THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase II Study of Low Dose Inotuzumab Ozogamicin in Patients with Relapsed and Refractory CD22 Positive Acute Lymphocytic Leukemia
2015-0870

Core Protocol Information

Short Title	Low-Dose INO in R-R ALL
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

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Phase II Study of Low Dose Inotuzumab Ozogamicin in Patients with Relapsed and Refractory CD22 Positive Acute Lymphocytic Leukemia

1.0 Objectives

1.1 Primary Objectives: To evaluate the objective response rate of low dose of inotuzumab ozogamicin as measured by the hematologic remission rate (CR + CRp + CRi) in patients in first, second or later salvage setting.

1.2 Secondary Objectives: To evaluate the overall safety profile and the efficacy; the efficacy is measured by the hematologic response rate (CR + CRi + PR), durations of response (DoR) and remission (DoR1), progression free survival (PFS), and overall survival (OS)

2.0 Patient Eligibility

Inclusion Criteria:

1. Patients at least 12 years of age.
2. Patients with a diagnosis of CD22-positive ALL based on local immunophenotying and histopathology) who have:
    a. Refractory disease, defined as disease progression or no response while receiving their most recent prior anti-cancer therapy.
    b. Relapsed disease, defined as response to their most recent prior anti-cancer therapy with subsequent relapse.
3. Performance status of 0 to 3.
4. Adequate renal function including serum creatinine ≤2 x upper limit of normal (ULN) or estimated creatinine clearance ≥15 mL/min as calculated using the method standard for the institution.
5. Adequate liver function, including total serum bilirubin ≤1.5 x ULN unless the patient has documented Gilbert syndrome, and aspartate and alanine aminotransferase (AST or ALT) ≤2.5 x ULN. If organ function abnormalities are considered due to tumor, total serum bilirubin must be ≤2 x ULN
6. No active or co-existing malignancy requiring chemotherapy or radiation within 6 months.
7. Female subjects of childbearing potential should be willing to use effective methods birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Effective methods of birth control include birth control pills or injections, intrauterine devices (IUDs), or double-barrier methods (for example, a condom in combination with spermicide).

8. Male subjects should agree to use an effective method of contraception starting with the first dose of study therapy through the duration of treatment.

Exclusion criteria:

1. Pregnant or nursing women
2. Known to be HIV+
3. Ph+ ALL
4. Active and uncontrolled disease/infection as judged by the treating physician
5. Unable or unwilling to sign the consent form
6. Prior allogeneic stem cell transplantation (ASCT) or other anti-CD22 immunotherapy within ≤4 months before first dose of study treatment.
7. Known CNS or extramedullary disease unless approved by the PI.
8. Monoclonal antibodies therapy within 2 weeks before study entry
9. Radiotherapy and cancer chemotherapy (except for intrathecal chemotherapy, hydroxyurea, and cytarabine. Cytarabine and hydroxyurea are allowed to be used emergently in case of leukocytosis) or any investigational drug within 2 weeks before study entry.
10. Evidence or history of veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS)

3.0 Treatment Plan

3.1 This is an open-label, single-arm, phase II clinical study.

3.2 All patients will be registered through CORe

3.3 Patients will receive inotuzumab ozogamicin at the dose of 0.8 mg/m^2 on Day 1 (+/- 3 days), and 0.5 mg/m^2 on Days 8 and 15 (+/- 3 days) of cycle 1. Subsequent cycles will consist of inotuzumab ozogamicin at the dose of 0.6 mg/m^2 on Day 1 (+/- 3 days) and 0.3 mg/m^2 on Day 8 (+/- 3 days). Patients will have a bone marrow aspiration performed on Day 14 and Day 21 (+/- 3 days). If marrow aspiration shows no disease, Cycle 2 could resume on Day 28 (+/-7 days) at the dose level recommended in section 8.1.6. If persistence disease (defined by bone marrow blasts >5%), Cycle 2 would resume as early as Day 22 (+/- 7 days). Responding (CR, CRi, CRp) patients could receive up to 5 additional cycles. A maximum of 6 cycles will be administered.

3.4 In patients with an allogeneic donor, an allogeneic stem cell transplantation will be offered at any time after the first cycle of treatment with inotuzumab ozogamicin. Cycles are to be repeated every 3 to 4 weeks.

3.5 Responders will be permitted to receive up to five additional consolidation cycles of treatment with inotuzumab ozogamicin.

3.6 CSF prophylaxis consisting of an intrathecal regimen according to institutional guidelines during and after inotuzumab treatment will be left to the investigator's discretion.

