Alliance A041703: A Phase II Study of Inotuzumab Ozogamicin Followed by Blinatumomab for Ph-negative CD22-positive B-lineage Acute Lymphoblastic Leukemia in Newly Diagnosed Older Adults or Adults with Relapsed or Refractory Disease

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Rationale

Nearly 6,000 people in the U.S. are diagnosed with acute lymphoblastic leukemia (ALL) each year and about half of the cases occur in people over the age of 18. Although long-term survival has dramatically improved in pediatric ALL over the last 30 years with cure in about 80 percent of cases, adults with ALL have a much poorer prognosis. Data for patients over the age of 65 to 70 is minimal as most trials have either excluded or failed to enroll significant numbers of patients in this age group. Outcomes for both older patients with B-ALL and relapsed B-ALL remain poor with 1 year EFS of approximately 10%.

Given the failure of traditional multi-agent chemotherapy in untreated Ph-negative B-cell ALL in older, transplant-ineligible patients, investigations into novel targeted agents as front-line therapy is warranted to reduce toxicity and improve long-term survival in this population. The use of inotuzumab ozogamicin followed by blinatumomab may have multiple beneficial effects:

1. Based on its excellent safety and toxicity profile in the relapsed setting, induction with inotuzumab ozogamicin is predicted to be safer and more tolerable than multi-agent chemotherapy in this population predicting lower induction mortality.
2. Remission rates with inotuzumab ozogamicin in untreated B-ALL are predicted to be high, likely 90% or greater.
3. MRD negativity rates ay CR are also predicted to be high.
4. Based on data from treatment of patients with persistent or recurrent MRD in the front line, consolidation with blinatumomab is predicted to prolong duration of remission and may be curative in a substantial percentage of patients.

Inotuzumab ozogamicin yields high CR/CRi rates in relapsed/refractory CD22-positive B-cell ALL but with short duration of response. Blinatumomab can yield prolonged remissions but is most effective in the presence of low burden disease at initiation of therapy. In addition, improving outcomes with T-cell-dependent therapies such as blinatumomab may be difficult as combinations with traditional lymphotoxic therapies might reduce or eliminate the effectiveness of the drug. The combination of inotuzumab ozogamicin followed by blinatumomab is predicted to increase response rates, increase remission durations, be safe and tolerable, and help bridge more patients with relapsed B-ALL to allogeneic hematopoietic cell transplantation (HCT).

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Objectives

Primary

- **Confirmation of Tolerability:** To confirm tolerability of the combination regimen of inotuzumab ozogamicin followed by blinatumomab.
- **Cohort 1:** To estimate the 1-year event-free survival of older, transplant-ineligible patients with newly diagnosed, Ph-negative, CD22-positive B-cell ALL treated with inotuzumab ozogamicin induction followed by blinatumomab consolidation.
- **Cohort 2:** To estimate the 1-year event-free survival of patients with relapsed or refractory Ph-negative, CD22-positive B-cell ALL treated with inotuzumab ozogamicin induction followed by blinatumomab consolidation.

Secondary

Cohort 1: Untreated Ph-negative, CD22-positive B-cell ALL in Transplant-ineligible Older Patients

- To estimate the median, 1-year, and 3-year overall survival (OS) and relapse-free survival(RFS) in all eligible patients.
- To estimate the median and 3-overall response rate (ORR, defined as complete response[CR]+ complete response with incomplete count recovery [CRi]) to inotuzumab ozogamicin followed by blinatumomab (regimen CR rate and ORR).
- To estimate the CR rate and ORR (CR + CRi) to inotuzumab ozogamicin induction alone (induction CR and ORR).
- To estimate the minimal residual disease year event-free survival (EFS) in all eligible patients.
- To estimate the CR rate and (MRD) negativity rate in subjects achieving a CR or CRi.
- To estimate the treatment-related mortality with this regimen.
- To describe the safety and tolerability of this regimen.

Cohort 2: Relapsed or Refractory Ph-negative, CD22-positive, B-cell ALL Patients

- To estimate the median, 1-year, and 3-year OS and RFS in all eligible patients.
- To estimate the median and 3-year EFS in all eligible patients.
- To estimate ORR (CR/CRi and CR/complete response with partial hematologic recovery [CRh]) to blinatumomab in patients with ALL refractory to inotuzumab ozogamicin.
- To estimate the CR, CRi, and CRh rates at defined time points and cumulatively for the entire regimen.
- To determine the MRD negativity (< 10-4) rate at defined time points including prior to allogeneic HCT and cumulatively in patients achieving a CR, CRh, or CRi.
- To determine the allogeneic HCT rate in eligible subjects.
- To estimate the treatment-related mortality with this regimen.
- To describe the safety and tolerability of this regimen.

