COG-AALL2321
A Phase 2 Study of Blinatumomab in Combination with Chemotherapy for Infants with Newly Diagnosed Acute Lymphoblastic Leukemia with Randomization of KMT2A-Rearranged Patients to Addition of Venetoclax A COG Groupwide Phase 2 Study

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 CONSENT TO ELIGIBILITY SCREENING (PART A) AND BE ENROLLED ON PROJECT: EVERYCHILD (APEC14B1) OBTAIN A DIAGNOSTIC SAMPLE BEFORE RECEIVING PROTOCOL THERAPY ON AALL2321 (For the purpose of this study, "protocol therapy" does not include a dose of intrathecal chemotherapy, hydroxyurea or steroid pretreatment as outlined in Section 3.2.6).

Study enrollment on AALL2321 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 enrollment unless otherwise indicated in the eligibility section below.

___2. Staged Consent

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

___3. Informed consent

Informed consent/parental permission **MUST** be signed before protocol therapy begins. Informed consent that provides a study overview and describes treatment with the Steroid Prephase will be obtained for infants newly diagnosed with B-ALL prior to starting treatment. All patients will receive treatment with the Steroid Prephase that includes PredniSONE or prednisoLONE administered for 7 days prior to the start of Induction, independent of any steroid pre-treatment. Once KMT2A status is determined by a COG-approved cytogenetics laboratory, informed consent for the assigned treatment stratum must be signed **prior to the start of Induction chemotherapy for all patients and prior to randomization for KMT2A-R patients during the expansion phase.** Induction therapy may begin early (< 7 days of steroids) if early disease progression (see Section 3.3.4.5) occurs during the Steroid Prephase, provided KMT2A status has been determined and callback completed.

Summary of Required Consents for COG AALL2321:

Consent Document	Time Point for Obtaining Consent	Population for Consent
APEC14B1 (Part A)	Prior to the start of Protocol Therapy	Newly Diagnosed Infant B-ALL or ALAL
Steroid Prephase	Prior to the start of Protocol Therapy	Newly Diagnosed Infant B-ALL or ALAL
Safety Phase	Prior to the start of Induction	*KMT2A*-Rearranged patients
Randomized Expansion Phase	Prior to the start of Induction	*KMT2A*-Rearranged patients
Arm C	Prior to the start of Induction	*KMT2A*-Germline patients
Venetoclax PK[#]	Prior to the start of Induction	*KMT2A*-Rearranged patients Safety Phase ONLY

[#] Included in Safety Phase Consent

___4. Callbacks for Treatment Assignment/Randomization

1) The study will use stratum-level reservations. Reservations are only needed for KMT2A-R patients.
2) The patient's KMT2A status will return during the Steroid Prephase. As soon as the KMT2A status is known, if a patient has a KMT2A-R, the site should immediately make a reservation in OPEN. See Section 3.1.7.
3) Callback is needed for both KMT2A-R and KMT2A-G patients. After the second consent has been signed, a callback will occur at this time. Patients will be grouped into KMT2A-R or KMT2A-G and be assigned treatment at callback.
4) KMT2A-G patients will be non-randomly assigned to Arm C at callback throughout the trial. 5) KMT2A-R patients will be assigned to therapy arms using the following algorithm:

- For the safety phase:
  - o If there is a dose level that has an available spot(s) at callback, a KMT2A-R patient will be assigned to that dose level.
  - o If no dose level has an available spot, a KMT2A-R patient will be taken off protocol at callback.
  - o The safety phase will follow a rolling six design. We will first allocate six spots at the dose level under investigation.

- For the expansion phase:
  - o At callback, KMT2A-R patients will be randomized (stratified by age at diagnosis) to Arm A or Arm B.
  - o KMT2A-R patients randomized to Arm B will be in either Cohort 1, Cohort 2, Cohort 3, or Cohort 4. Rules for the assignments of patients to each of the four cohorts are specified in Section 9.2.2.
  - o If KMT2A-R randomization needs to be suspended at any time during the trial, KMT2A-R patients who have not been randomized will be taken off protocol at the end of Steroid Prephase without randomization.

To ensure timely treatment assignment of KMT2A-R patients, sites are encouraged to make reservations as soon as they know of the patient's KMT2A-R status. For a patient who is anticipated to be randomized during a weekend, it is highly recommended that sites make a reservation during a weekday. If there is no available spot for a patient in a KMT2A-R stratum, sites should contact the COG study Research Coordinator (RC) immediately.