3.7 Patients who relapse after achieving a response for at least 3 months can be retreatedfor up to 6 additional cycles.

4.0 Pretreatment evaluation

Procedure	Comments	Schedule
Informed Consent	Obtain standard informed consent approved by IRB	Within 21 days before therapy
Medical History	History of present illness, known allergies, prior cancer history as far as traceable including ALL regimens and drugs uses, and past medical/ surgical history as far as relevant.	Within 14 days of therapy
Physical Examination	Vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status.	Within 14 days of therapy
Concomitant Medications	Document concomitant medications in the medical record	Within 14 days of therapy
Hematology	CBC with differential and platelet count	Within 14 days of therapy
Biochemistry	at least creatinine, total bilirubin, uric acid, LDH, SGPT or SGOT	Within 14 days of therapy
Bone marrow	Aspirate and/or biopsy with flow cytometry for confirmation of diagnosis; a sample will be stored for PCR assessment	Within 21 days of therapy
Pregnancy test	Serum or urine, if female *and* child-bearing potential only	Within 14 days of therapy
Imaging studies	Chest X-ray and/or PET/CT as clinically indicated	Within 14 days of therapy

5.0 Evaluation During Study

Procedure	Comments	Schedule
Hematology	CBC with differential and platelet count	Weekly during cycles 1 to 6
Biochemistry	at least creatinine, total bilirubin, SGPT or SGOT	Cycle 1, prior to study drug infusion Cycle 2-6, prior to each study drug infusion and/or at the discretion of the treating physician.
Physical Examination	Focused physical examination	Prior to each treatment cycle
Bone marrow	Aspirate and/or biopsy (MRD) by flow multicolor cytometry and by polymerase chain reaction (PCR).	On day 14, 21 +/- 3 days of the first cycle, then every 2-3 cycles.

5.1 Follow-up

Patients will be followed up to 30 days after completion of treatment. Afterward they may be enrolled and followed for survival under protocol DR09-0223.

6.0 Criteria for Response

Complete remission (CR):
Normalization of the peripheral blood and bone marrow with 5% or less blasts with a granulocyte count of 1 x 10^9/L or above and a platelet count of 100 x 10^9/L or above and absence of extramedullary disease.

Complete remission without platelet recovery (CRp):
As above except platelets < 100x10^9/L

Complete remission with incomplete count recovery (CRi):
CR without recovery of neutrophils or platelet counts

Partial response (PR):
As above, except for the presence of 6-25% marrow blasts.
MRD negativity:

MRD levels will be continuously assessed during induction and consolidation therapy by 6-color multiparameter flow. MRD negativity will be defined by a value of no more than 10^{-4} and confirmed on a second bone marrow aspiration/biopsy performed after a subsequent cycle.

No response (NR):

Patients will be considered non-responders if no response is achieved after 2 cycles.

7.0 Background

7.1 Salvage therapy in acute lymphoblastic leukemia (ALL).

Despite an exceptionally high rate of initial CR, many adults with ALL will relapse. Current strategies to induce a second remission translating into long-term survival are lacking. Cytotoxic chemotherapy results in modest CR rates of 30-40% in first salvage and 10-20% in later salvages. Few patients can be bridged to allo-SCT, 5-10% in some studies but as high as 30-40% in the German trials[1,2]. This bridging to allo-SCT offers a chance of long term remissions and cures (<20-30%). One of the most exciting groups of compounds under investigation in relapsed refractory (R/R) ALL are monoclonal antibodies

targeting CD19 and CD22. Of these antibodies, blinatumomab and inotuzumab ozogamicin are in the most advanced investigational phases (Table 1). Blinatumomab was granted FDA approval for the treatment of R/R ALL in December 2014. Furthermore, inotuzumab was found to be superior to best available therapy in a randomized trial in patients with R/R ALL and was granted FDA approval for the treatment of R/R B-cell precursor ALL in August 2017.

The randomized trial confirmed the findings of the initial phase II studies. Inotuzumab induces responses in 80% of the patients with a median survival of 7.7 months. The rate of VOD was 10%. The aim of this study is to reduce the rate of VOD without minimizing efficacy.

Table 1. Monoclonal antibodies in relapsed/refractory ALL

	N (%)			
	Blinatumomab		**Inotuzumab**	
Parameter	Pivotal Study, n=36	Confirmatory Study, n=189	Single dose n=49	Weekly n=40
Overall Response	25 (69)	81 (43)	28 (57)	24 (60)
Salvage Status				
Salvage 1	11 (31)	38 (20)	13 (27)	16 (40)
Salvage 2+	10 (28)	151 (80)	36 (73)	24 (60)
Median survival (months)	9.8	6.1	5.0	9.5

7.2 Inotuzumab ozogamycin

7.2.1 Description

Inotuzumab ozogamicin (INO) consists of a semisynthetic derivative of N-acetyl ɣ-calicheamicin 1, 2-dimethyl hydrazine dichloride (NAc ɣ-calicheamicin DMH), a potent DNA-binding cytotoxic antibiotic, attached to a humanized monoclonal IgG4 antibody, G544, directed against the CD22 antigen present on B cells in all patients with mature B-ALL and most patients (>90%) with precursor B-ALL[3]. Anti-CD22 monoclonal antibody without conjugated cytotoxic drug has shown to have no anti-tumor activity in preclinical models; instead conjugation with cytotoxic agent provides potent dose-depending cellular damage[4]. This is likely because IgG4 antibodies poorly fix complement, therefore cannot cause apoptosis via complement-mediated and antibody-dependent cytotoxicity[5]. Calicheamicin is natural product of Micromonospora echinospora species, and considered to be intolerantly toxic when not bound to the antibody[6].

