

COG-AALL1731: A Phase 3 Trial Investigating Blinatumomab (IND# 117467, NSC# 765986) in Combination with Chemotherapy in Patients with Newly Diagnosed Standard Risk or Down syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients with Localized B-Lymphoblastic Lymphoma (B-LLy)

FAST FACTS

Eligibility Reviewed and Verified By

MD/DO/RN/LPN/CRA Date _____

MD/DO/RN/LPN/CRA Date _____

Consent Version Dated _____

Timing

PATIENTS WITH B-ALL MUST CONSENT TO ELIGIBILITY SCREENING (PART A) AND BE ENROLLED ON PROJECT:EVERYCHILD (APEC14B1) BEFORE RECEIVING ANY SYSTEMIC PROTOCOL THERAPY ON AALL1731. (For the purpose of this study, “systemic protocol therapy” does not include the first dose of intrathecal chemotherapy or selected cases of steroid pretreatment). **PATIENTS THAT BEGIN SYSTEMIC PROTOCOL THERAPY ON AALL1731 PRIOR TO ENROLLMENT ON APEC14B1 ARE INELIGIBLE FOR AALL1731.**

B-LLy PATIENTS MUST SUBMIT SAMPLES FOR CENTRAL RETROSPECTIVE PATHOLOGY REVIEW. SPECIFIC INSTRUCTIONS REGARDING REQUIRED TISSUE SUBMISSION ARE OUTLINED IN SECTION 13.0. EVERY EFFORT SHOULD BE MADE TO ACQUIRE AS MUCH TISSUE AS POSSIBLE.

PATIENTS WITH B-LLy ARE ELIGIBLE FOR PROJECT:EVERYCHILD (APEC14B1) BUT ENROLLMENT IS NOT AN ELIGIBILITY REQUIREMENT FOR AALL1731.

All Patients:

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

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 protocol directed systemic therapy unless otherwise indicated in the eligibility section below. Diagnostic biopsy for B-LLy must be performed within 14 days of starting therapy.

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

Staged Consent

Informed consent will be obtained at critical stages of treatment for the different groups of patients on this study.

Summary of Required Consents for AALL1731:

Consent Document	Time Point for Obtaining Consent	Population for Consent
APEC14B1	Prior to the start of Protocol Therapy	B-ALL (required) B-LLy (optional, but strongly encouraged)
Induction	Prior to the start of Induction	SR B-ALL DS B-ALL
Post-Induction	Prior to the start of Consolidation	SR-Fav B-ALL DS SR-Fav B-ALL (non-randomized)
		SR-Avg B-ALL DS SR-Avg B-ALL (possibility of randomization)
		SR-High B-ALL (possibility of randomization)
		DS-High B-ALL (non-randomized)
All phases of therapy	Prior to the start of Induction	B-LLy and DS B-LLy

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.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to protocol directed systemic therapy unless otherwise indicated. Diagnostic biopsy for B-LLy must be performed within 14 days prior to enrollment. Imaging studies, if applicable, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

- ___ 1. Eligibility Screening
All B-ALL patients must be enrolled on APEC14B1 and consented to Eligibility Screening (Part A) prior to treatment and enrollment on AALL1731.
APEC 14B1 is not a requirement for B-LLy patients. B-LLy patients may directly enroll on AALL1731 and MUST submit eligibility studies as outlined in Section 13.0.

- ___ 2. Age at diagnosis
Patients must be ≥ 365 days and < 10 years of age (B-ALL patients without DS)
Patients must be ≥ 365 days and ≤ 31 years of age (B-ALL patients with DS)
Patients must be ≥ 365 days and ≤ 31 years of age (B-LLy patients with or without DS)

- ___ 3. White Blood Cell Count (WBC) Criteria
• B-ALL patients without DS must have an initial white blood cell count $< 50,000/\mu\text{L}$
• B-ALL patients with DS are eligible regardless of the presenting WBC

- ___ 4. Diagnosis
Patient has newly diagnosed B-cell ALL, with or without Down syndrome: $> 25\%$ blasts on a BM aspirate;

OR if a BM aspirate is not obtained or is not diagnostic of B-ALL, the diagnosis can be established by a pathologic diagnosis of B-ALL on a BM biopsy;

OR a complete blood count (CBC) documenting the presence of at least $1,000/\mu\text{L}$ circulating leukemic cells;

OR patient has newly diagnosed B-cell LLy Murphy Stages I or II (see Appendix VII for staging), with or without Down syndrome.

