COG-AALL1331: Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND#100135, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
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.

___1. 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.

___2. 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

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	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. 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).

___4. Age - Patients ≥1 year and < 31 years of age at the time of relapse will be eligible.

___5. 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.

___6. Prior Therapy - Please see Section 4.1.2 for the concomitant therapy restrictions for patients during treatment.
- No waiting period for patients who relapse while receiving standard Maintenance therapy
- 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.
- 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.
- 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.
- Stem cell transplant or rescue: Patient has not had a prior stem cell transplant or rescue.
- Patient has not had prior treatment with blinatumomab.
- 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).

___7. 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

___8. Organ Function Requirements
- Adequate Renal Function Defined As:
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m2 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 (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Adequate liver function defined as a direct bilirubin < 3.0 mg/dL.
- Adequate Cardiac Function Defined As:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by radionuclide angiogram.

EXCLUSION CRITERIA:

___1. Patients with Philadelphia chromosome positive/BCR-ABL1+ ALL are not eligible
___2. Patients with Burkitt Leukemia/Lymphoma or mature B-cell leukemia are not eligible
___3. Patients with T-Lymphoblastic Leukemia (T-ALL)/Lymphoblastic Lymphoma (T- LL) are not eligible
___4. Patients with B-Lymphoblastic Lymphoma (B-LL) are not eligible
___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.
___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.
___7. Patients with known HIV infection.
___8. Patients with known allergy to mitoxantrone, cytarabine, or both etoposide and etoposide phosphate (Etopophos).
___9. Lactating females who plan to breastfeed.
___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.
___11. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.
___12. 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)
___13. 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.)

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 $\geq$ 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 $\geq$ 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.

REQUIRED OBSERVATIONS:
STUDIES TO BE OBTAINED
HR/IR Patients

- Hx/PE with VS/Wt (BSA)
- CBC/diff/plts
- Bilirubin, ALT, creatinine, BUN
- Local Bone Marrow (BM) Evaluation [1]
- Bone Marrow (BM) for Immunophenotyping [2, 5]
- CSF cell count and cytospin
- Echocardiogram
- Pregnancy test [3]
- Testicular exam
- Testicular biopsy [4]

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

LR Patients

- Hx/PE with VS/Wt (BSA)
- CBC/diff/plts
- Bilirubin, ALT, creatinine, BUN
- Local Bone Marrow (BM) Evaluation [1]
- Bone Marrow (BM) for Immunophenotyping [2, 5]
- CSF cell count and cytospin
- Echocardiogram
- Pregnancy Test [3]
- Testicular Biopsy [4]

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

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
Marrow and Blood at pre study, Blood on Day 1. Also see Section 13.0

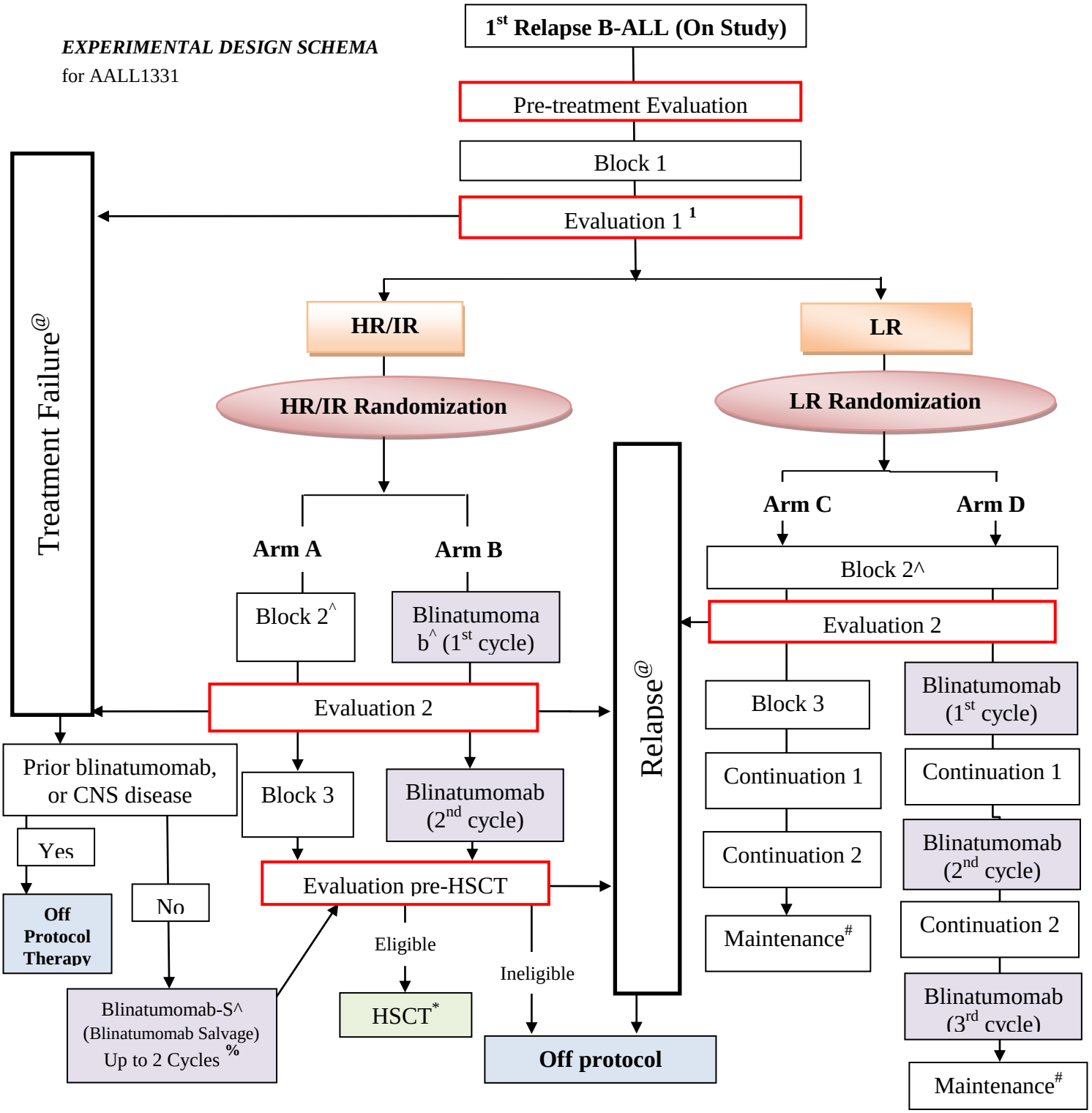
For patients who are not having a BM for medical reasons at diagnosis or other time points and have an absolute blast count of at least 1,000/μL, PB may be submitted to the Reference Laboratories instead of BM. Submit 2 mL of PB for each 1 mL of required marrow.

Required Samples:
Bone Marrow to Borowitz for immunophenotyping (MRD)

Optional Samples:
- Marrow and Blood for banking
- See 13.6 for protein cell stress pathyways blood samples

TREATMENT PLAN:

EXPERIMENTAL DESIGN SCHEMA
for AALL1331



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 Post Block 1 Evaluation Callback (completed via OPEN)
2 End Block 2 Callback (completed via OPEN, see Section 3.1.6-3.1.7) for eligible and consenting TF patients on Arm A
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.