COG-AALL1631: International Phase 3 Trial in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Ph+ ALL Testing Imatinib in Combination with Two Different Cytotoxic Chemotherapy Backbones

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. **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).**

___2. Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment.

___3. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section above.

___4. Randomization

Via OPEN, randomization for SR Ph+ ALL patients will take place at the end of Induction IB when MRD has been determined. The treatment will be randomly assigned based on the statistical design of the trial.

___5. Availability of Diagnostic Bone Marrow Sample

___6. **For patients enrolled on APEC14B1 prior to enrollment on AALL1631, the required diagnostic bone marrow sample has been fulfilled.**

___7. **For patients who have not previously enrolled on APEC14B1 prior to enrollment on AALL1631, a baseline diagnostic sample (or peripheral blood sample with blasts if marrow sample unavailable) must be available to develop an MRD probe. Please submit the sample within 72 hours of study entry. See Section 14.1 for specimen and shipping details.**

___8. **In addition, laboratory reports detailing evidence of *BCR-ABL1* fusion must be submitted for rapid central review within 72 hours of study enrollment. Please see Section 18.0 for additional details.**

___9. Age

> 1 year and < 21 years at ALL diagnosis

___10. Diagnosis

- Ph+ (*BCR-ABL1* fusion): newly diagnosed de novo ALL (B-ALL or T-ALL) or mixed phenotypic acute leukemia (MPAL meeting 2016 WHO definition) with definitive evidence of *BCR-ABL1* fusion by karyotype, FISH and/or molecular methodologies.
- ABL-class fusion: newly diagnosed B-ALL with definitive evidence of ABL-class fusions. ABL-class fusions are defined as those involving the following genes: *ABL1, ABL2, CSF1R, PDGFRB, PDGFRA*. Methods of detection include fluorescence in-situ hybridization (FISH, e.g. using break-apart or colocalization signals probes), multiplex or singleplex reverse-transcription polymerase chain reaction (RT-PCR), whole transcriptome or panel-based RNA-sequencing (e.g. TruSight RNA Pan-Cancer Panel; Illumina, San Diego, CA, USA or similar).

___11. Prior Therapy

Please see Section 4.1 for the concomitant therapy restrictions for patients during treatment.

- Ph+ patients must have previously started Induction therapy, which includes vincristine, a corticosteroid, pegaspargase, with or without anthracycline, and/or other standard cytotoxic chemotherapy.
- Ph+ patients have not received more than 14 days of multiagent Induction therapy beginning with the first dose of vinCRIStine.
- Ph+ patients may have started imatinib prior to study entry but have not received more than 14 days of imatinib.
- ABL-class fusion patients must have previously completed the 4 or 5 weeks of multiagent Induction chemotherapy (Induction IA phase).
- ABL-class fusion patients may have started imatinib during Induction IA, at the same time of or after the first vinCRIStine dose.

___12. Performance Status

Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2.
Please refer to performance status scale per Appendix IX

___13. Organ Function Requirements

- Adequate liver function defined as:
  - Direct bilirubin ≤ 2.0 mg/dL.
- Adequate cardiac function defined as:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by radionuclide angiogram or echocardiogram.
  - Corrected QT Interval, QTc < 480mSec

  Note: Repeat echocardiogram and electrocardiogram are not required if they were performed at or after initial ALL diagnosis, before study enrollment.
- Adequate renal function is defined as:
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 , or
  - Serum creatinine within normal limits 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

EXCLUSION CRITERIA:

1. Known history of chronic myelogenous leukemia (CML).
2. ALL developing after a previous cancer treated with cytotoxic chemotherapy.
3. Active, uncontrolled infection or active systemic illness that requires ongoing vasopressor support or mechanical ventilation
4. Down syndrome
5. Pregnancy and Breast Feeding.
   a. 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.
   b. Lactating females who plan to breastfeed their infants.
   c. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of treatment according to protocol.
6. Patients with congenital long QT syndrome, history of ventricular arrhythmias or heart block.
7. Prior treatment with dasatinib, or any TKI inhibitor other than imatinib.

REQUIRED OBSERVATIONS:

Required Observations in Induction IA Part 2

- Physical exam
- Height, weight
- CBC with diff/platelets
- Bilirubin, ALT, and creatinine
- Pregnancy test, if applicable
- Bone age
- ECG (Can be collected prior to or during Days 1-15 of Induction IA)
- MUGA or ECHO (Can be collected prior to or during Days 1-15 of Induction IA)
- Performance status
- TPMT and NUDT15 genotype (optional)
- For patients who did not enroll on APEC14B1, submit COG-approved laboratory reports of Ph+ status or ABL1-class fusion status
- for central review. Please refer to Section 18.0.

TREATMENT PLAN:

AALL1631 is an international collaborative protocol conducted by COG and EsPhALL with the primary objective of reducing treatment-related morbidity and mortality without adversely impacting disease-free survival (DFS) in Ph+ ALL patients classified as Standard Risk (SR) based on low MRD at week 10-12 of therapy. Ph+ ALL patients will enter the trial at Day 15 of Induction IA and begin daily imatinib at that time. Patient may have started imatinib prior to study entry but has not received more than 14 days of imatinib. After the Induction IB phase (week 10-12), minimal residual disease (MRD) will be assessed by immunoglobulin/T-cell receptor (IgH-TCR) PCR, and patients will be classified as SR (those with MRD < 5 x 10-4) or High Risk (HR; MRD > 5 x 10^{-4}). SR patients will be randomized to receive one of two cytotoxic chemotherapy backbones: 1) the EsPhALL backbone (Arm A) used in previous EsPhALL protocols and COG AALL1122 or 2) a less intensive regimen similar to those typically administered to non-Ph+ ALL HR patients on COG trials (Arm B). Patients on both arms will continue to receive imatinib until the completion of all planned chemotherapy (two years of treatment).

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

Diagnostic Bone Marrow Samples for the Minimal Residual Disease (MRD) Concordance Study between IgH-TCR PCR and Next Generation Sequencing, the *BCR-ABL1* fusion variant (p190 vs p210) Study, and the *IKZF1* Deletions/Mutations Study.

For patients who consent, bone marrow and/or blood specimens submitted at the time of diagnosis to the COG Leukemia Biospecimen Bank at Nationwide Children's Hospital via enrollment on AALL08B1 (ALL Classification study) or Project Every Child (APEC14B1), or at the time of study entry to AALL1631, will be evaluated for the following:

- The prognostic significance of *BCR-ABL1* fusion variants (p190 vs p210) in Ph+ ALL.
- The prognostic significance of *IKZF1* gene aberrations and deletions in Ph+ ALL.

No additional samples are needed.

AALL1631 Amendment #4 extends eligibility to patients with ABL-class fusion positive B-ALL, which represents a recently defined subgroup of ALL with biological features very similar to Ph+ ALL