

**COG-AALL1231: A Phase III Randomized Trial Investigating Bortezomib (NSC# 681239; IND# 58443) on a Modified Augmented BFM (ABFM) Backbone in Newly Diagnosed T- Lymphoblastic Leukemia (T-ALL) and T- Lymphoblastic Lymphoma (T-LLy)**

**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**

- **T-ALL PATIENTS MUST BE ENROLLED ON AALL08B1 OR PROJECT: EVERY CHILD (APEC14B1, IF OPEN FOR CLASSIFICATION OF NEWLY DIAGNOSED ALL PATIENTS) BEFORE ENROLLING ON AALL1231.**

**PATIENTS WITH T-LLY ARE INELIGIBLE FOR AALL08B1.**

**EVERY EFFORT SHOULD BE MADE TO ACQUIRE AS MUCH TISSUE AS POSSIBLE. SPECIFIC INSTRUCTIONS REGARDING TISSUE SUBMISSION ARE OUTLINED IN SECTION 13.6. OF NOTE, T-LLY SPECIMENS, INCLUDING DIAGNOSTIC MRD, ARE SUBMITTED AS PER THE INSTRUCTIONS IN AALL1231 AS OUTLINED IN SECTIONS 13 AND 14.**

- **Study enrollment:** Patients are randomized to receive or not receive bortezomib before protocol therapy begins. Accordingly, **Patients must be enrolled on AALL1231 before protocol therapy begins.** The only exceptions are the first dose of intrathecal chemotherapy may be given before enrollment when administered as part of the initial diagnostic lumbar puncture, and in select circumstances, corticosteroids or emergent radiation may be given before enrollment as defined in Section 3.2.2 and Section 3.3.  
The date protocol therapy is projected to start must be no later than *five (5)* calendar days after the date of study enrollment.
- **Initiation of systemic protocol therapy:** Systemic Induction therapy, with the exception of steroid pretreatment as outlined below (Section 3.2.2), must begin within 72 hours of the first dose of intrathecal chemotherapy.

2. Randomization will take place at the time a patient is enrolled via OPEN. Randomization will occur prior to Induction therapy for all patients (T-ALL and T-LLy).

**3. Patient Eligibility Criteria**

**All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. 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.

**4. INCLUSION CRITERIA**

- **Classification Study:**
  - T-ALL: T-ALL patients must be enrolled on AALL08B1 or Project: Every Child (APEC14B1, if open for the classification of ALL patients) prior to treatment and enrollment on AALL1231.
- **Age at Diagnosis:** All patients must be > 1 and < 31 years of age.
- **Diagnosis:** Patients must have newly diagnosed T-Lymphoblastic Leukemia (T-ALL) or T-Lymphoblastic Lymphoma (T-LLy) Stages II-IV (see Appendix VIII).  
For T-LLy patients with tissue available for flow cytometry, the criterion for diagnosis should be analogous to T-ALL. For tissue processed by other means (i.e. paraffin blocks), the methodology and criteria for immunophenotypic analysis to establish the diagnosis of T-LLy defined by the submitting institution will be accepted. See pathologic diagnosis recommendation in Section 13.4 and required studies in Table 7.2 including diagnostic bone marrow MRD.

### EXCLUSION CRITERIA:

- \_\_\_1. **Prior Therapy:** Patients must not have received any cytotoxic chemotherapy for either the current diagnosis of T-ALL, T-L-Ly or for any cancer diagnosis prior to the initiation of protocol therapy on AALL1231, with the exception of:
  - Steroid pretreatment [60mg/m<sup>2</sup>/day prednisone (or 48 mg/m<sup>2</sup>/day of methylprednisolone) for ≤ 120 (5 days) hours in the 7 days prior to initiating Induction chemotherapy or for ≤ 336 hours (14 days) in the 28 days prior to initiating Induction chemotherapy]. Prior exposure to ANY steroids that occurred > 28 days before the initiation of protocol therapy does not affect eligibility.
  - Intrathecal cytarabine (The CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in Section 3.3) Systemic chemotherapy must begin within 72 hours of this IT therapy; or
  - Pretreatment with hydroxyurea; or
  - 600 cGy of chest irradiation, if medically necessary.Pre-treatment with dexamethasone in the 28 days prior to initiation of protocol therapy is not allowed with the exception of a single dose of dexamethasone used during sedation to prevent or treat airway edema. Inhalation steroids and topical steroids are not considered pretreatment.
- \_\_\_2. **Peripheral neurotoxicity:** Pre-existing ≥ grade 2 sensory or motor peripheral neurotoxicity.
- \_\_\_3. **Seizures disorder:** Uncontrolled seizure disorder
- \_\_\_4. Diagnosis of Down syndrome (Trisomy 21)
- \_\_\_5. 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.
- \_\_\_6. Lactating females who plan to breastfeed.
- \_\_\_7. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.
- \_\_\_8. Patient has hypersensitivity to bortezomib, boron, or mannitol.
- \_\_\_9. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
- \_\_\_10. Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and within 30 days of any dose of bortezomib.