Calicheamicin is linked to the antibody through 4-(4-acetylphenoxy) butanoic acid (acetyl butyrate) which provides stability in physiologic pH and successful

calicheamicin release inside the acidic environment of the lysosomes[7]. INO binds to CD22 receptor on the surface of B-cell, and the CD22 receptor-INO complex is internalized forming an endosome. Subsequently, CD22 receptor-INO complex containing endosome fuses with lysosomes. This is followed by intracellular release of calicheamicin. Calicheamicin binds to the minor groove of DNA in a sequence specific manner, and breaks double-stranded DNA, resulting in cell death.

7.2.2 Pharmacodynamics

Treatment with INO has been shown to provide greater therapeutic benefit, as single agent, compared to CVP or CHOP in B-cell NHL xenografts[8]. INO also showed anti-tumor activity in CVP- and CHOP-refractory tumors; however duration of the INO effect was not as sustained as it was in treatment naïve B-cell NHL xenografts. This observation shows that INO treatment may regress tumor growth in chemotherapy refractory cases, but eventually, some malignant B-cells can escape the anti-tumor activity and re-grow. Gemtuzumab Ozogamicin (GO), another antibody-drug conjugate of NAc γ-calicheamicin DMH, is directed against CD33 antigen, and has been used in treatment acute myeloid leukemia (AML)[9]. However, drug resistance had negative impact on clinical outcome of patients treated with GO[10]. It is proposed that the drug resistance was associated with P-glycoprotein (P-gp) expression. P-gp is a membrane glycoprotein that actively pumps cytotoxic agents out of the cells and decreases intracellular concentration the drug[11] [Takeshita et al., 2005]. As with GO, INO was also found to be effected with the same resistance mechanism. In a study, INO had no effect on CD22-positive malignant cell lines with P-gp expression compared to parental cells[11]. In clinical samples, the toxic effect of the INO was inversely related to the amount of P-gp ($p=0.003$). In contrast, the cytotoxicity of INO positively correlated with the amount of CD22 ($p=0.010$).

INO is a CD22-targated cytotoxic chemotherapy agent without any effector capabilities; in contrast rituximab is a CD20-targated immunotherapeutic agent with the capability of complement-mediated and antibody-dependent cellular toxicity. Combination of INO and rituximab has been tested in vitro setting, and showed increased cytotoxicity[12]. Anti-tumor efficacy of INO and rituximab combination has also been tested in B-cell NHL preclinical models, and demonstrated superior activity with the combination[13]. In a phase 2 clinical trial evaluating the efficacy of INO in relapsed and refractory ALL patients, rituximab was added to the patients with stable or progressive disease after two courses of INO. Addition of rituximab in nine patients with CD20 positive ALL did not provide any additional benefit[6]. Nevertheless, it was a single-arm study with a small number of patients. Efficacy of this combination in ALL patients needs to be evaluated in larger clinical trials.

7.2.3 Pharmacokinetics

Maximum tolerated dose (MTD) was determined as 1.8 mg/m^2 by a first-in-human clinical trial evaluating the safety of INO in 79 relapsed and refractory NHL patients[5]. Most patients had follicular lymphoma (FL) (44%) and diffuse large B-cell lymphoma (DLBCL) (44%), and 61% of the patients had received ≥ 4 prior chemotherapies. Following dose escalation schedules were evaluated: 0.4, 0.8, 1.34, 1.8 and 2.4 mg/m^2 intravenously (as a 1-hour infusion) once every 3 weeks in MTD lead-in cohort (36 patients). Escalation stop criteria were met as 2 of 6 cohort patients had dose limiting toxicities (one grade 4 neutropenia, one grade 4 thrombocytopenia) at 2.4 mg/m^2. Thus, 1.8 mg/m^2 was established as MTD. Reversible thrombocytopenia is one of the main (90%) side effects of INO, and it led to a number of treatment delays. Therefore, declared MTD was evaluated in once every 4 weeks schedule to allow platelet recovery. Dose limiting toxicity was not observed in the six-patient cohort of 1.8 mg/m^2 once every 4 weeks. As a result, this regimen was used in extended MTD cohort (43 patients). At the end of treatment, objective response rate was 39% among 79 enrolled patients. Administration of INO with a weekly dosing schedule (same total dose of 1.8 mg/m^2 per cycle) compared to single-dose schedule allowed similar response rates and less toxicity in multiply relapsed B-ALL patients[14]. The data showed that inotuzumab ozogamycin disposition was non-linear with number of dose or increasing dose. Non-linearity is seen commonly with other antibodies as well[15]. Non-linear pharmacokinetics of monoclonal antibodies is due to target-mediated drug disposition, in which elimination and distribution are affected by the antibody and target cell interaction[16]. Anti-CD22 antibody and total calicheamicin followed similar elimination trend, and the free calicheamicin concentration remained less than 50 pg/mL overtime, suggesting that the acetyl butyrate linker is noticeably stable in plasma[5].