Required Samples for Submission

Adequate diagnostic samples must be provided to a COG-approved cytogenetics laboratory to allow completion of the studies needed for risk assignment (KMT2Astatus) and the APEC14B1 Part A eligibility screening sample must be sent. This APEC14B1 sample will be used for the baseline assessment of leukemia immunophenotype for subsequent centralized assessment of MRD at response timepoints. If a bone marrow (BM) aspirate is not performed, or adequate material cannot be obtained, a peripheral blood (PB) sample with at least 1,000/μL blasts must be submitted for the patient to be eligible. Alternatively, a leukapheresis sample may be submitted as the diagnostic sample. If a diagnostic sample is not submitted, the patient will not be eligible. Diagnostic BM, PB or leukapheresis samples are submitted through APEC14B1 (see APEC14B1 Manual of Procedures (MOP) for details of required testing)

As part of APEC14B1 Part A, patients must submit specimens to a COG-approved cytogenetics laboratory and results must be submitted for central review within three weeks of diagnosis. It is essential that KMT2A (MLL) fluorescence in situ hybridization (FISH) data for AALL2321 be entered by the local institution in RAVE as soon as results are available but no later than Day 10 of protocol therapy; the local institution must enter all other FISH data by Day 21 of protocol therapy. All chromosome analysis must be submitted by Day 21 to ensure that central review can be completed before the end of Induction.

In addition to diagnostic samples submitted through APEC14B1, this study requires additional samples at the end of Induction (EOI), at the end of Blinatumomab Block 1 (EOB1), and for certain patients at the end of Consolidation (EOC) for BM MRD assessments.

The CIRB has determined that assent of children age ___ 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 XIV.

___5. 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: complete blood count (CBC) with differential, bilirubin, ALT, and serum creatinine. Laboratory tests need not be repeated if therapy starts within 7 days of their most recent prior assessment.

___6. Disease/Staging Imaging
Disease/staging imaging studies, if applicable, must be obtained within 21 days prior to enrollment and start of protocol therapy (repeat if necessary).

See Section 4.5.2 for required studies to be obtained prior to starting protocol therapy.

___7. Eligibility Screening
All patients must be enrolled on APEC14B1 and consented to Eligibility Screening (Part A) prior to treatment and enrollment on AALL2321. See Section 3.1.4 for details regarding timing.

___8. Age
Infants (aged 365 days or less) on the date of diagnosis are eligible; infants must be > 36 weeks gestational age at the time of enrollment.

___9. Diagnosis
Patients must have newly diagnosed B-acute lymphoblastic leukemia (B-ALL, 2017 WHO classification), also termed B-precursor ALL, or acute leukemia of ambiguous lineage (ALAL), which includes mixed phenotype acute leukemia. For patients with ALAL, the immunophenotype of the leukemia must comprise at least 50% B lineage.

Diagnostic immunophenotype: Leukemia cells must express CD19.

EXCLUSION CRITERA:

___1. Patients with Down Syndrome

___2. Patients with secondary B-ALL that developed after treatment of a prior malignancy with cytotoxic chemotherapy.

___3. Prior therapy: Patients must not have received any cytotoxic chemotherapy for either the current diagnosis of infant ALL or for any cancer diagnosis prior to the initiation of protocol therapy, with the exception of:

Steroid pretreatment:
PredniSONE, prednisoLONE, or methylPREDNISolone for ≤ 72 hours (3 days) in the 7 days prior to enrollment. The dose of predniSONE, prednisoLONE or methylPREDNISolone does not affect eligibility.

Inhaled and topical steroids are not considered pretreatment.

Note: Pretreatment 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 or within 6 hours prior to or after sedation to prevent or treat airway edema. However, prior exposure to ANY steroids that occurred > 28 days before enrollment does not affect eligibility.

Intrathecal cytarabine or methotrexate:
An intrathecal dose of cytarabine or methotrexate in the 7 days prior to enrollment does not affect eligibility.

Note: The preference is to defer the diagnostic lumbar puncture with intrathecal chemotherapy to Day 1 of Induction to allow for cytoreduction of circulating blasts and decrease the potential for CNS contamination due to a traumatic tap. If done prior to Day 1 of Induction, these results will be used to determine CNS status.

Hydroxyurea: Pretreatment with ≤ 72 hours (3 days) of hydroxyurea in the 7 days prior to enrollment does not affect eligibility.