### REQUIRED OBSERVATIONS:

#### Required Observations: Arms A and B T-ALL ONLY

- Hx/PE with VS/Wt (BSA)
- CBC/diff/plts
- CSF cell count & cytopsin
- Bilirubin (total and direct), ALT, AST creatinine
- Performance Status
- Pregnancy Test <sup>1</sup>
- Bone Marrow MRD and cytomorphology Assessment <sup>\$</sup>
- Chest x-ray

#### Required Observations: Patients receiving bortezomib (Arm B) T-ALL ONLY

- Pulse Oximetry (O2 saturation), Chest x-ray
- Electrolytes including PO<sub>4</sub>

#### Optional Observations: Arms A and B T-ALL ONLY (All optional studies require patient consent)

- Bone Marrow (BM)/Peripheral Blood (PB) for bortezomib response (ETP-ALL) study <sup>2</sup>
- Cell Banking <sup>3</sup>

1. 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
2. See Section 15.1 for details. Peripheral blood can be substituted if >80% blasts. Please send AALL1231 specimen transmittal form and institutional immunophenotype report with the sample submission to the laboratory
3. See AALL08B1 protocol or Project: Every Child Manual of Procedures for details. Also note that specimens are requested at time of relapse as part of AALL08B1 or Project: Every Child.

\$ Done as part of AALL08B1 or Project: Every Child

**Required & Optional Clinical, Laboratory and Disease Evaluations: Diagnosis, Induction, Consolidation: Arm A and Arm B: T-LLy ONLY**

**Required Observations: Arms A and B T-LLy ONLY**

- Hx/PE with VS/Wt (BSA)
- CBC/diff/plts
- CSF cell count & cytospin
- Bilirubin (total and direct), ALT, AST, creatinine
- Performance Status
- Pregnancy Test <sup>1</sup>
- Chest & neck CT/Chest x-ray <sup>2</sup>
- Abdomen/Pelvis CT or MRI <sup>6</sup>
- Bone scan <sup>4</sup>
- Diagnostic Biopsy/Cytology <sup>3</sup>
- Bone Marrow MRD Assessment <sup>5</sup>
- Bilateral bone marrow aspirate and biopsy cytomorphology <sup>3, 5</sup>

**Optional Observations: Arms A and B T-LLy ONLY (All optional studies require patient consent)**

- PET Scan (Recommended)
- Cell Banking <sup>5</sup>

1. 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
2. Obtain chest CT for all T-LLy patients at Baseline and at end-Induction. The baseline chest CT may be delayed until the patient is stable. If patient has CR at end-Induction, no subsequent chest CT is required but a chest x-ray will be performed at end- Consolidation and end of therapy. If patient does not have CR at end-Induction, a chest CT will be performed at end-Consolidation. Patients who have PD at end of consolidation are off protocol therapy.
3. Determined by morphology on bilateral bone marrow aspirates/biopsies (not MRD or flow). Bilateral bone marrow aspirates and biopsies are strongly preferred but not required for study eligibility. A unilateral bone marrow aspirate for morphology and for central MRD bone marrow assessment are required to be eligible.
4. Bone scan only if patient has bone symptoms; follow-up exams only if baseline demonstrates disease.
5. Done as part of Project: Every Child. If Project Every Child is not available, submit as part of this protocol (see Section 13.6 for details)
6. Many patients will have no disease below the diaphragm; if the abdominal and pelvic CTs at baseline are negative, no repeat scans are required.

**TREATMENT PLAN:**

See Section 4.0.

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 5.0.

**SPECIMEN REQUIREMENTS:**

Per AALL08B1 or Project Every Child. See the protocol for additional required and optional specimen time points.