7.3 Inotuzumab in R/R ALL

7.3.1 Single agent inotuzumab ozogamicin

Initial studies in patients with lymphoma established an MTD of 1.8 mg/m^2 IV given every 3 to 4 weeks, with reversible thrombocytopenia emerging as a frequent adverse effect.[5] This led to a single institution phase II study in patients with relapsed-refractory ALL[6]. The starting dose was 1.3 mg/m^2 IV every 3 to 4 weeks for the first three patients; later patients received 1.8 mg/m^2.

Acetaminophen, diphenhydramine, and hydrocortisone were administered to prevent infusion reactions. Forty-nine patients were treated, 73% of whom received inotuzumab for Salvage 2 or later. The ORR was 57%, and the median survival was 5.1 months (Table 2). Nearly half of the patients treated with inotuzumab were able to proceed to ASCT (n = 22), including four patients who were receiving their second ASCT. Survival was similar whether patients underwent subsequent ASCT or not.

To optimize the benefit:risk of inotuzumab, a weekly dosing regimen was evaluated based on preclinical studies indicating that toxicity might be minimized while maintaining efficacy (Table 2).[14] Inotuzumab was given at 0.8 mg/m^2 on Day 1, and 0.5 mg/m^2 on Days 8 and 15, every 3-4 weeks. This is the same cumulative dose per course compared with single infusion inotuzumab every three to four weeks. With the weekly regimen, ORR was similar to the single-dose schedule (59% versus 57%). The median survival was 9.5 months. The weekly regimen was less toxic. Additionally, 37 patients with relapsed/refractory ALL received weekly inotuzumab in a multicenter phase I/II study[17]. Seventeen (46%) patients were in Salvage 1, 9 (24%) in Salvage 2, and 11 (30%) in Salvage 3 or later. The CR and CR without count recovery rates were 79% (19/24) and 46% (6/13) in the dose expansion and dose escalation cohorts, respectively. Eighteen of the nineteen patients in the dose escalation cohort and four of the six in the dose expansion cohort achieved MRD negativity. These encouraging results led to an international study comparing weekly inotuzumab to standard ALL chemotherapy (FLAG at MD Anderson) in ALL salvage 1-2. The objective response rates were 81% and 33%, respectively. Among responders, the MRD-negativity rates were 78% and 28%, respectively. The median response duration was 4.6 versus 3.1 months (p=0.017), respectively.

Table 2. Activity of inotuzumab ozogamicin in patients with relapsed/refractory ALL

	N (%)		
Parameter	Single-Dose, n=49	Weekly, n=40	Overall, n=89
Response			
CR	9 (18)	8 (20)	17 (19)
CRp	16 (33)	13 (33)	29 (33)
CRi, bone marrow CR	3 (6)	3 (8)	6 (7)
PR	0	0	0
Resistant	18 (37)	14 (35)	32 (36)
Death < 4 weeks	3 (6)	2 (5)	5 (6)
Salvage			
Salvage 1	13 (27)	16 (40)	29 (33)
Salvage 2+	36 (73)	24 (60)	60 (67)
Median survival (months)	5.0	9.5	6.2

7.3.2 Combination of inotuzumab ozogamicin with chemotherapy

Given the promising results in the salvage studies, inotuzumab was evaluated in combination with chemotherapy. A group of patients with ALL who may particularly benefit from a more targeted regimen is elderly patients (age greater than 60 years). This group is predisposed to severe toxicity from conventional chemotherapy, which is associated with high mortality rate (30-35%) during consolidation-maintenance in CR. Thirty-four older patients (median age of 69 years; range, 60 to 79) with newly diagnosed ALL were treated in a phase II study combining inotuzumab and low-intensity hyperCVAD therapy.[18] The

regimen eliminated doxorubicin in induction, used cyclophosphamide and steroids at 50% of the dose of previous regimens, and reduced methotrexate to 250 mg/m^2 on Day 1 and cytarabine to 0.5 mg/m^2 x4 (Days 2 and 3) of even courses. Inotuzumab 1.3-1.8 mg/m^2 was given once with each of the first 4 courses. The ORR was 97% (CR 83%). All patients with cytogenetic abnormalities achieved complete cytogenetic response. All patients achieving response also had a negative MRD status, 75% of them after one cycle. The 2-year progression-free and overall survival rates were 87% and 70%, respectively. The 2-year survival rate was superior to previous results obtained with HCVAD +/- rituximab in similar patient populations (2-year survival rates 70% and 38%, respectively).

