

COG-AALL15P1: A Groupwide Pilot Study to Test the Tolerability and Biologic Activity of the Addition of Azacitidine (IND# 133688, NSC# 102816) to Chemotherapy in Infants with Acute Lymphoblastic Leukemia (ALL) and KMT2A (MLL) Gene Rearrangement

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. Prior to obtaining informed consent and enrolling a patient, a reservation must be made. See Section 3.1.3
- ___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. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible. The only exceptions to this are steroid pretreatment or the administration of intrathecal methotrexate or intrathecal cytarabine as described in Section 3.2.3.4.**
- ___3. **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).**
- ___4. Age
Infants less than 1 year of age on the date of diagnosis are eligible; infants must be >36 weeks gestational age at the time of enrollment.
- ___5. Diagnosis
Patients must have newly diagnosed B lymphoblastic leukemia (2008 WHO classification) also termed B-precursor acute lymphoblastic leukemia) or acute leukemia of ambiguous lineage (ALUL), which includes mixed phenotype acute leukemia (MPAL). For patients with ALUL, the morphology and immunophenotype must be at least 50% B lymphoblastic.
CNS status must be determined based on a sample obtained prior to the administration of any systemic or intrathecal chemotherapy, with the exception of steroid pretreatment.
- ___6. **KMT2A Rearrangement (KMT2A-R) Status**
All patients must undergo cytogenetic FISH testing at a COG-approved laboratory for KMT2A-R determination. Results must be submitted for central review and confirmation of KMT2A-R status. Patients will be eligible to remain on protocol therapy post-Induction if KMT2A-R is determined and confirmed by central review. Please refer to Appendix X and Section 14.7 for sample requirements and details regarding central review.

EXCLUSION CRITERIA:

- ___1. Patients with known absence of KMT2A-Rearrangement leukemia prior to enrollment.
- ___2. Patients with Down syndrome.
- ___3. Patients with secondary B-ALL that developed after treatment of a prior malignancy with cytotoxic chemotherapy.
- ___4. With the exception of steroid pretreatment (defined in Section 3.4) or the administration of intrathecal methotrexate or intrathecal cytarabine, receipt of any other prior cytotoxic chemotherapy for either the current diagnosis of B-ALL or any cancer diagnosed prior to the initiation of protocol therapy on AALL15P1.

REQUIRED OBSERVATIONS:

- History & physical exam (including weight, height, BSA)
- CBC/diff/platelets
- Electrolytes/BUN/Cr/AST/ALT/total bili
- Echo or MUGA
- CrCl or GFR (may be estimated using Schwartz formula)
- CSF cell count/diff/cytospin
- 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 5.7))
- Local bone marrow evaluation (pre-treatment must include *KMT2A* FISH and standard cytogenetic studies performed at COG-approved cytogenetics laboratory). Peripheral blood may be substituted pre-treatment if the bone marrow cannot be performed for medical reasons or inadequate marrow material is obtained, refer to Appendix X for sample requirements. SUBMIT RESULTS BY INDUCTION DAY 10 FOR CENTRAL REVIEW, see Section 14.7 and Appendix X
- Peripheral blood for the **optional** (CAR) T-cell study (Section 14.5).
- Bone marrow aspirate for the **optional** molecular profiling study (peripheral blood may be substituted in some cases, see Section 14.3).
- If apheresis is performed for clinical purposes, submit an apheresis sample for the **optional** molecular profiling study (Section 14.3).

TREATMENT PLAN:

Any infant < 1 year of age on the day of diagnosis with ALL or acute ambiguous lineage leukemia (ALUL) that is predominantly B lymphoblastic, which includes mixed phenotype acute leukemia (MPAL), is potentially eligible for enrollment on AALL15P1. Patients will be treated with a common 5-week Induction course, as detailed in Section 4.2. After Induction, only subjects with *KMT2A*-rearrangement (*KMT2A*-R) are eligible to continue on protocol therapy at which point they will receive azacitidine designated “EPI” prior to chemotherapy during 4 cycles of post-Induction therapy.

Phases of Therapy:

Post-Induction therapy includes 4 cycles of Azacitidine epigenetic therapy, Consolidation, 1 Interim Maintenance phase with high dose methotrexate and high dose cytarabine, 2 Delayed Intensification phases (as based on 1 OCTADAD phase from the Interfant backbone) and Maintenance.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0

SPECIMEN REQUIREMENTS:

Optional blood and bone marrow. See Section 14.0 for the optional details.

BIOLOGY REQUIREMENTS:

Pharmacodynamic Assessment of DNA Methylation (Required) – also see Section 14.1

Timing of Pharmacodynamic Sampling

Collect peripheral blood from patients just prior to the dose of azacitidine on Day 1 and again on Day 5, for the first 2 courses of azacitidine. Please refer to Appendix VI for additional details.

- EPI Block #1
 - Day 1
 - Day 5
- EPI Block #2
 - Day 1
 - Day 5

Sample Collection and Processing

- Collect 3-4 mL of peripheral blood in a sodium heparin tube (green top).
- Samples can be stored for up to 48 hours at room temperature.