COG-AALL1131: A Phase III Randomized Trial for Newly Diagnosed High Risk B-Lymphoblastic Leukemia (B-ALL) Including a Stratum Evaluating Dasatinib (IND#73789, NSC#732517) in Patients with Ph-like Tyrosine Kinase Inhibitor (TKI) Sensitive Mutations

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. **TO ENROLL ONTO AALL1131: PATIENTS MUST EITHER:**
- **HAVE NCI HIGH RISK B-ALL AND BE ENROLLED IN COG AALL08B1 OR PROJECT: EVERYCHILD (APEC14B1, if available for ALL patients). PATIENTS THAT BEGIN PROTOCOL THERAPY ON THIS STUDY (AALL1131) PRIOR TO ENROLLMENT ON AALL08B1 OR APEC14B1 ARE INELIGIBLE**

___2. Study enrollment must take place no later than five (5) calendar days after 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. For NCI standard risk patients from AALL0932 enrolling on this study at the end of Induction, protocol therapy must begin only after enrollment has taken place.

___3. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment.

___4. Staged Consent

Informed consent for non Down syndrome patients will be in 2 stages. Informed consent that describes the first 4 weeks of Induction therapy will be obtained for all non Down syndrome patients before starting treatment. All non Down syndrome patients will receive a 4-drug Induction regimen that includes either dexamethasone for 14 days (for patients aged < 10 years) or prednisone for 28 days (for patients aged ≥ 10 years). At the end of Induction, after patients have been stratified into risk subgroups, a second informed consent that describes post-Induction therapy will be discussed with patients and their families. There are separate post-Induction consents for children with HR B-ALL and VHR B-ALL. **Effective March 19, 2018 the HR randomization closed. Patients who meet criteria for HR randomization should not be approached for post-induction therapy on AALL1131.**

Patients in the VHR B-ALL subset with MRD ≥ 0.01% (excluding those with primary induction failure or hypodiploidy) will be approached with a post-Induction consent prior to beginning Consolidation therapy that describes VHR standard Consolidation therapy. Effective Amendment #6, EOI MRD negative NCI HR patients will go off-protocol therapy and should proceed to receive standard of care therapy. SR B-ALL patients on AALL0932 who meet criteria for HR B-ALL post-Induction are not eligible to continue on AALL0932, and due to the closure of the HR randomization, should not be approached for post-induction therapy on AALL1131.

HR B-ALL patients receiving Induction therapy and randomization for the HR subgroup on AALL1131 and identified as Ph-like (LDA card positive) and subsequently confirmed to have a predicted TKI sensitive mutation, will be approached with a post-Induction consent prior to beginning Consolidation therapy that describes a non-randomized regimen with dasatinib added to the MBFM-IMHDM backbone (Dasatinib Arm) of AALL1131. Patients who are identified to have a genetic lesion predicted to respond to ruxolitinib will be eligible for participation on AALL1521 when open at their institution or the successor trial, if applicable. The post-Induction informed consents for eligible non Down syndrome HR B-ALL patients will include the option of enrolling on the *Longitudinal, Computerized Assessment of Neurocognitive Functioning* ancillary studies.

Children with DS HR B-ALL will be presented with a single informed consent that describes their entire therapy on study at enrollment. DS SR B-ALL patients on AALL0932 who meet criteria for DS HR B-ALL post-Induction and, are not eligible to continue on that study will also be approached with a post-Induction consent prior to beginning Consolidation therapy, to continue post-Induction therapy on this study (AALL1131).

Summary of Required Consents for AALL1131

	Time Point for Obtaining Consent	Population for Consent*
Induction Consent	Prior to the start of Induction	• All HR- and VHR B-ALL without Down syndrome.
Post-Induction Consent	Prior to the start of Consolidation	• VHR B-ALL without Down syndrome (non-randomized)
		• Ph-like with predicted TKI-sensitive mutation without Down syndrome (non-randomized)
Informed consent	Prior to the start of Induction	• DS HR B-ALL (non-randomized)
Informed consent	Prior to the start of Consolidation	• DS HR B-ALL completing Induction therapy on AALL0932^ (non-randomized)
Neurocognitive study	Prior to the start of Consolidation (embedded in post-Induction consent)	• All HR- B-ALL <u>without</u> Down syndrome 6 - > 13 years old at time of ALL diagnosis.

***** *Each of these groups will sign a separate consent at the designated time points*
^Please note that DS SR B-ALL patients on AALL0932 who meet the criteria for DS HR B-ALL post-Induction are eligible to continue therapy on AALL1131 prior to the start of Consolidation.

___5. Randomizations for all non Down syndrome patients will take place after completion of Induction therapy and risk assignment, and prior to the beginning of Consolidation therapy via RDE. **Randomization for all HR and VHR are closed effective March 19, 2018 and February 15, 2017, respectively.**

___6. Patients must be > 365 days and < 31 years of age

___7. <u>White Blood Cell Count (WBC) Criteria</u>
- Age 1-9.99 years: WBC ≥ 50 000/μL
- Age 10-30.99 years: Any WBC
- Age 1-30.99 years: Any WBC with:
  - Testicular leukemia
  - CNS leukemia (CNS3)
  - Steroid pretreatment (see Section 3.3)

___8. Patients must have newly diagnosed B lymphoblastic leukemia (2008 WHO classification) (also termed B-precursor acute lymphoblastic leukemia). Patients with Down syndrome are also eligible.