This combination was also assessed as a salvage therapy in 48 patients. The ORR was 74% (CR 52%) The 12-month progression-free and overall survival rates were 88% and 81%, respectively[19].

7.4 Inotuzumab ozogamicin toxicity profile

Transient fever and hypotension were the 2 most frequent non-hematologic adverse events, and typically occurred shortly after the inotuzumab infusion. Liver function abnormalities were also observed, but tended to be reversible. Serious toxicity in the transplant group included the development of veno-occlusive disease (VOD) in five patients (23%). Four of the 5 patients had received multiple alkylating agents in the transplant preparative regimen, including clofarabine which may have predisposed them to VOD. Two of the 4 patients undergoing second ASCT developed VOD, suggesting this group of patients to be also at higher risk for VOD. In elderly ALL and in combination with low intensity chemotherapy, 4 patients (11%) developed a VOD, one of them post allogeneic stem cell transplantation. All but one patient had mild VOD that resolved subsequently. Only one patient developed a Grade 5 VOD after 2 cycles, was switched to miniHCVD and ofatumumab, received 2 more additional courses, developed anasarca and multiple organ failure and expired thereafter. The safety profile of inotuzumab ozogamicin vs standard of care (SOC) was consistent with the initial studies. For inotuzumab vs SOC, Gr≥3 hepatobiliary AEs occurred in 9% vs 3% patients; any grade VOD occurred in 15 (14%) vs 1 (0.9%) patient (Gr≥3, 13 vs 1 patients). More patients proceeded to ASCT with inotuzumab (n=48) vs SOC (n=20); in the inotuzumab arm, 5 VOD cases (2 in patients with prior ASCT) occurred during treatment and 10 after subsequent SCT (2 fatal).

8.0 Background Drug Information

8.1 Inotuzumab

8.1.1 Formulation and packaging

Inotuzumab ozogamicin is a white to off-white powder or cake, lyophilized, unpreserved 1- mg or 4-mg protein equivalent powder for intravenous injection in an amber vial.

8.1.2 Preparation and dispensing

Specific preparation and dispensing instructions for inotuzumab ozogamicin are provided in the Dosage and Administration Instructions. Once inotuzumab ozogamicin has been prepared following the Dosage and Administration Instructions, the site pharmacist will label the study medication in accordance with local requirements. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

8.1.3 Administration

All patients must be weighed within 7 days prior to every cycle day 1 dosing to ensure they did not experience either a weight loss or gain >10% from the prior weight used to calculate the amount of inotuzumab ozogamicin required for dose preparation. Decision to recalculate the dose of inotuzumab ozogamicin based on the weight obtained at each cycle can be in accordance with institutional practice; however, if the patient experienced either a weight loss or gain >10%, the required amount of inotuzumab ozogamicin needed for study drug preparation and administration must be recalculated using this most recent weight/BSA obtained. If the dose administered is 10% greater or lower than the one prescribed, it will be reported as a dosing medication error.

Inotuzumab ozogamicin is administered intravenously. Subjects will receive a dose of 1.8 mg/m^2 over the first cycle (0.8 mg/m^2 on D1, 0.5 mg/m^2 on D8 and D15 [+/- 3 days]) of 21 to 28 days cycle. The remaining 5 cycles (total of 6 overall) will consist of 0.9 mg/m^2 administered in 2 divided weekly doses of inotuzumab ozogamicin (0.6 mg/m^2 on Day 1 [+/- 3 days], 0.3 mg/m^2 on day 8 [+/- 3 days]) over a 21- to 28-day cycle.

Pretreatment: Prior to inotuzumab ozogamicin treatment, subjects should receive pretreatment medications to reduce the incidence and severity of an anticipated infusion syndrome characterized by fever and chills, and less commonly hypotension. Pretreatment prior to inotuzumab ozogamicin includes corticosteroid, antipyretic, and antihistamine. Premedication before inotuzumab ozogamicin may also include antiemetics. Antiemetics with the least potential of side effects are recommended. Subjects should be pretreated with methylprednisolone (or other corticosteroid), acetaminophen/paracetamol and diphenhydramine (or other antihistamine) approximately 0.5 to 2 hours before each inotuzumab ozogamicin administration. In cases of infusion reactions, discontinue infusion and institute appropriate medical treatment as needed (eg, glucocorticosteroids, epinephrine, bronchodilators, or oxygen). Depending on the

severity of the infusion reaction and interventions required, the investigator could consider restarting the infusion at a reduced rate.

