COG-AALL1621, A Phase 2 Study of Inotuzumab Ozogamicin (NSC# 772518, IND#133494) in Children and Young Adults with Relapsed or Refractory CD22+ B-Acute Lymphoblastic Leukemia (B-ALL)

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 be enrolled before treatment with InO 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 exception to this is for intrathecal therapy (IT), which can be given up to 7 days prior to administration of InO. If IT chemotherapy is given prior to enrollment, a separate institutional consent must be obtained for the IT therapy according to institutional standards for consent. 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. 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, total and direct 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. Bone marrow evaluation and imaging studies, if applicable, must be obtained within 2 weeks prior to start of protocol therapy (repeat these studies if necessary).

___3. Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps found in protocol Section 3.1.3.

___4. Age

Patients must be ≥1 year and < 22 years of age at the time of enrollment.

___5. Diagnosis

- Patients must have B-ALL, or previously diagnosed B-LL, with ≥ 5% (M2 or M3) bone marrow blasts with or without extramedullary disease.
  NOTE: Relapsed patients previously diagnosed with B-lymphoblastic lymphoma (B-LL) are eligible if they have an M2 or M3 marrow at the time of enrollment on this study.
- Patients with ALL or B-LL who have M2 morphology must have local confirmatory testing showing ≥ 5% blasts by flow cytometry, FISH testing or other molecular method.
- Leukemic blasts must demonstrate surface expression of CD22 at the time of relapse by local/institutional flow cytometry of a bone marrow aspirate sample. (Assessment of CD22 using a bright fluorophore such as PE is strongly recommended.)
  - In the case of an inadequate aspirate sample (dry tap) or if bone marrow aspirate is unable to be performed due to patient clinical status, flow cytometry of peripheral blood specimen may be substituted if the patient has at least 1000/μL circulating blasts. Alternatively, CD22 expression may be documented by immunohistochemistry of a bone marrow biopsy specimen.
- Patients with and without Down syndrome are eligible and must have one of the following:
  - Second or greater relapse;
  - Primary refractory disease with at least 2 prior induction attempts;
  - First relapse refractory to at least one prior re-induction attempt.
  - Any relapse after HSCT

Patients with Down syndrome are also eligible with:
  - First relapse with no prior re-induction attempt.
- Patients with Ph+ ALL must have had two prior therapy attempts including two different tyrosine kinase inhibitors (TKIs).

___6. Prior Therapy

Please see Section 4.2 for the concomitant therapy restrictions for patients during treatment.
Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy, defined as resolution of all such toxicities to ≤ Grade 2 or lower per the inclusion/exclusion criteria prior to entering this study.

- Myelosuppressive chemotherapy:
  - No waiting period will be required for patients receiving standard "maintenance-like" chemotherapy including oral mercaptopurine, weekly low-dose oral methotrexate, and intermittent vincristine. Otherwise, at least 14 days must have elapsed since the completion of cytotoxic therapy, with the exceptions of hydroxyurea or corticosteroids used cytoreduction (See Section 4.1.1 for cytoreduction details).
  - Intrathecal cytotoxic therapy: No waiting period is required for patients having received intrathecal cytarabine, methotrexate, and/or hydrocortisone. Intrathecal chemotherapy given at the time of diagnostic LP to evaluate for relapse prior to study enrollment is allowed.
- Hematopoietic growth factors: At least 7 days must have elapsed since the completion of therapy with a growth factor. At least 14 days must have elapsed after receiving pegfilgrastim.
- Biologic (anti-neoplastic agent): At least 7 days must have elapsed since completion of therapy with a biologic agent (including tyrosine kinase inhibitors). For agents that have known adverse events occurring beyond 7 days after administration, this period prior to enrollment must be extended beyond the time during which adverse events are known to occur.
- Monoclonal antibodies: At least 3 half-lives must have elapsed since prior therapy that included a monoclonal antibody with the exception of blinatumomab. See posting of half-lives for commonly used monoclonal antibodies in the table of myelosuppressive anti-cancer agents on the DVL committee page under the Tools and Reference materials tab at https://cogmembers.org/site/disc/devtherapeutics/default.aspx. Patients must have been off blinatumomab infusion for at least 3 days and all drug related toxicity must have resolved to grade 2 or lower as outlined in the inclusion/exclusion criteria.
- Radiotherapy: ≥ 2 weeks must have elapsed since local palliative XRT (small port); ≥ 3 months must have elapsed if prior cranial or craniospinal XRT was received, if ≥ 50% of the pelvis was irradiated, or if TBI was received; ≥ 6 weeks must have elapsed if other substantial bone marrow irradiation was given.
- Stem Cell Transplant or Rescue without TBI: At least 90 days must have elapsed since stem cell transplant and at least 30 days from donor lymphocyte infusion. Patient must have had no more than one previous HSCT and currently have no evidence of active graft vs. host disease (GVHD).
- Chimeric Antigen Receptor (CAR) T-Cell Therapy: At least 30 days must have elapsed from the last CAR-T cell infusion.