___9. <u>Organ Function Requirements for Patients with Ph-like ALL and a Predicted TKI-Sensitive Mutation</u>
Patients identified as Ph-like with a TKI-sensitive kinase mutation must have assessment of organ function performed within 3 days of study entry onto the dasatinib arm of AALL1131.

To be eligible for the Dasatinib Arm (For patients who are Ph-like with a predicted TKI-sensitive mutation), patients must have:

- Adequate Renal Function Defined As
  - Creatinine clearance or radioisotope GFR >70mL/min/1.73 m^2 or
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
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
  - Direct bilirubin ≤3 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤10x upper limit of normal (ULN) for age.
- Adequate Cardiac Function****** Defined As
  - Shortening fraction ≥27% by echocardiogram, or - Ejection fraction ≥ 50% by gated radionuclide study. **** Patients must have an EKG fewer than 6 days prior to enrollment on the dasatinib arm.** Patients who have had cardiac assessments by echocardiogram or radionuclide scan at the beginning of Induction do **NOT** need to have these repeated prior to study entry.-QTc < 450 msec on baseline electrocardiogram as measured by the Frederica or Bazett formula
  - No major conduction abnormality (unless a cardiac pacemaker is present)
- Adequate Pulmonary Function Defined As
  - No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% at sea level if there is clinical indication for determination.
- Central Nervous System Function Defined As
  - Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled. However, drugs that induce CYP3A4/5 (carbamazepine, oxcarbazepine, phenytoin, primidone, phenobarbital) should be avoided

___10. Eligibility criteria for the *Longitudinal, Computerized Assessment of Neurocognitive Functioning* study
  - Patients must be aged 6 to 13 years at time of B-ALL diagnosis, enrolled on AALL1131
  - Patients must be English-, French- or Spanish-speaking (languages in which the assessment is available)
  - Patients must have no known history of neurodevelopmental disorder prior to diagnosis of B-ALL (e.g., Down syndrome, Fragile X, William‘s Syndrome, mental retardation)
  - Patients must have no significant visual impairment that would prevent computer use and recognition of the visual test stimuli

___11. Patients enrolled on AALL0932, <u>with</u> Down syndrome, meeting the following criteria will <u>NOT</u> be eligible to continue on AALL0932 but <u>WILL BE</u> eligible to enroll on the **DS HR-B-ALL stratum** of this study at the end of Induction:
- Day 29 MRD ≥ 0.01%
- *MLL* rearrangement
- Hypodiploidy (n< 45 chromosomes and/or DNA index < 0.81)
- DS-HR B-ALL patients initially enrolled on AALL0932 or this study who have Induction Failure (M3 BM Day 29) or Philadelphia chromosome (*BCR-ABL1*) will not be eligible for post-Induction therapy on either trial (AALL0932 or AALL1131).

EXCLUSION CRITERIA:

___1. With the exception of steroid pretreatment (defined in Section 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 any cancer diagnosed prior to the initiation of protocol therapy on AALL1131. Patients cannot have secondary B-ALL that developed after treatment of a prior malignancy with cytotoxic chemotherapy.
Patients receiving prior steroid therapy may be eligible for AALL1131 (see Section 3.3).

___2. Patients with *BCR-ABL1* fusion are not eligible for post-Induction therapy on this study but may be eligible to enroll in a successor COG Ph+ ALL trial by Day 15 Induction.

___3. DS HR-B-ALL patients with Induction failure or *BCR-ABL1*

___4. Female patients who are pregnant are ineligible since fetal toxicities and teratogenic effects have been noted for several of the study drugs.

___5. Lactating females are not eligible unless they have agreed not to breastfeed their infant.

___6. Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

___7. Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation.

EXPERIMENTAL DESIGN SCHEMA(s) for NON DOWN SYNDROME PATIENTS and DOWN SYNDROME PATIENTS

See current protocol.

REQUIRED OBSERVATIONS:

Required and Optional Clinical, Laboratory and Disease Evaluations – HR-B-ALL

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

Studies	Induction
REQUIRED	
Hx/PE/Wt/Ht [1]	Weekly
CBC/diff/platelets	Weekly
Bone Marrow	Baseline & Day 29 [2]
Peripheral Blood	Day 29 [3]
CSF cell count and cytospin	With each IT
Bilirubin, ALT, and Creatinine	Baseline, & Day 29
Echocardiogram	Baseline
Pregnancy test, if applicable	Baseline
OPTIONAL	
TPMT and NUDT15 genotype	During Induction
Risk Classifiers [4]	Baseline

[1] The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle.
[2] Send Day 29 BM to both the ALL Molecular Reference Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).
NOTE: IF THE DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY).
[3] Send Day 29 PB sample to B-ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 for shipping requirements)
<u>NOTE</u>: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED B-ALL FLOW CYTOMETRY REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG B-ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.
[4] Send diagnostic BM to both B-ALL Molecular and Flow Cytometry References Labs (see AALL08B1 for shipping requirements and addresses).