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

Assent: The CIRB has determined that the assent of children age 14 and older is a necessary condition for proceeding with the research.

EXCLUSION CRITERIA:

- ___ 1. Patient must not have secondary ALL that developed after treatment of a prior malignancy with cytotoxic chemotherapy. Note: patients with Down syndrome with a prior history of transient myeloproliferative disease (TMD) are not considered to have had a prior malignancy. They would therefore be eligible whether or not the TMD was treated with cytarabine.
- ___ 2. Prior Therapy
With the exception of steroid pretreatment (defined in [Section 3.3.3](#)) or the administration of intrathecal cytarabine, patients must not have received any prior cytotoxic chemotherapy for either the current diagnosis of B-ALL or B-LLy or for any cancer diagnosed prior to initiation of protocol therapy on AALL1731.
Please see [Section 4.1.4](#) for the concomitant therapy restrictions for patients during treatment.
- ___ 3. For patients receiving steroid pretreatment (See [Section 3.3.3](#)), the following additional exclusion criteria apply:
 - Non-DS B-ALL patients must not have received steroids for more than 24 hours in the 2 weeks prior to diagnosis without a CBC obtained within 3 days prior to initiation of the steroids.
 - DS and non-DS B-LLy patients must not have received > 48 hours of oral or IV steroids within 4 weeks of diagnosis.
- ___ 4. B-ALL who do not have sufficient diagnostic bone marrow submitted for APEC14B1 diagnostic testing and who do not have a peripheral blood sample submitted containing >1,000/ μ L circulating leukemia cells.
- ___ 5. Patient must not have acute undifferentiated leukemia (AUL).
- ___ 6. Non-DS B-ALL patients with CNS3 leukemia (see definition in [Section 3.3.4](#), CNS status must be known prior to enrollment)
Note: DS patients with CNS3 disease are eligible but will be assigned to the DS-High B-ALL arm. CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in [Section 3.3.3](#).
- ___ 7. Non-DS B-ALL patients with testicular leukemia. (Note: DS patients with testicular disease are eligible but will be assigned to the DS-High B-ALL arm)
- ___ 8. For LLy patients, the following additional exclusion criteria apply:
 - T-Lymphoblastic Lymphoma.
 - Morphologically unclassifiable lymphoma.
 - Absence of both B-cell and T-cell phenotype markers in a case submitted as lymphoblastic lymphoma.
 - CNS positive disease (see [Section 3.3.4](#) for details) or testicular involvement.
 - M2 (5%-25% blasts) or M3 (>25% blasts) marrow.
- ___ 9. Patients with known Charcot-Marie-Tooth disease.
- ___ 10. Patients with evidence of a MYC translocation associated with mature (Burkitt) B-cell ALL, regardless of blast immunophenotyped.
- ___ 11. Female 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.
- ___ 12. Lactating females who plan to breastfeed their infants.
- ___ 13. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

REQUIRED OBSERVATIONS:

Required Observations in Induction – Non-DS SR B-ALL

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

- a. Hx/PE/Wt/Ht/BSA (Note: Height is only required at the beginning of this course)
- b. CBC/diff/platelets
- c. Creatinine
- d. Total bilirubin, ALT
- e. CSF cell count and cytospin (obtain with each IT administration)
- f. *TPMT* and *NUDT15* genotype (*TPMT* highly recommended for all subjects; *NUDT15* is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects).
- g. **Required peripheral blood (PB).** Send Day 8 PB sample to COG-approved ALL Flow Cytometry Lab for MRD testing. This sample should be drawn prior to Day 8 IT MTX or VCR. This sample should be drawn no more than one day early or late. **If Day 8 PB sample is not obtained and shipped to COG-approved ALL flow cytometry reference laboratory, then the patient will not be eligible to continue on a COG ALL trial following completion of Induction therapy. This sample is absolutely essential.** See [Section 14.1](#) for a list of COG-approved labs.
- h. **Required bone marrow (BM)** evaluation to assess response by morphology (at local institution), flow minimal residual disease (MRD), and high-throughput sequencing (HTS) MRD. BM specimen for flow MRD testing should be sent to a COG-approved flow MRD laboratory (See [Section 14.1](#) for a list of labs). BM specimen for HTS MRD should be sent to the COG ALL Molecular Reference Lab (See [Section 14.2](#) for additional details). This sample should be drawn no more than two days early or late, with a preference for early rather than late to avoid potentially missing a high MRD level. **If Day 29 BM sample is not obtained and shipped to a COG-approved flow lab for MRD testing and to the COG ALL Molecular Reference lab then the patient will not be eligible to continue on a COG ALL trial following completion of Induction therapy. These samples are absolutely essential.**
- i. For patients who consent, send Day 29 PB and BM specimens to the ALL Molecular Reference Lab for cell banking. Done through APEC14B1. Refer to the APEC14B1 protocol for additional details.
- j. For patients who consent to optional biobanking for EOI PB, send specimen to the COG ALL Molecular Reference Lab. Refer to [Section 14.3](#) for additional details.
- k. For patients who consent, send CSF specimens to the ALL Molecular Reference Lab for optional biobanking. Refer to [Section 14.7](#) for additional details.
- l. For patients who consent, complete assessment for the Household Material Hardship study prior to Day 29 LP. Refer to [Section 17.1](#) for additional details.

TREATMENT PLAN:

See Section 4

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

For B-ALL patients, 5cc marrow, 5cc blood at diagnosis to COG Molecular Lab (for future HTS options) If a diagnostic marrow sample is not obtained 10cc of peripheral blood with at least 1,000/ μ L circulating leukemic cells must be submitted for future HTS testing. A banked sample of diagnostic material is required for the end of induction HTS testing.

Day 8 – blood to ATL

Day 29 – bone marrow to COG Molecular Lab (plus optional banking)*

*The submission of a bone marrow sample for MRD testing by HTS is required at the end of Induction therapy for NCI SR B-ALL patients (DS and non-DS). Sites must order this test using the Adaptive Portal. See the Adaptive Portal Walk-Through Slides and Adaptive SOP for instructions for initial set-up of Adaptive Portal account, ordering high-throughput sequencing (HTS) MRD assessments, and interpreting HTS MRD results.

NOTE: Although all patients risk-stratified as SR-Avg must have this sample sent to the COG ALL Molecular Reference Laboratory, those patients with Double Trisomies 4 and 10 who are determined to have EOI flow MRD 0.01-<0.1% do not need to have HTS testing ordered through the Adaptive Portal. These patients are considered to have sufficiently high EOI MRD and will therefore be randomized.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix XV.

MATERIALS TO SEND FOR RETROSPECTIVE CENTRAL PATHOLOGY REVIEW

H&E Stained Slides	• 2 H&E stained slides from each block
Paraffin Blocks Send one of the following:	• Surgical biopsy specimen: One paraffin block (formalin preferred) • Cytology cell block: One paraffin block (specify fixative) • If blocks cannot be sent, submit twenty unstained and unbaked sections (4 µm) from 1 representative block on salinized slides.
Cytology Slides Send the following:	• One stained (Romanowsky stain) and • 10 unstained slides
Specimens Demonstrating Relapse	• A recut slide (hematoxylin and eosin stain) from each of the paraffin blocks from each of these types of biopsy specimens • Corresponding pathology report
Pathology Reports Send all of the following	• Final reports of biopsy and bone marrow specimens (even if negative) • All immunophenotyping reports of diagnostic biopsy and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available) • Results of any genotypic studies (i.e., gene rearrangement studies) • Results of any cytogenetic (karyotype and FISH) analysis
Collection Forms	• Pathology Data Collection Form (Institutional Pathology Form) • Transmittal Form