COG-AALL2131
An International Pilot Study of Chemotherapy and Tyrosine Kinase Inhibitors with Blinatumomab in Patients with Newly-Diagnosed Philadelphia Chromosome-Positive or ABL-class Philadelphia Chromosome-Like B-cell Acute Lymphoblastic Leukemia

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

Patients must be enrolled before study treatment begins. Timing of enrollment is different for patients with Ph+ (by Day 15 of Induction) and ABL-class Ph-like BALL (by Day 1 of Blinatumomab Block 1). The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. Protocol therapy for AALL2131 begins on Day 15 of Induction Part 2for Ph+ B-ALL patients and Day 1 of Blinatumomab Block 1 for ABL-class Phlike B-ALL patients, respectively.

PATIENTS MUST SIGN THE INFORMED CONSENT DOCUMENT BEFORE RECEIVING PROTOCOL THERAPY ON AALL2131.

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

___2. Staged Consent

Consent Document	Time Point for Obtaining Consent	Population for Consent
APEC14B1	Prior to the start of frontline ALL Protocol Therapy	Optional but strongly encouraged for all patients.
Induction and Post-Induction therapy	Prior to the start of Induction Day 15 on AALL2131.	Patients with Ph^+ B-ALL
Post-Induction therapy	Prior to Day 1 of Blinatumomab Block 1 on AALL2131	Patients ABL-class Ph-like B-ALL

___3. Patient Eligibility Criteria

Laboratory Studies
All laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated.

The following laboratory studies must be repeated prior to the start of protocol therapy if >7 days have elapsed from their most recent prior assessment: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. Laboratory tests need not be repeated if therapy starts within seven (7) days of their most recent prior assessment.

If the result of a laboratory study that is repeated at any time post-enrollment and prior to the start of protocol therapy is outside the limits for eligibility, then the evaluation must be rechecked within 48 hours prior to initiating protocol therapy. The results of the recheck must be within the limits for eligibility to proceed. If the result of the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Clinical Studies
Clinical studies (e.g., cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary).

___**4.** Age
Patients must be >365 days and < 18 years (for AIEOP-BFM), >365 days and < 22 years (for COG) and >365 days and < 46 years (for ALLTogether sites) at the time of enrollment.

___5. Diagnosis
Newly-diagnosed Ph+ or ABL-class Ph-like B-ALL. Leukemic blasts must express CD19. ABL-class fusions are defined as rearrangements involving the following genes predicted to be sensitive to imatinib and/or dasatinib: ABL1, ABL2, CSF1R, and PDGFRB.

Evidence of BCR::ABL1 should be documented by a clinically-validated assay prior to study entry on Day 15 from the first dose of vinCRIStine during Induction therapy. ABL-class Ph-like B-ALL gene rearrangements should be documented by a clinically-validated assay and enrolled on study by Day 1 of Blinatumomab Block 1. Accepted methods of detection include fluorescence in situ hybridization (FISH) using break-apart of colocalization signal probes, singleplex or multiplex reverse-transcription polymerase chain reaction (RT-PCR), wholetranscriptome or panel-based RNA sequencing (e.g., Hematologic Cancer Fusion Analysis, TruSight RNA Pan-Cancer Panel or equivalent). Confirmation of 5' fusion partner genes is not required for study enrollment.

___6. Prior Therapy
Please see Section 4.1.5 for the concomitant therapy restrictions for patients during treatment.

- Patients with Ph+ B-ALL must have previously started Induction therapy, which includes vinCRIStine, a corticosteroid, pegaspargase or calaspargase pegol, with or without anthracycline, and/or other standard cytotoxic chemotherapy.
- Patients with Ph+ B-ALL have not received more than 14 days of systemic Induction therapy beginning with the first Induction dose of vincristine
- Patients with ABL-class Ph-like B-ALL must have previously completed 4 or 5 weeks of multiagent Induction chemotherapy (Induction 1A).
- Patients may have started either imatinib or dasatinib prior to study entry but should have received no more than 14 days of TKI for Ph+ B-ALL or no more than 35 days of TKI for ABL-class Ph-like B-ALL.

___7. Performance Status
Patients must have a performance status corresponding to ECOG scores of ≤ 2 or Karnofsky and Lansky performance scores ≥ 50%. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Please refer to performance status scale per Appendix X.

___8. Organ Function Requirements
Adequate renal function defined as:

- For pediatric patients (age 1-17 years): a GFR ≥ 50 mL/min/1.73 m2 , as determined by one of the following methods:

1. Estimated GFR (eGFR) ≥ 50 mL/min/1.73 m2

"Bedside" Schwartz formula (2009): eGFR = 0.413 x (height/Serum creatinine) An online calculator is available through the National Kidney Foundation at https://*www.kidney.org/professionals/kdoqi/gfr_calculatorp ed*

2. Measured GFR ≥ 50 mL/min/1.73 m2 (any age). If measured GFR is used, it must be performed using direct measurement with a nuclear blood sampling method or small molecule clearance method (iothalamate or other molecule per institutional standard).