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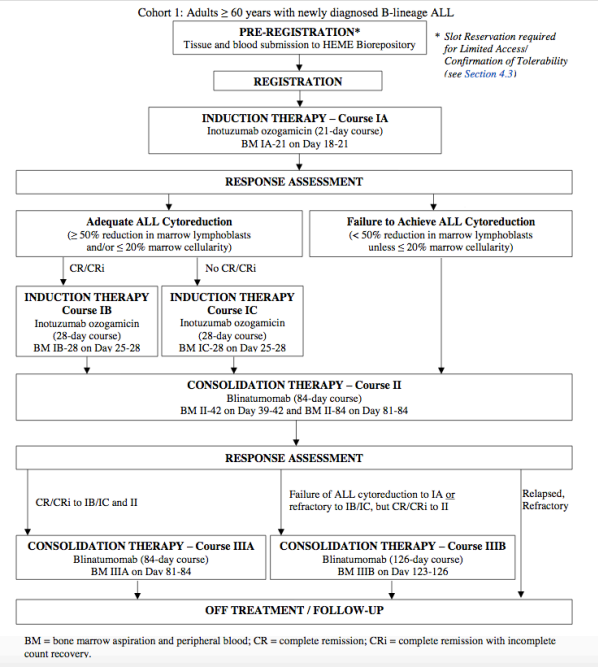
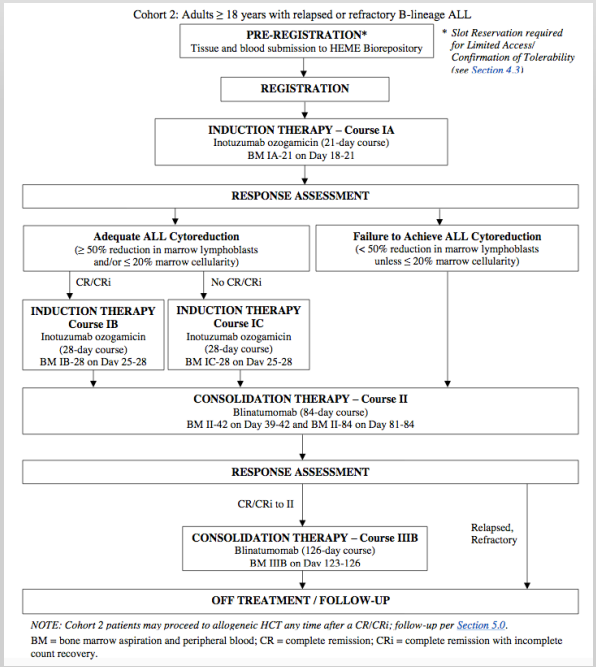
Study Schema

Patient Enrollment Pathway–Cohort 1



Patient Enrollment Pathway–Cohort 2



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Treatment Plan

- There will be a limited-access confirmation of tolerability portion prior to full access enrollment to the phase II study. Six patients will be enrolled to either cohort before enrollment of the entire study to assess safety and tolerability.

- Patients will be assigned to one of two groups (cohorts) based on their diagnosis.
  - **Cohort 1** will include patients 60 years and older with newly diagnosed B-lineage ALL.
  - **Cohort 2** will include patients 18 years and older with relapsed or refractory B-lineage ALL.

  Both Cohort 1 and Cohort 2 will undergo the same induction therapy with either one courses of inotuzumab ozogamicin for 21 days with response and MRD assessment. This will determine whether a patient will receive an additional course of induction therapy with inotuzumab ozogamicin (if adequate cytoreduction) or whether a patient will move on to consolidation therapy with blinatumomab. Cohort 1 and Cohort 2 will receive an 84-day course of consolidation therapy with blinatumomab given 28 days on 14 day off followed by response and MRD assessment. For Cohort 1, a patient will receive another 84-day (if CR/CRi to inotuzumab) or 126-day course (if no CR/CRi to inotuzumab) of consolidation with blinatumomab if in CR/CRi after first blinatumomab course. For Cohort 2, a patient will receive either a 126-day course of consolidation with blinatumomab if in CR/CRi after first blinatumomab course.

- After treatment, patients from both cohorts will continue with follow-up every three months for three years then every six months for seven more years for a total of 10 years after starting study treatment. In addition, investigators will collect the results of any of the usual blood or bone marrow tests patients have done in the subsequent five years to see if their DNA has changed.

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Rationale
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Eligibility Criteria

Inclusion Criteria

Pre-registration Eligibility Criteria (Step 0)

- Submission of bone marrow aspirate and peripheral blood for MRD analysis is mandatory prior to registration; the bone marrow sample should be from the first aspiration (i.e., first pull). It should be initiated as soon as possible after pre-registration. The specimens should be sent to the HEME Biobank.
    - Lumbar Puncture (Spinal Tap) and Intrathecal Methotrexate

Registration Eligibility Criteria (Step 1)

- ·Morphologic diagnosis of precursor B-cell acute lymphoblastic leukemia (ALL) based on World Health Organization (WHO) criteria. Patients with Burkitt lymphoma/leukemia are not eligible.
- CD22-positive disease defined as CD22 expression by >= 20% of lymphoblasts by local hematopathology evaluation.
- Philadelphia chromosome/BCR-ABL1-negative ALL by cytogenetics, fluorescence in situ hybridization (FISH), and/or polymerase chain reaction (PCR). If any test is positive for Philadelphia chromosome/BCR-ABL1, then the patient is ineligible.
- No active central nervous system (CNS) leukemia (i.e., only CNS-1 disease allowed).
- Patients with known or suspected testicular involvement by leukemia are allowed provided that the patient receives concomitant scrotal/testicular radiotherapy.
- Not pregnant and not nursing.
- ECOG Performance Status 0-2

Cohort 1 Patients Only

- Age $\geq$ 60 years
- No prior treatment for ALL except a single dose of intrathecal chemotherapy, corticosteroids, hydroxyurea, and/or leukapheresis to reduce peripheral blast count and prevent ALL complications.
- No plan for allogeneic or autologous hematopoietic cell transplantation (HCT).

Cohort 2 Patients Only

- Age $\geq$ 18 years
- Relapsed or refractory disease in salvage 1 or 2.
- No isolated extramedullary relapse.
- Prior allogeneic HCT permitted.
- Patients with prior allogeneic HCT must have completed transplantation $\geq$ 4 months prior to registration.
- Patients with prior allogeneic HCT must have no evidence of graft-versus-host disease and must have completed immunosuppressive therapy $\geq$ 30 days prior to registration.
- Prior treatment with inotuzumab ozogamicin, blinatumomab, other CD22-directed therapy, or other CD19-directed therapy is not allowed.

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