Reconstituted inotuzumab ozogamicin will be administered over approximately 1 hour by intravenous infusion unless the subject requires temporary interruption of the administration.

Vital Signs during inotuzumab administration:

- Cycle 1 Day 1 (first inotuzumab infusion): Prior to inotuzumab, approximately 30 minutes into infusion, just prior to end of infusion, approximately 1 hour and approximately 2 hours after end of infusion. All Subsequent infusions: Prior to inotuzumab and at end of infusion (+/- 15 min).

8.1.4 Recommended dose modifications

In the event of significant toxicity, dosing may be delayed as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Dose modifications may occur as follows:

1. Within a cycle: dose interruption until adequate recovery (Grade ≤1) or omission of a dose during a given treatment cycle.
2. Between cycles: next cycle administration may be postponed due to toxicity in the previous cycle.
3. In the next cycle (Cycle 3 and beyond): dose reduction based on worst toxicity or to 0.6 mg/m^2/cycle if hematologic remission is achieved in the previous cycle.

8.1.5 Dose delays

If patients do not meet the criteria below on the day of the scheduled treatment, the administration of the dose will be delayed.

1. No evidence of progressive disease or relapse prior to the start of each cycle; however, treatment may continue, at the judgment of the investigator, in patients with only extramedullary CNS and/or testis relapse.
2. Prior to the start of each cycle, decrease in blast percentage or stable disease (ie, not more than a 50% increase in blast percentage) based on the most recent bone marrow evaluation.
3. Recovery to grade 1 or baseline non-hematologic clinically significant test article-related toxicity (including liver function test abnormalities, not including alopecia).

4. Serum bilirubin ≤1.5 x ULN, and AST or ALT ≤2.5 x ULN (or if elevated due to tumor, bilirubin ≤2 x ULN). Isolated AST or alkaline phosphatase elevations need not result in dose delays if not related to hepatobiliary organs (eg, alkaline phosphatase elevations due to bone involvement). Inotuzumab ozogamicin dosing should be permanently discontinued for any patients with possible, probable or confirmed VOD or other severe liver toxicity.
5. Any serum creatinine level associated with a measured or calculated creatinine clearance ≥ 15 mL/min using the method standard for the institution.
6. Prior to the start of each cycle, for subjects with pre-treatment ANC ≥1 x 10^9/L: ANC ≥1 x 10^9/L.
7. Prior to the start of each cycle, for subjects with pre-treatment platelets ≥50 x 10^9/L: platelets ≥50 x 10^9/L.
8. Subjects with pre-treatment ANC <1 x 10^9/L and/or platelets <50 x 10^9/L: ANC and platelets must recover to baseline values obtained for the prior cycle, or ANC ≥1 x 10^9/L and platelets ≥ 50 x 10^9/L, or the most recent bone marrow must demonstrate stable or improved disease, and the ANC and platelets are believed to be low due to disease.

There are no ANC or platelet count requirements for Cycle 1 day 1, as dosing criteria are relative to pre-treatment values. While doses given within a treatment cycle (ie, day 8) need not be delayed due to neutropenia or thrombocytopenia, dose delays within a cycle are recommended for non-hematologic toxicity.

Dose delays due to drug toxicity ≤7 days during a treatment cycle are permitted. Dose delays of >7 days within a cycle will result in omission of the subsequent dose; the subject remains eligible to receive the subsequent planned doses. If a treatment interruption continues beyond day 14 of the current cycle, then the day when treatment is restarted will be considered day 1 of the next cycle. Dose delays due drug toxicity >28 days at the end of a treatment cycle (ie, delay of day 1 dosing of subsequent cycle) will result in permanent discontinuation of study treatment. All toxicity grades are according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v 4.03).

8.1.6 Dose reductions

Dose reductions may also be required based on the worst toxicity experienced in the previous cycle. Patients experiencing a treatment interruption due drug toxicity ≥14 days may resume dosing at the next lower dose level (if a lower dose level is available) for the subsequent cycle once adequate recovery is achieved. Dose reductions to the next lower dose level (if a lower dose level is available) should also be considered for patients with CRi, whose platelet counts have not recovered to values obtained prior to the start of the previous cycle. Once a patient has a dose reduction for a drug-related toxicity, the dose will not be re-

escalated. Patient requiring more than two dose reductions will be withdrawn from treatment study.

