FAST FACTS

A041501 - A PHASE III TRIAL TO EVALUATE THE EFFICACY OF THE ADDITION OF INOTUZUMAB OZOGAMICIN (A CONJUGATED ANTI-CD22 MONOCLONAL ANTIBODY) TO FRONTLINE THERAPY IN YOUNG ADULTS (AGES 18-39 YEARS) WITH NEWLY DIAGNOSED PRECURSOR B-CELL ALL

Pre-registration Eligibility Criteria (Step 0)

1. Bone marrow submission for LDA Assav

Submission of bone marrow aspirate for LDA assay is mandatory prior to registration for stratification. If marrow is inaspirable, please send peripheral blood. It should be initiated as soon as possible after pre-registration. The specimen should be sent as outlined in Section 6.2.2. Please note: Bone marrow aspirate and peripheral blood should also be submitted at this time for central MRD analysis and FISH as outlined in Section 6.2.3.

Registration Eligibility Criteria (Step 1)

1. Documentation of Disease:

- Newly diagnosed patients with CD-22 positive B-cell acute lymphoblastic leukemia (WHO criteria) are eligible. Patients with Burkitt type ALL are NOT eligible.
- Patients who have BCR-ABL fusion transcript determined by FISH or RT-PCR or t(9;22)(q34;q11) by cytogenetics are not eligible and should be considered for enrollment on studies that incorporate imatinib during induction.

Please note: Patients must also be assessed for CD20 positivity and other markers as outlined in Section 5.0.

Positivity for CD22 and CD20 is defined as baseline expression of the CD22 or CD20 antigen in more than 20% of leukemic cells using local multiparameter flow-cytometric immunophenotyping with the use of CD45 expression as a marker to gate the ALL blast population, according to recommendations from the European LeukemiaNet.

2. Prior Treatment

- No prior therapy for ALL except for limited treatment (≤ 7 days) with corticosteroids or hydroxyurea and a single dose of intrathecal cytarabine. However, patients who are being treated with chronic steroids for other reasons (for example, to treat asthma, autoimmune disorders, lupus, etc.) are eligible.
- No prior therapy for acute leukemia except emergency therapy (corticosteroids or hydroxyurea) for blast cell crisis, superior vena cava syndrome, or renal failure due to leukemic infiltration of the kidneys. When indicated, leukapheresis or exchange transfusion is recommended to reduce the WBC.
- Single-dose intrathecal cytarabine is allowed prior to registration or prior to initiation of systematic therapy for patient convenience. This is usually done at the time of the

diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. Systemic chemotherapy must begin within 72 hours of this intrathecal therapy.

3. Not pregnant and not nursing, because this study involves agents that have known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 8 days prior to registration is required.

- 4. Age \geq 18 years and < 40 years
- 5. ECOG Performance Status 0-2
- **6. Patients with Down Syndrome are excluded from this study** due to the likelihood of excessive toxicity resulting. These patients should be treated in consultation with a pediatric oncologist.
- 7. Lab Values

AST, ALT ≤ 3 x upper limit of normal (ULN),

unless suspected leukemic involvement of the liver

Direct Bilirubin ≤ 3 x upper limit of normal (ULN),

unless suspected leukemic involvement of the liver

Calc. Creatinine Clearance ≥ 50 mL/min by Cockcroft-Gault

Randomization Eligibility Criteria (Step 2)

1. Completion of remission induction therapy (per Section 7.2).

2. Patients with M2 marrow or better (see table below) are eligible. Patients with M3 or M4 marrow (greater than 25% lymphoblasts) will not be eligible to be randomized.

Rating	Blast Cells (%)*
M_0	0 - 5.0
M_1	0 - 5.0
M_2	5.1 - 25.0
M_3	>25.0 - 50.0
M_4	> 50.0

^{*} The term "blast cell" includes any cell that cannot be classified as a more mature normal element, and includes "leukemic cells," pathologic lymphocytes, and stem cells.

3. Lab Values

Absolute Neutrophil Count (ANC) $\geq 750/\text{mm}^3$

Platelet Count $\geq 75,000/\text{mm}^3$

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN), except

for patients with known Gilbert's syndrome

AST $\leq 8 \text{ x upper limit of normal (ULN)}$

Alliance A041501 PATIENT ENROLLMENT PATHWAY Schema Page 2 of 10 PRE-REGISTRATION (Step 0) BM sent to UNM for LDA for Stratification (see Section 3.2.1) & other baseline bone marrow specimens sent to HEME (see Section 6.2) Eligibility Confirmed per Section 3.3 REGISTRATION (Step 1)** COURSE I Remission Induction Therapy BM on Day 29 for local response assessment RESPONSE ASSESSMENT M₀, M₁, M₂ M₃ or M₄ <25% blasts >25% blasts RANDOMIZATION (Step 2) *Patients registered to Confirmation PATIENT NOT of Tolerability phase will be assigned RANDOMIZED. to treatment with the Arm 2 regimen WILL BE FOLLOWED FOR SURVIVAL ARM 1 ARM 2 EVERY 6 MOS. COURSE II MRD+ Treatment INOTUZUMAB (2 cycles)* Remission Consolidation BLINATUMOMAB COURSE II (up to 4 cycles) COURSE III Remission Consolidation LDA RESULTS Subsequent treatment Interim Maintenance COURSE III at investigator SHARED WITH COURSE IV Interim Maintenance TREATING discretion. Patients Delayed Intensification PHYSICIAN will be followed per COURSE IV study calendar in COURSE V Delayed Intensification Section 5.0. Prolonged Maintenance COURSE V Prolonged Maintenance

- Patients should receive IT methotrexate between cycles 1 and 2 of inotuzumab.
- *** If at any time a patient progresses or relapses on Arms 1 or 2, LDA results will be shared with the treating physician upon documentation of relapse or progression.
- For patients who are MRD positive after 2 cycles of inotuzumab or course 2 or any subsequent marrow ONLY.