REQUIRED OBSERVATIONS:

Required Baseline Observations – Prior to Start of Steroid Prephase

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

a) History and physical exam
b) Height, weight, BSA
c) CBC with diff/platelets
d) Peripheral blood blast cell count
e) Electrolytes including Ca^{++}, PO_4, Mg^{++}, BUN, creatinine
f) Total bilirubin, AST, ALT, albumin
g) IgG, IgM, IgA
h) GFR or creatinine clearance (calculated)
i) Local bone marrow evaluation (pre-treatment marrow evaluation must include *KMT2A* FISH and standard cytogenetic studies performed at a COG-approved cytogenetics laboratory). Peripheral blood may be substituted if the bone marrow cannot be performed for medical reasons or inadequate marrow material is obtained, refer to Appendix XIII for sample requirements. FISH results must be entered in RAVE by the local institution as soon as the result is available (ideally by Day 7), but no later than Day 10 of starting protocol therapy. Results must be submitted by the cytogenetics laboratory for central review no later than Day 21 of starting protocol therapy. See Section 14.1.
j) Baseline local flow cytometry at a COG-approved laboratory (local flow cytometry will be used to establish diagnosis)
k) ECG*
l) ECHO*
m) HTS clonality ID test (Recommended). See Section 14.4.
n) Baseline leukemia correlative biology sample (Optional). See Section 14.7.
o) APEC14B1 eligibility screening sample (Required). See Section 7.2 and APEC14B1 manual of procedures for details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

*Baseline ECG and ECHO can be performed anytime after enrollment during the Steroid Prephase but must be completed prior to Day 1 of Induction therapy.

Required Observations – Safety Phase Cohort – Induction

a) Physical exam
b) Height, weight, BSA
c) CBC with diff/platelets
d) Peripheral blood blast cell count
e) Electrolytes including Ca^{++}, PO_4, Mg^{++}, BUN, creatinine
f) Total bilirubin, AST, ALT, albumin
g) *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). See Section 5.10.
h) CSF cell count and cytospin
i) Bone marrow evaluation
j) Central flow cytometry MRD assessment (Required). See Section 14.2.
k) HTS tracking MRD test (Recommended if trackable clone detected at diagnosis). See Section 14.4.
l) Venetoclax PK (Required). See Section 14.5.
m) Leukemia correlative biology samples (Optional). See Section 14.7.
n) APEC14B1 biorepository samples (Optional). See Section 7.3.
o) Asparaginase activity level (Clinical testing: Required)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Required Observations – Arm A – Induction

a) Physical exam
b) Height, weight, BSA
c) CBC with diff/platelets
d) Peripheral blood blast cell count
e) Electrolytes including Ca^{++}, PO_4, Mg^{++}, BUN, creatinine
f) Total bilirubin, AST, ALT, albumin
g) *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). See Section 5.10.
h) CSF cell count and cytospin
i) Bone marrow evaluation
j) Central flow cytometry MRD assessment (Required). See Section 14.2.
k) HTS tracking MRD test (Recommended if trackable clone detected at diagnosis). See Section 14.4.
l) Calaspargase pegol-mknl PK (Optional). See Section 14.6.
m) Leukemia correlative biology samples (Optional). See Section 14.7.
n) APEC14B1 biorepository samples (Optional). See Section 7.3.
o) Asparaginase activity level (Clinical testing: Required)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Required Observations – Arm B – Induction + Venetoclax (Cohorts 1, 2, 3 & 4)

a) Physical exam
b) Height, weight, BSA
c) CBC with diff/platelets
d) Peripheral blood blast cell count
e) Electrolytes including Ca^{++}, PO_4, Mg^{++}, BUN, creatinine
f) Total bilirubin, AST, ALT, albumin
g) *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). See Section 5.10.
h) CSF cell count and cytospin
i) Bone marrow evaluation
j) Central flow cytometry MRD assessment (Required). See Section 14.2.
k) HTS tracking MRD test (Recommended if trackable clone detected at diagnosis). See Section 14.4.
l) Venetoclax PK (Optional). See Section 14.5.
m) Leukemia correlative biology sample (Optional). See Section 14.7.
n) APEC14B1 biorepository samples (Optional). See Section 7.3.
o) Asparaginase activity level (Clinical testing: Required)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Required Observations – Arm C – Induction

a.	Physical exam
b.	Height, weight, BSA
c.	CBC with diff/platelets
d.	Peripheral blood blast cell count
e.	Electrolytes including Ca^{++}, PO_4, Mg^{++}, BUN, creatinine
f.	Total bilirubin, AST, ALT, albumin
g.	*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). See Section 5.10.
h.	CSF cell count and cytospin
i.	Bone marrow evaluation
j.	Central flow cytometry MRD assessment (Required). See Section 14.2.
k.	HTS tracking MRD test (Recommended if trackable clone detected at diagnosis). See Section 14.4.
l.	Calaspargase pegol-mknl PK (Optional). See Section 14.6.
m.	APEC14B1 biorepository samples (Optional). See Section 7.3.
n.	Asparaginase activity level (Clinical testing: Required)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

TREATMENT PLAN: Review Experimental Design Schema for the phase being considered.

TOXICITIES AND DOSAGE MODIFICATIONS: See Section 5

SPECIMEN REQUIREMENTS: All patients must be enrolled on APEC14B1 and consented to eligibility screening-Part A

See Section 14 for required and optional samples.