Dose Level	Day 1 Dose (mg/m^2)	Day 8 Dose (mg/m^2)	Total dose Per Cycle (mg/m^2)
0 (Starting dose beyond C1)	0.6	0.3	0.9
-1	0.4	0.2	0.6
-2	0.3	0.1	0.4

8.2 Drug storage and drug accountability

The amber vials of inotuzumab ozogamicin are to be stored at 2°C to 8°C (36°F to 46°F). Inotuzumab ozogamicin is light sensitive and should be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. Preparation of inotuzumab ozogamicin should occur in full compliance with institutional or local regulations for reconstitution of IV medications under aseptic conditions. Refer to the Dosage and Administration Instructions in the Study Manual for more information on stability, time frame of administration once reconstituted, and administration. Inotuzumab ozogamicin must be stored as indicated. Deviations from the storage requirements for any products supplied (shipped) by Pfizer, including any actions taken, must be documented and reported to Pfizer. Once a deviation is identified, the product must be quarantined and not used until Pfizer provides documentation of permission to use the investigational product. Inotuzumab ozogamicin will be labeled according to regulations. Storage conditions stated in the Investigator's Brochure may be superseded by the label storage.

The investigator must maintain a complete and current accountability record. Investigational product accountability applies to such products when they are required by the protocol and supplied (shipped) by the supporter. All unopened investigational product must be returned in the original containers to the supporter/contract distribution center with the appropriate form, or transferred to another site as applicable for this study. The site and the site monitor are to contact the supporterfor detailed information before the transfer of investigational product to another site, or return to the supporteris to take place. Investigational product return must be documented on the accountability record. The site may destroy unused investigational product in an open container (ie, investigational product left after the vial was opened and/or reconstituted) and empty investigational product containers after accountability has been performed. Investigational product destruction must be documented on the accountability record. Investigational product is destroyed at the site only with the supporters permission. For this protocol, investigational product is destroyed at the site only

with the supporter's permission and after accountability has been performed by the supporter's monitor. The process of return, destruction, and accountability and reconciliation for controlled (eg, narcotics), hazardous (eg, investigational product used in oncology) and/or isotopically labeled substances, is performed in accordance with local laws and regulations. Shipment of an investigational product that is a hazardous substance or whose shipment may expose humans to risk will be done according to local laws and regulations.

8.3 Recommendations to reduce the risk of VOD for patients proceeding to ASCT

- For patients planning to receive an allogeneic ASCT, it is recommended that treatment with inotuzumab ozogamicin be limited to 2 cycles of induction or the fewest number of cycles required to achieve a CR/CRi/CRp (if CR/CRi/CRp not achieved after 2 cycles).
- The risk of relapse must be balanced against the potential risk of toxicity associated with beginning ASCT soon after the last dose of inotuzumab ozogamicin; however, approximately 5-6 weeks between inotuzumab and ASCT may be reasonable for most patients.
- Healthcare providers should use their clinical judgment to determine the most appropriate course of therapy for prophylactic treatment before the start of conditioning therapy according to standard of care (eg, prophylactic ursodeoxycholic acid at 12-15 mg/kg/day, beginning 2 weeks before the start of conditioning therapy.
- Use the least hepatotoxic conditioning regimen and, specifically, avoid using regimens that contain 2 alkylating agents and or that combine an alkylating agent with higher dose TBI (defined as >12 Gy).
- If using a busulfan-containing conditioning regimen, please consider using pharmacokinetically-dosed busulfan.
- When possible, avoid the concomitant use of hepatotoxic drugs peri-transplant.
- If significant liver toxicity occurs, consult a gastroenterology and/or hepatology service.
- When evaluating liver toxicity, inform the radiologist of the potential for hepatic vascular disease. When VOD is in the differential diagnosis, a right upper quadrant ultrasound with colorflow doppler (including resistive indices to hepatic artery flow and evaluation of hepatic venous outflow) should be performed. In addition, the radiology report should describe the degree of gall bladder wall thickening in millimeters and the volume of ascites should be estimated as closely as possible (i.e., small and localized, moderate and generalized, or large and generalized).
- Defibrotide may be used in the setting of severe VOD
- If a patient will proceed to ASCT under the care of different physicians, these recommendation should be reviewed with the new treating physicians.

9.0 Evaluation of Toxicity

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

10.0 Criteria for Removal from the Study

Criteria for removal from study include, but are not restricted to, the following:

10.1 No response after 2 cycles or progressive disease, unless considered by the treating physician and after discussion with the PI to be in the best interest of the patient. In this situation, if the treatment is well tolerated, patient can receive up to a maximum of 4 cycles.

