Alliance 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

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Dana-Farber Cancer Institute

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Rationale

Inotuzumab ozogamicin is an antibody targeting CD22 conjugated with a cytotoxic antitumor antibiotic (calicheamicin). This agent is in development for the treatment of acute lymphoblastic leukemia (ALL). CD22 is expressed on the malignant cells of the majority of B-lymphocyte malignancies, including on the surface of lymphoblasts in the vast majority of patients with ALL (approximately 95%). Weekly dosing on days 1, 8, and 15 every 4 weeks is chosen for use in this trial as it has been shown to be generally safe and well tolerated in the previously Pfizer Pharmaceuticals Study B1931010.

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Objective

Primary

- To confirm tolerability of the combination regimen with the addition of inotuzumab ozogamicin to the pediatric-inspired regimen of CALGB 10403.
- To determine whether the addition of inotuzumab ozogamicin significantly improves the event-free survival (EFS) in patients who achieve an induction response achieved with the pediatric-inspired regimen of CALGB 10403, without censoring for transplant.

Secondary

- To determine the impact of inotuzumab ozogamicin on disease-free (DFS) and overall survival (OS) in patients who achieve an induction response.
- To determine whether the addition of inotuzumab ozogamicin significantly improves the event-free survival (EFS) in patients who achieve an induction response achieved with the pediatric-inspired regimen of CALGB 10403, with censoring for transplant.
- To determine the impact of inotuzumab ozogamicin on minimal residual disease (MRD) and correlate this with the EFS, DFS and OS.
- To determine the prognosis based on patients' LDA gene signature in terms of EFS, DFS, and OS after treatment with or without inotuzumab ozogamicin when added to the C10403 backbone regimen.
- To evaluate the toxicity and tolerability of the addition of inotuzumab ozogamicin to the pediatric-inspired regimen of CALGB 10403.

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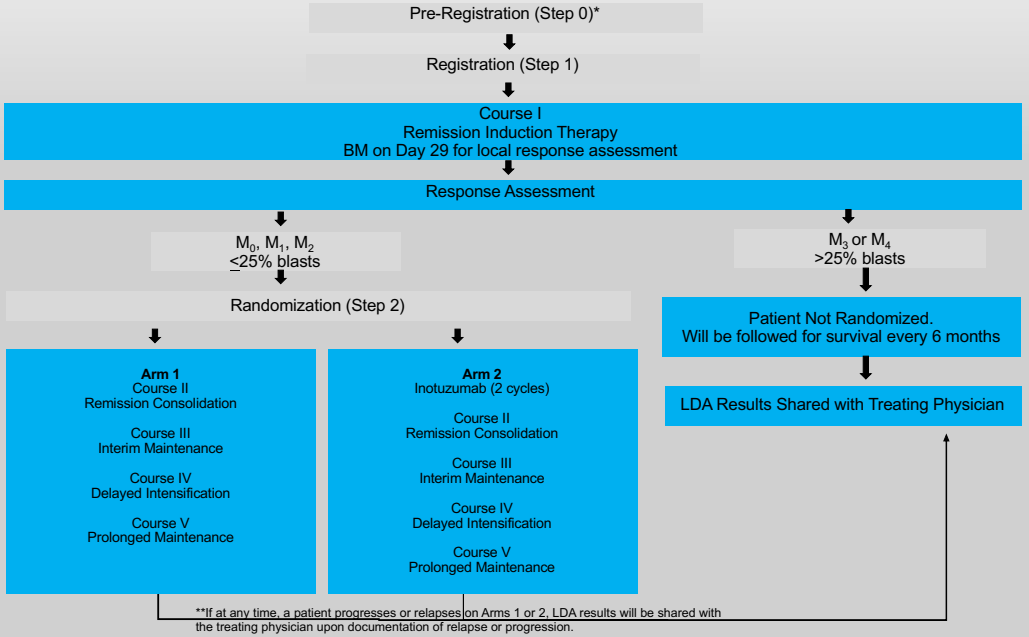
Study Schema



Limited Access Participating Alliance Institutions (Confirmation of Tolerability portion): MA036/Dana-Farber Cancer Institute, IL057/University of Chicago Comprehensive Cancer Center, NC007/University of North Carolina at Chapel Hill, OH007/Ohio State University Medical Center.

Participating NCTN Groups (Phase III only): ALLIANCE/Alliance for Clinical Trials in Oncology, ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG

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Treatment Plan

- Prior to initiation of therapy, patients need to be evaluated for CNS and testicular disease at diagnosis.
- Course I is to begin ≤ 5 days of registration (Step 1).
- Patients must meet eligibility in the protocol in order to be randomized.
- Randomization must occur within 21 days after completion of remission induction therapy.
- Patients will be assigned to treatment Arms 1 or 2 according to the results of Day I-29 bone marrow. Patients who achieve M2 or better (M0, M1, M2) will be randomized to Arm 1(C10403 backbone) or Arm 2 (C10403 backbone with two 28-day cycles of inotuzumab (1.5 mg/m2 per cycle unless found to not be sufficiently tolerable)).
- Patients who fail remission induction (M3 or M4) not be eligible for randomization, and the treating physician will be provided with LDA results.
- For patients who relapse at any time on Arms 1 or 2, LDA results will be provided to the treating physician. Patients randomized to Arm 1 will go straight to Consolidation Course II (refer to schema).
- Patients on Arm 1 should not receive inotuzumab.
- Patients randomized to Arm 2 will receive two 28-day cycles of inotuzumab.

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Eligibility Criteria

Key Registration Eligibility Criteria

- Newly diagnosed patients with CD-22 positive B-cell acute lymphoblastic leukemia (WHO criteria). Burkitt type ALL is 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 for this trial and should be considered for enrollment on studies that incorporate imatinib or other tyrosine kinase inhibitors during induction.
- Prior Treatment
  - No prior therapy for acute leukemia except emergency therapy (corticosteroids or hydroxyureafor ≤ 7 days) for blast cell crisis, or renal failure due to leukemia infiltration of the kidneys
  - Single-dose intrathecal cytarabine is allowed prior to registration (see also Section 7.1.1.2).
  - Prior steroid therapy is allowed.
- Not pregnant and not nursing.
- Age ≥ 18 years and < 40 years.
- ECOG Performance Status 0-2
- Patients with Down Syndrome are excluded from this study due to the likelihood of excessive toxicity. These patients should be treated in consultation with a pediatric oncologist

Confirmation of Tolerability

- To ensure safety and tolerability, researchers will treat the first 6 patients who respond to induction therapy with the Arm 2 regimen (i.e., the inotuzumab combination regimen) and will evaluate and confirm the tolerability of this regimen when inotuzumab is given at Dose Level 0 (0.5 mg/m2/day on Day 1, 8, and 15 of a 28-day cycle [total dose per cycle is 1.5 mg/m2/cycle]).

Phase III

- No prior therapy with the only exceptions being prior treatment with corticosteroids or hydroxyurea and a single dose of intrathecal cytarabine. Systemic chemotherapy must begin within 72 hours of this intrathecal therapy.

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