- For adult patients (age 18 years or older):
  Creatinine clearance ≥ 30 mL/min, as estimated by the Cockcroft and Gault formula. The creatinine value used in the calculation must have been obtained within 28 days prior to registration. Estimated creatinine clearance is based on body weight.

  Estimated creatinine clearance = (140 – age) x weight in kg†
  72 x creatinine (mg/dl)
  Multiply this number by 0.85 if the participant is a female.

  †The kilogram weight is the participant weight with an upper limit of 140% of the ideal body weight (IBW).

Adequate liver function defined as:
- Direct bilirubin < 2.0 mg/dL (34.2 micromoles/L)
- ALT and AST ≤ 10 x ULN

Adequate cardiac function defined as:

- Shortening fraction of ≥ 27% by echocardiogram
OR
- Left Ventricular Ejection fraction of ≥ 50% by radionuclide angiogram or echocardiogram
AND
- 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.

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

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

EXCLUSION CRITERA:

___1. Known history of chronic myeloid leukemia (CML)
___2. ABL-class Ph-like B-ALL who are CNS2 or CNS3 at end of Induction phase.
___3. ALL developing after a previous cancer treated with cytotoxic chemotherapy.
___4. Active, uncontrolled infection or active systemic illness that requires ongoing vasopressor support or mechanical ventilation
___5. Down syndrome (trisomy 21)
___6. 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 negative pregnancy test is required for female patients of childbearing potential within 7 days prior to enrollment.
b. Lactating females who plan to breastfeed their infants.
c. Sexually active male and female patients of reproductive potential who have not agreed to use an effective contraception method for the duration of treatment according to protocol.
NOTE: Patients who could become pregnant or could father a child must use effective contraception during protocol treatment and for 30 days after the last dose of dasatinib or 14 days after the last dose of imatinib dose or per institutional standard of care for multiagent chemotherapy, whichever is longer

___7. Prior treatment with TKIs before study entry with the exception of imatinib or dasatinib

___**8.** Patients with congenital long QT syndrome, history of ventricular arrhythmias, or heart block.
___**9.** Patients with known Charcot-Marie-Tooth disease.
___**10.** Patients with significant central nervous system pathology that would preclude treatment with blinatumomab, including history of severe neurologic disorder or autoimmune disease with CNS involvement.

Note: Patients with a history of seizures that are well controlled on stable doses of anti-epileptic drugs are 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. Please see Section 4.1.5 for the concomitant therapy restrictions for patients during treatment.

___**11.** HIV-infected patients are eligible if on effective anti-retroviral therapy that does not interact with planned study agents and with undetectable viral load within 6 months of treatment.

REQUIRED OBSERVATIONS:

4.2.2 Required Observations – Induction Part 2

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

a. Physical exam
b. Height, weight
c. CBC with diff/platelets
d. Bilirubin, AST, ALT, and creatinine
e. IgG and absolute lymphocyte count
f. Strongly recommended: vaccine titers for varicella, measles, tetanus and Hemophilus influenzae
g. Performance status
h. Pregnancy test (if applicable)
i. Testicular exam for male patients.
j. ECG (Can be collected prior to or during Days 1-15 of Induction)
k. MUGA or ECHO (Can be collected prior to or during Days 1-15 of Induction)
l. TPMT and NUDT15 genotype (optional but strongly recommended)
m. Submit a diagnostic bone marrow sample for NGS MRD B-cell clonality testing. NOTE: Unstained bone marrow slides are strongly encouraged to be used for clonality assessment. If bone marrow is unavailable, peripheral blood with circulating blasts may be used instead. Please refer to Section 14.1.
n. Optional bone marrow (BM) for future research. (Collected at diagnosis ONLY for patients not enrolled on APEC14B1). Collect at End of Induction for all patients who consented to optional studies. See Section 14.6 for additional details.
o. CSF cell count and cytospin.
p. Required bone marrow. Bone marrow (BM) evaluation to assess response by morphology and MRD by flow cytometry. EOI MRD samples should be sent to a COG-approved flow MRD laboratory, see Section 14.2.
q. Optional peripheral blood (PB) and BM for immune function studies. See Section 14.7 for additional details.
r. Optional PB and CSF for TKI (dasatinib) therapeutic drug monitoring (TDM) study. PB sample should be drawn prior to the morning TKI dose. See Section 14.8 for additional details.

TREATMENT PLAN:
Overview of Treatment Plan

All patients will begin Induction chemotherapy according to the institutional standard of care or frontline protocol. The timing of study enrollment differs between patients with Ph+ and ABL-class Ph-like B-ALL.