___7. Performance Status

Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. Please refer to performance status scale at: https://members.childrensoncologygroup.org/_files/protocol/Standard/PerformanceStatusScalesScoring.pdf. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

___8. Organ Function Requirements

- Adequate renal function defined as:
  - Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m2 or
  - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Adequate liver function defined as:
  - Direct bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 3 x ULN for age. For the purpose of this study, the ULN for ALT will be 45 U/L and the ULN for AST will be 50 U/L.

EXCLUSION CRITERIA:

___1. SOS: Patients with any prior history of SOS irrespective of severity.
___2. Patients with isolated CNS, testicular, or other extramedullary site of relapse.
___3. Patients who have been previously treated with inotuzumab ozogamicin.
___4. History of allergic reaction attributed to compounds of similar or biologic composition to inotuzumab ozogamicin or other agents in the study.
___5. Patients with active optic nerve and/or retinal involvement are not eligible. Patients who are presenting with visual disturbances should have an ophthalmologic exam and, if indicated, an MRI to assess optic nerve or retinal involvement.
___6. Concomitant Medications

- Investigational Drugs: Patients who are currently receiving another investigational drug.
- Anti-cancer Agents: Patients who are currently receiving or plan to receive other anti-cancer agents (except hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy, and intrathecal chemotherapy).
- Anti-GVHD or agents to prevent organ rejection post-transplant. Patients who are receiving cyclosporine, tacrolimus or other agents to prevent either graft-versus-host disease post bone marrow transplant or organ rejection post-transplant are not eligible for this trial. At least 3 half-lives must have elapsed after the last dose of GVHD meds.
- Corticosteroids: Patients who are currently receiving or plan to receive corticosteroids except as described below.
  - Systemic corticosteroids may be administered for cytoreduction up to 24 hours prior to the start of protocol therapy (Section 4.1.1), as a premedication for InO and as treatment for allergic reactions or for physiologic replacement/stress dosing of hydrocortisone for documented adrenal insufficiency. Corticosteroids are not allowed for other indications.

___7. Infection:

- Patients with known HIV, hepatitis B or C infections. Testing to prove negative status is not required for enrollment unless it is deemed necessary for usual medical care of the patient.
- Patients who have an active uncontrolled infection defined as:
  - Positive bacterial blood culture within 48 hours of study enrollment;
  - Fever above 38.2°C within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability.
  - A positive fungal culture within 30 days of study enrollment or active therapy for presumed invasive fungal infection.
  - Patients may be receiving IV or oral antibiotics to complete a course of therapy for a prior documented infection as long as cultures have been negative for at least 48 hours and signs or symptoms of active infection have resolved. For patients with *c. difficile* diarrhea, at least 72 hours of antibacterial therapy must have elapsed and stools must have normalized to baseline.
  - Active viral or protozoal infection requiring IV treatment.

___8. Patients known to have one of the following concomitant genetic syndromes: Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Shwachmann syndrome or any other known bone marrow failure syndrome.

___9. Pregnancy and Breastfeeding

There have been no human studies of InO in pregnant women and no reports of exposure in utero. Based on nonclinical safety studies, InO has the potential to impair human male and female fertility and to adversely affect human embryo-fetal development. Women of childbearing potential should be advised to avoid becoming pregnant while receiving InO. There is no information regarding the presence of InO in human milk, the effects on the breast-fed infant, or the effects on milk production. Because of the potential for adverse reactions in breast-fed infants, women should not breast-feed during treatment with InO and for at least 2 months after the final dose.

- Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained within 7 days prior to enrollment.
- Female patients who are sexually active and of reproductive potential are not eligible unless they agree to use an effective contraceptive method for the duration of their study participation and for 8 months after the last dose of InO.
- Men with female partners of childbearing potential should use effective contraception during treatment with InO and for at least 5 months after the last dose of InO.
- Lactating females are not eligible unless they agree not to breastfeed their infants.

