifungals
  - Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- Arthritis medications
  - Leflunomide, tofacitinib
- Anti-rejection medications
  - Cyclosporine
- Antiretrovirals and antivirals
  - Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir
- Anti-seizure medications
  - Carbamazepine, fosphenytoin, 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, ivacaftor, lomitapide, mifepristone, modafinil, natalizumab, pimozide

Food and supplements that may interact with etoposide
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Fludarabine

Drugs that may interact with fludarabine
• Clozapine, leflunomide, natalizumab, pentostatin, tofacitinib

Food and supplements that may interact with fludarabine
• Echinacea

Leucovorin

Drugs that may interact with leucovorin
• Glucarpidase • Some antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone) • Trimethoprim

Food and supplements that may interact with leucovorin
• Folic acid

Methotrexate (by mouth or by vein)

Drugs that may interact with methotrexate
• Some antibiotics (amoxicillin, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline, trimethoprim/sulfamethoxazole) • Some anti-inflammatory drugs (aspirin, ibuprofen, naproxen, ketorolac, sulfasalazine, sulindac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, fosphenytoin, gemfibrozil, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, ranolazine, retinoids, teriflunomide, theophylline, tolvaptan, 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

Mercaptopurine

Drugs that may interact with mercaptopurine
• Artiritis medications: leflunomide, tofacitinib • Other medications, such as adalimumab, allopurinol, azathioprine, certolizumab pegol, clozapine, etanercept, febuxostat, golimumab, infliximab, natalizumab, olsalazine, sulfasalazine, warfarin

Food and supplements that may interact with mercaptopurine
• Echinacea

Mitoxantrone

Drugs that may interact with mitoxantrone
• Aripiprazole • Clozapine • Cyclosporine • Eltrombopag • Leflunomide • Natalizumab • Tofacitinib

Food and supplements that may interact with mitoxantrone
• Echinacea

Mycophenolate mofetil

Drugs that may interact with mycophenolate mofetil
• Antacids such as aluminum hydroxide, magnesium hydroxide • Arthritis medications such as leflunomide, tofacitinib • Some antibiotics and antiviral medications (be sure to talk to your doctor about this) • Some heartburn medications including esomeprazole, lansoprazole, omeprazole, pantoprazole • Other medications such as cholestyramine, cyclosporine, natalizumab, oral contraceptives ("birth control"), probenecid, rifabutin, rifampin, rifapentine, sevelamer, tolvaptan, teriflunomide

Food and supplements that may interact with mycophenolate mofetil
• Echinacea • Vitamins and supplements containing magnesium

Pegaspargase

Drugs that may interact with pegaspargase
• Leflunomide, natalizumab, pegloticase, tofacitinib

Food and supplements that may interact with pegaspargase
• Echinacea

Tacrolimus

Drugs that may interact with tacrolimus

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Citalopram, clozapine, escitalopram, nefazodone, paliperidone, quetiapine, thioridizine, ziprasidone
• Antifungals
  ○ Caspofungin, fluconazole, isavuconazole,itraconazole, ketoconazole, posaconazole, voriconazole
• Anti-inflammatory, arthritis, or pain medications
  ○ Leflunomide, tofacitinib
• Anti-rejection medications
  ○ Cyclosporine, sirolimus
• Antiretrovirals and antivirals
  ○ Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir, tipranavir
• Anti-seizure medications
  ○ Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart medications
  ○ Amiodarone, diltiazem,dronedenarone, disopyramide, procainamide, propafenone, quinidine, ranolazine, sotalol, verapamil
• Kidney medications
  ○ Amiloride, spironolactone, triamterene
• Stomach and reflux medications
  ○ Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Aprepitant, bosentan, cobicistat, colchicine, conivaptan, mifepristone, modafinil, natalizumab, pimozide

Food and supplements that may interact with tacrolimus
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

Thioguanine

Drugs that may interact with thioguanine
• Arthritis medications: leflunomide, tofacitinib • Other medications, such as adalimumab, allopurinol, azathioprine, certolizumab pegol, clozapine, etanercept, golimumab, infliximab, natalizumab, olsalazine, sulfasalazine

Food and supplements that may interact with thioguanine
• Echinacea

Thiotepa

Drugs that may interact with thiotepa
• Arthritis medications like leflunomide or tofacitinib • Other medications like bupropion, clozapine, efavirenz, methadone, promethazine, or natalizumab

Food and supplements that may interact with thiotepa
• Echinacea

Vincristine

Drugs that may interact with vincristine

• Antibiotics
   o Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antifungals
   o Fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
   o Leflunomide, tocilizumab, tofacitinib
• Anti-rejection medications
   o Cyclosporine
• Antiretrovirals and antivirals
   o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lapatinib, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir, tenofovir, tipranavir
• Anti-seizure medications
   o Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart medications
   o Amiodarone, carvedilol, diltiazem, dronedenarone, propafenone, quinidine, ranolazine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:

○ Aprepitant, bosentan, cobicistat, conivapatan, deferasirox, fosnetupitant, ivacaftor, mifepristone, modafinil, natalizumab, nefazodone, netupitant

Food and supplements that may interact with vincristine
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

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