Required and Optional Clinical, Laboratory and Disease Evaluations – DS HR-B-ALL

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

Studies	Induction
REQUIRED	
Hx/PE/Wt/Ht [1]	Weekly
CBC/diff/platelets	Weekly
Bone Marrow	Baseline, Day 15 [2] & Day 29 [2]
Peripheral Blood	Day 29 [4]
CSF cell count and cytospin	With each IT
Bilirubin, ALT, and Creatinine	Baseline
Echocardiogram	Baseline [5]
IgG	Baseline
Pregnancy test, if applicable	Baseline
OPTIONAL	
Varicella titer	Baseline
TPMT and NUDT15 genotype	During Induction
Risk Classifiers [6]	Baseline

[1] The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle.
[2] Send Day 15 BM for morphology. ***This sample is very important.***
[3] Send Day 29 BM to both B-ALL Molecular and Flow Cytometry References Labs (see AALL08B1 for shipping requirements and addresses).
NOTE: IF DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO COG ALL FLOW CYTOMETRY REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG B-ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.
[4] Send Day 8 peripheral blood sample to ALL Flow Cytometry Lab for MRD and Day 29 PB sample to Molecular Reference Lab for studies of genetic variation (see AALL08B1 for shipping requirements)
[5] Must be done prior to Day 15, if unable to obtain at baseline.
[6] Send diagnostic BM to <u>both</u> ALL Molecular and Flow Cytometry References Labs (see AALL08B1 for shipping requirements and addresses).

Required and Optional Clinical, Laboratory and Disease Evaluations – VHR-B-ALL

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

Studies	Induction
REQUIRED	
Hx/PE/Wt/Ht [1]	Weekly
CBC/diff/platelets	Weekly
Bone Marrow	Baseline & Day 29 [2]
Peripheral Blood	Day 29 [3]
CSF cell count and cytospin	With each IT
Bilirubin, ALT, AST, Lipase and Creatinine	Baseline, & Day 29
Echocardiogram	Baseline
Pregnancy test, if applicable	Baseline
OPTIONAL	
TPMT and NUDT15 genotype	During Induction
Risk Classifiers [4]	Baseline

[1] The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle.
[2] Send Day 29 BM to <u>both</u> ALL Molecular and Flow Cytometry References Labs (see AALL08B1 for shipping requirements and addresses).
[2] Send Day 8 peripheral blood sample to ALL Flow Cytometry Lab for MRD and Day 29 PB sample to ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 for shipping requirements)
<u>NOTE</u>: IF DAY 8 PB AND 29 BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO COG ALL FLOW CYTOMETRY REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.
[3] Perform prior to Day 1 therapy. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.
[4] Send diagnostic BM to both ALL Molecular and Flow Cytometry Reference Labs (see AALL08B1 for shipping requirements and addresses)

Required and Optional Clinical, Laboratory and Disease Evaluations – Dasatinib Arm

Studies	Induction
REQUIRED	
Hx/PE/Wt /Ht	Weekly
CBC/diff/platelets	Weekly
Bone Marrow	Baseline, & Day 29 [2]
Peripheral Blood for MRD	Day 29 [3]
CSF cell count and cytospin	With each IT
Bilirubin, ALT, and Creatinine	Baseline, & Day 29
Echocardiogram	Baseline
Pregnancy test, if applicable	Baseline
OPTIONAL	
TPMT and NUDT15 genotype	During Induction
Risk Classifiers [4]	Baseline

1 The measurement of height (Ht) for the calculation for BSA is only required at the beginning of each treatment course/cycle.
2 Send Day 29 BM to both the ALL Molecular Lab and a COG-Approved ALL Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).
NOTE: IF THE DAY 29 BM MRD SAMPLE IS NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE ON A COG ALL TRIAL FOLLOWING COMPLETION OF INDUCTION THERAPY.
3 Send Day 29 PB sample to the ALL Molecular Reference Lab for studies of genetic variation (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements)
4 Send diagnostic BM to both the ALL Molecular Reference Lab and a COG-Approved Flow Cytometry Lab (see AALL08B1 or APEC14B1 (*if available for ALL patients*) for shipping requirements and addresses).

TREATMENT PLAN:
See Section 4.0.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0.

SPECIMEN REQUIREMENTS:
Per AALL08B1 **PLUS**
Sample and Shipping Information for Optional MRD on Day 1 of Interim Maintenance I or End Consolidation [1] for consenting VHR Patients.

Specimen	Studies	Laboratory
Bone marrow 2 mL	MRD	Flow Cytometry Laboratory

[1] Samples to be obtained at the end of Consolidation upon count recovery in patients with Induction failure or severe hypodiploidy who are going to SCT after completing Consolidation.