10.2 Non-compliance by the patient with protocol requirements

10.3 Patient's request to be removed from the study

10.4 Occurrence of CTCAE grade 4 adverse event at least possibly related to inotuzumab. For CTCAE grade 4 adverse events that are numerically defined laboratory parameters, independent investigator assessment should be used to determine the risk:benefit for each individual patient to continue or discontinue inotuzumab treatment

10.5 Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol specified safety criteria or desirable in the investigator’s and/or the subject´s opinion

10.8 Investigator’s decision that a subject does not benefit from treatment anymore, e.g., non-response or development of progressive disease

11.0 STATISTICAL CONSIDERATIONS

This is a single-arm phase II study of a single agent of low dose inotuzumab ozogamicin in adult patients with relapsed or refractory CD22-positive ALL. Patients will receive inotuzumab ozogamicin for up to 6 cycles. The primary endpoint of this study is hematologic remission, defined as CR + CRp + CRi occurred any time during the treatment. The Simon’s optimal two-stage design will be used for interim futility monitoring. The null hypothesis is that the hematologic remission rate is 35% and our target rate under the alternative hypothesis is 50%. Under the design, we will enroll 18 patients in the first stage. If 6 or fewer patients achieve the primary endpoint, enrollment of future patients will be halted. If 7 or more out of the first 18 patients have met the primary endpoint, accrual will continue until a total of 48 patients are enrolled. If 21 or more out of these 48 patients achieve the primary endpoint, the treatment will be

considered efficacious and is worth further investigation. Under this Simon's optimal two-stage design, the type I error is 0.113, the power is 78.3%, the probability of early termination is 0.549 if the true hematologic remission rate is 35% and the expected sample size is 31.5 patients. After the first stage, if not at least 7 responders are observed in the first 18 patients, we will temporarily suspend the accrual until enough number of responders (i.e., >/=7) is reached.

We will also monitor treatment emergent toxicities using a Bayesian design by Thall, Simon and Estey [Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in medicine.1995;14(4):357-379], in cohort size of 8. For monitoring purpose, toxicities are defined as [any grade VOD that is deemed as related to inotuzumab] and the associated toxicity stopping rule is to stop the trial if $\text{Prob}\{p(TOX) > 0.20 | \text{data}\} > 0.92$, where p(TOX) is the toxicity rate and a beta(0.4, 1.6) distribution was assumed for the prior. That is, if at any time during the trial we determine that there is more than 92% chance that the toxicity rate is more than 20%, we will stop the trial due to safety concern. The corresponding stopping boundaries are shown in Table 3 below and the operating characteristics of the toxicity monitoring are illustrated in Table 4. Multc Lean Desktop (v2.1.0) (https://biostatistics.mdanderson.org/SoftwareDownload/) was used for generating the stopping boundaries and the OC table.

An Efficacy/Toxicity Summary will be submitted to the IND Office Medical Monitor, after the first 8 evaluable, and every 8 evaluable patients thereafter, in an accumulating method.

Table 3. Toxicity stopping boundaries in cohort size of 8.

Number of patients	Stop the trial if there are this many patients having toxicity
8	4-8
16	6-16
24	8-24
32	11-32
40	12-40
48	Always stop with this many patients

Table 4: Operating characteristics for toxicity monitoring.

True Toxicity Rate	Early Stopping Probability	Average number of patients treated	25^{th}, 75^{th} percentile
0.10	0.008	47.7	48, 48
0.15	0.05	46.4	48, 48
0.20	0.17	43.0	48, 48
0.25	0.40	37.1	24, 48
0.30	0.65	29.8	16, 48
0.35	0.85	23.0	8, 40
0.40	0.95	17.8	8, 24
0.45	0.99	14.3	8, 16

Analysis Plan:

The hematologic remission rate will be estimated along with the 95% credible interval. Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study but did not take any of the study drug and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by AE category, severity and frequency. The proportion of patients with AEs will be estimated, along with the Bayesian 95% credible interval. Kaplan-Meier method will be used to assess the overall survival (OS), progression-free survival (PFS), duration of response (DoR) and durations of remission (DoR1). The rate of hematologic response (CR + CRi + PR) will also be estimated.

12.0 Reporting Requirements

Adverse event reporting and recording will be as per the NCI criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines. All subjects will be monitored for AEs during the study. AEs will be recorded from the first dose through 30 days after the last dose. Serious Adverse Events (SAEs) will be captured starting from the date of consent. Any serious adverse events that occur after the 30 day time period that are related to the study treatment will also be reported.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

The Principal Investigator will sign and date the Adverse Event Record (AE log) for each patient at the completion of each course. Following signature, the AE logs will be used as source documentation for the adverse events for attribution.

12.1 Serious Adverse Events

Serious Adverse Event Reporting (SAE) Language for MD Anderson-sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs,

expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

12.2 Investigator Communications with Pfizer

Reporting to Pfizer:

Reporting of Serious Adverse Events. Within twenty-four (24) hours of first awareness of the event (immediately if the event is fatal or life-threatening), from after the first dose of inotuzumab ozogamicin until twenty-eight (28) calendar days after the last dose of inotuzumab ozogamicin. Principal Investigator will report to Pfizer by facsimile any Serious Adverse Event (SAE) for which reporting is required. Principal Investigator should report SAEs as soon as they are determined to meet the definition, even if complete information is not yet available using a reporting form approved by the local regulatory authority (eSAE). Forms should be faxed to Pfizer at 1-866-997-8322.

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