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 systemic chemotherapy including inotuzumab ozogamicin 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 the start of systemic chemotherapy. 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 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 (Cohort 1 only)

- Patients with Down syndrome or prior HSCT are NOT eligible for Cohort 2 combination therapy.
- Patients with Ph+ ALL must have had two prior therapy attempts including two different tyrosine kinase inhibitors (TKIs).

Note: Patients with Down syndrome or prior HSCT are NOT eligible for Cohort 2 combination therapy.

___6. Prior Therapy

With amendment #4B, Cohort 1 accrual is complete. Revisions on eligibility criteria with Amendment #5 only apply to Cohort 2. Please see Section 4.3 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.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See DVL homepage for the Myelosuppressive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (https://cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx). For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
   - A waiting period prior to enrollment is not required for patients receiving standard cytotoxic maintenance chemotherapy (i.e., corticosteroid, vincristine, 6MP, and/or methotrexate).
   - A waiting period is not required for patients receiving a single dose of intrathecal methotrexate, hydrocortisone, and/or cytarabine within 7 days prior to enrollment
   - ≥ 14 days must have elapsed after the completion of other cytotoxic therapy, with the exception of hydroxyurea, for patients not receiving standard maintenance therapy. Additionally, patients must have fully recovered from all acute toxic effects of prior therapy.

     Note: Cytoreduction with hydroxyurea must be discontinued ≥ 24 hours prior to the start of protocol therapy.

b. Anti-cancer agents not known to be myelosuppressive (e.g., not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for the Myelosuppresive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (https://cogmembers.org/uploadedFiles/Site/Disc/DVL/Documents/TableOfMyelosuppressiveAnti-CancerAgents.pdf). For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
c. Anti-cancer agents that are antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1. There is an exception for blinatumomab infusions, for which patients must have been off 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. See DVL Homepage for the Myelosuppressive, Non- Myelosuppressive, and Antibody Anti-Cancer Agents table (https://cogmembers.org/uploadedFiles/Site/Disc/DVL/Documents/TableOfMyelosuppressiveAnti-CancerAgents.pdf).
d. Corticosteroids: See Section 3.3.8.4. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid. A waiting period prior to enrollment is not required for patients receiving corticosteroid for leukemia therapy/cytoreduction.
e. 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.
f. Stem Cell Transplant or Rescue without TBI: For Cohort 1, 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). For Cohort 2, no prior HSCT is allowed.
g. 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. Patients who have previously received HSCT (Cohort 2 only).
___5. Patients with Down syndrome (Cohort 2 only).
___6. History of allergic reaction attributed to compounds of similar or biologic composition to inotuzumab ozogamicin or other agents in the study.
Note: Patients with history of allergy to pegaspargase are eligible for enrollment on Cohort 2 if asparaginase *Erwinia* can be obtained.
___7. 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.
___8. 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 or anti-rejection medications.
- 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 (Cohort 1 only) (Section 4.4.1) For all patients, corticosteroids may be administered as a premedication for inotuzumab ozogamicin 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.

___9. 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.

___10. Patients known to have one of the following concomitant genetic syndromes: Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Shwachmann (Shwachmann-Diamond-Blackfan) syndrome or any other known bone marrow failure syndrome.

___11. Pregnancy and Breastfeeding

There have been no human studies of inotuzumab ozogamicin in pregnant women and no reports of exposure in utero. Based on nonclinical safety studies, inotuzumab ozogamicin 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 inotuzumab ozogamicin. There is no information regarding the presence of inotuzumab ozogamicin 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 inotuzumab ozogamicin 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 inotuzumab ozogamicin.
- Men with female partners of childbearing potential should use effective contraception during treatment with inotuzumab ozogamicin and for at least 5 months after the last dose of inotuzumab ozogamicin.
- Lactating females are not eligible unless they agree not to breastfeed their infants.

REQUIRED OBSERVATIONS:
Required Observations in Cohort 2, Cycle 1 (Dose level -2) Also see Section 4.1
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.
- ECG.
- 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.
- Evaluation of testicular and extramedullary disease if applicable.
- Bone marrow for HTS MRD and mechanisms of InO resistance at study entry and Day 36. (Optional-consent required, See Section 13.1 and Section 13.5)
- Blood for SOS biomarkers at study entry and Day 36. (Optional-consent required, See Section 13.2)
- Blood for B-cell development at study entry and Day 36. (Optional-consent required See Section 13.3)
- Bone marrow for CD22 site density at study entry. (Optional-consent required, See Section 13.4)

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 4.4.1.1 for details. For Cohort 2, inotuzumab ozogamicin is administered in combination with augmented mBFM Consolidation chemotherapy. A cycle of therapy is 36 days.

Dose limiting toxicity will be evaluated during Cycle 1. Patients will receive 2 cycles in the absence of treatment failure or unacceptable toxicity.

Cohort 2 Inotuzumab ozogamicin Dose Levels
The dose level will be assigned via eRDES at the time of study enrollment. The current dose level is -2 effective as of Amendment 9.

Dose Level	Cycle 1 Inotuzumab ozogamicin dose by day (mg/m^2)	Cycle 2 Inotuzumab ozogamicin dose by day (mg/m^2)	Chemotherapy
-2	Day 1: 0.6 Day 8: 0.3	Day 1: 0.3 or 0.6* Day 8: 0.3	Augmented mBFM consolidation without 6-MP; cyclophosphamide 25% dose reduction

6-MP = mercaptopurine
*Cycle 2, Day 1 inotuzumab ozogamicin dose depends on disease status at the end of Cycle 1

If excessive toxicity occurs at Dose Level -2, the study will be closed to accrual.

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).

Intrathecal Therapy
Due to frequent IT therapy for patients with CNS 2 and CNS 3 status and risk for neurotoxicity, these patients will receive leucovorin 5 mg/m2 IV/PO at hours 24 and 30 after all IT methotrexate or IT triple chemotherapy during Cycle 1 and after IT triple chemotherapy during Cycle 2.

If a patient has a history of severe methotrexate-related neurotoxicity with prior therapy before enrollment on study, and the treating physician deems administration of further IT methotrexate is not in the patient's best interest, the physician may consider substitution of IT cytarabine +/- hydrocortisone for IT therapy with approval of the study chair. If IT methotrexate is omitted, leucovorin rescue is not necessary.

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:
See Section 13.0 for details of optional research studies.

13.0 SPECIAL STUDIES SPECIMEN

Optional Studies, Patient Consent Req

	Baseline (before systemic chemo begins)
HTS MRD Section 13.1	X
SOS Biomarkers Section 13.2	X
B-Cell Development/ Intracellular Signaling Section 13.3	X
CD22 Site Density Section 13.4	X
Mechanisms of Inotuzumab ozogamicin Resistance Section 13.5	X

EXPERIMENTAL DESIGN SCHEMA—COHORT 2 (EFFECTIVE WITH AMENDMENT #9)

InO = Inotuzumab Ozogamicin
Cycle = 42 Days