REQUIRED OBSERVATIONS:

Required Observations in Cycle 1

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

- Physical exam with vital signs.
- Height, weight.
- CBC, differential and platelets.
- Total and direct bilirubin, ALT.
- AST, GGT, alkaline phosphatase, lipase, creatinine, albumin, electrolytes including Ca++, Mg++, PO4, BUN and ferritin.
- IgG.
- IgM, IgA, absolute lymphocyte count with T and B subset quantification.
- Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment.
- EKG.
- Obtain with each IT administration: CSF cell count, differential and cytospin.
- Bone marrow evaluation. BM evaluation at study entry should include morphology, immunophenotyping & cytogenetics/FISH. Cytogenetic/FISH analysis must be performed at a COG approved cytogenetics lab. (https://www.cogmembers.org/uploadedFiles/Site/Admin/Uploaded_Documents/Cytogenetics_Approved_Labs.pdf). If cytogenetics/FISH are not available from study enrollment, please document from prior diagnostic/relapse specimen. BM at end of cycle for morphology (FISH/cytogenetics not required)
- Bone marrow for MRD by flow cytometry. MRD analysis must be performed at a COG approved flow cytometry laboratory.
- Evaluation of testicular and extramedullary disease if applicable.
- Bone marrow for HTS MRD and mechanisms of InO resistance at study entry and Day 28. (Optional-consent required, See Section 13.1 and Section 13.5)
- Blood for SOS biomarkers at study entry and Day 28. (Optional-consent required, See Section 13.2)
- Blood for B-cell development at study entry and Day 28. (Optional-consent required See Section 13.3)
- Bone marrow for CD22 site density at study entry and Day 28. (Optional-consent required, See Section 13.4)
- Blood for post-InO dose PK on Day 1* (Optional-consent required, See Section 13.6)
- Blood for ADA/Nab Immunogenicity at study entry and Day 22. (Required, See Section 13.7)

TREATMENT PLAN:

Overview of Treatment Plan

This is a single-arm open label trial of inotuzumab ozogamicin in patients with relapsed/refractory CD22 positive B-ALL. All patients will receive inotuzumab ozogamicin intravenously on Days 1, 8 and 15. Premedication with corticosteroid, acetaminophen and antihistamine is strongly recommended. See Section 4.3.1 for details. A cycle of therapy is 28 days.

Dose limiting toxicity will be evaluated during Cycle 1. Patients will receive 2 cycles in the absence of treatment failure or unacceptable toxicity. Patients with CR or CRi after Cycle 2 may continue treatment for up to an additional 4 cycles for a total of 6 cycles.

For patients planning to receive an allogeneic HSCT, it is recommended that treatment with inotuzumab ozogamicin be limited to the fewest number of cycles required to achieve a CR/CRi. For patients achieving CR/CRi following Cycle 1, HSCT evaluation should proceed as quickly as possible so the patient does not receive more than 2 cycles of inotuzumab ozogamicin (see Appendix III for guidelines regarding HSCT after InO).

- Cytoreduction is strongly recommended for patients with ≥ 10,000/μL peripheral lymphoblasts. Hydroxyurea or corticosteroids may be administered up to 24 hours prior to the first dose of inotuzumab ozogamicin.

Concomitant Therapy - No other cancer chemotherapy, radiotherapy, or systemic immunomodulating agents may be used. Topical anti-inflammatory or immunomodulating agents are allowed.

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5

SPECIMEN REQUIREMENTS:

Research studies for which patient participation is required

InO/calicheamicin Pharmacokinetics and ADA/Nab Immunogenicity (See section 13.6 and section 13.7)

- Peripheral blood will be collected at the following time points:
  - Pre-InO dose samples will be collected during Cycle 1 on Day 8 and 15 and Cycle 2 on Day 1, 8, 15.
  - Random samples will be collected on Cycle 1 day 22 and Cycle 2 day 22.
  - ADA and Nab Immunogenicity samples will be collected during Cycle 1 at Baseline and Day 22 and Cycle 2 on Day 22

See Section 13.0 for optional research studies.

EXPERIMENTAL DESIGN SCHEMA

InO = Inotuzumab Ozogamicin
Cycle = 28 Days