Study Entry according to Ph+ vs. ABL-class Ph-like B-ALL

Ph+ B-ALL: Patients with Ph+ B-ALL begin AALL2131 protocol therapy on Day 15 of Induction. Regardless of whether imatinib or dasatinib was started or not, dasatinib should be given beginning at Day 15 of Induction. Section 4.2 describes the Induction Part 2 treatment for patients with Ph+ B-ALL who begin AALL2131 protocol therapy on Day 15 of Induction. After study entry mid-Induction, patients should receive at least 14 days of dasatinib along with the rest of Induction therapy (i.e., until Day 29). Patients with any CNS status at diagnosis can follow their frontline intrathecal therapy schedule as long as they are not CNS3 at study entry (Day 15 of Induction). Patients with persistent CNS3 disease at study entry should receive twice weekly intrathecal therapy alternating between cytarabine and methotrexate until their CSF is cleared. At the end of Induction, a bone marrow aspirate will be performed, and patients will proceed to post-Induction therapy regardless of morphologic or MRD response. Patients with persistent CNS2/3 disease at the end of Induction will be removed from protocol therapy.

ABL-class Ph-like B-ALL: Patients with ABL-class Ph-like B-ALL enter and begin AALL2131 protocol therapy on Day 1 of Blinatumomab Block 1, following completion of at least 4 weeks of multiagent induction chemotherapy as per institutional standard of care or frontline protocol. The addition of TKI is strongly recommended to start during Induction as soon as the underlying ABL-class gene fusion is identified. The use of either imatinib or dasatinib is allowable prior to study entry, but patients must receive the protocol-required TKI at the time of study entry. The type of TKI differs between PDGFRB fusions vs. non-PDGFRB ABL-class fusions. Patients with PDGFRB fusions should receive imatinib as the study TKI, whereas non-PDGFRB ABL-class fusions (ABL1, ABL2, CSF1R) should receive dasatinib as the study TKI. In the scenario where PDGFRB or CSF1R gene rearrangements cannot be distinguished based on FISH (because PDGFRB and CSF1R genes are adjacent to each other), we strongly recommend sending clinical fee-for-service molecular testing if this has not already been done. Unstained diagnostic bone marrow slides are strongly recommended to be kept locally for further molecular testing; however, the banked APEC14B1 sample could be requested for this purpose in the absence of available diagnostic material at the local institution. While waiting for confirmatory molecular testing, imatinib should be initiated and can be subsequently changed to dasatinib if molecular testing confirms the presence of CSF1R fusion. If molecular testing confirms the presence of PDGFRB fusion, the patient should continue on imatinib until treatment completion.

TOXICITIES AND DOSAGE MODIFICATIONS: See section 5.

SPECIMEN REQUIREMENTS:

Required Bone Marrow Sample and Shipping Information

Diagnostic Bone Marrow for B-cell clonality testing by NGS MRD (clonoSEQ):

- **All enrolled patients should submit 3 to 6 unstained bone marrow slides from diagnosis directly to Adaptive for B-cell clonality testing at study entry, irrespective of if they are enrolled on APEC14B1 or not.**

- If unstained bone marrow slides are not available, the following diagnostic specimens are accepted by Adaptive for B-cell clonality testing. Please refer to the clonoSEQ website (*https://ous.clonoseq.com/wpcontent/uploads/NP-US-cSEQ-0025-2_FORM-00538- 6_clonoSEQ_TestSpecimenRequirements_TestingService_WEB.pdf*) for the full repertoire of accepted specimens, sample preparation details and shipping instructions. **All samples sent to Adaptive directly should contain two (2) patient identifiers**.

a. Fresh peripheral blood with at least 1,000 circulating blasts/µL (i.e., a WBC count of 10,000/µL with 10% blasts or a WBC count of 5,000/µL with 20% blasts): 2 mL or more in EDTA tube.
b. Fresh bone marrow aspirate: 2 mL or more in EDTA tube.
c. Frozen peripheral blood with at least 1,000 circulating blasts/µL or frozen bone marrow samples: 50,000 cells or more.

• If the above diagnostic specimens are not available and the patient is enrolled on APEC14B1, the APEC14B1 diagnostic bone marrow sample could be used for B-cell clonality testing. Since NGS MRD testing will be done as a clinical test on AALL2131, the Biopathology Center at Nationwide will send the diagnostic bone marrow submitted for APEC14B1 back to the site and the site will send the sample directly to Adaptive after putting in the appropriate order through Adaptive's online portal.

MRD by Next-Generation Sequencing (NGS) in Bone Marrow at End of Blinatumomab Block 2– REQUIRED
See Section 14.4

BIOLOGY REQUIREMENTS:
Immune Function Studie-OPTIONAL
See 14.7 for schedule.
1st sample is induction Part 2, Day 29