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**Fractionated Gemtuzumab Ozogamicin Followed by Non-engraftment Donor Leukocyte Infusions
for Relapsed/Refractory Acute Myeloid Leukemia**

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1. OBJECTIVES

Phase 1

1.1 Primary Objective:

1. Determine the maximum tolerated dose of nonengraftment donor leukocyte infusions administered with fractionated gemtuzumab ozogamicin in patients with relapsed/refractory AML.

Phase 2

1.2 Primary Objective:

1. Assess the response rate, as defined as complete remission or complete remission with incomplete count recovery, after one cycle of infusional gemtuzumab ozogamicin followed by nonengraftment donor leukocyte infusions in patients with relapsed/refractory acute myeloid leukemia. Rationale for including CRi: CRi has previously been used in gemtuzumab ozogamicin trials because of incomplete platelet recovery seen with this drug.

1.3 Secondary Objectives:

1. Assess the event free survival and overall survival of infusional gemtuzumab ozogamicin followed by nonengraftment donor leukocyte infusions in patients with relapsed/refractory acute myeloid leukemia.
2. Evaluate the rate of dose limiting toxicities of gemtuzumab ozogamicin followed by nonengraftment donor leukocyte infusions in patients with relapsed/refractory acute myeloid leukemia.

1.4 Exploratory Objectives:

1. Determine kinetics of CD33 expression with infusional gemtuzumab ozogamicin.
2. Determine host effector cell numbers pre and post non-engraftment donor leukocyte infusions.
3. Characterization of leukemia cell immune checkpoints that help the leukemia cell evade the host immune system.

2. BACKGROUND

Despite recent advancements in the pathogenesis and molecular mechanisms responsible for acute myeloid leukemia (AML), the overall prognosis remains dismal. In AML even after complete response and allogeneic stem cell transplantation, there is a 30% probability of disease relapse with a 2-year overall survival of 10-14% in patients who experience a relapse (Schmid, et al 2012). The 5 year overall survival for AML is 27% in all patients and <10% in patients 65 and older thereby reflecting the need for more effective therapies (Howlader N 2016). Since AML is primarily a disease of older individuals, therapies that are applicable to this patient population which limit treatment related toxicities while providing an anti-cancer response are needed.

Gemtuzumab ozogamicin (GO) is an antibody drug conjugate developed for the treatment of AML. As a single agent in relapsed/refractory AML the complete remission and complete remission with incomplete count recovery rate is 26% when two doses of GO are given at 9mg/m² as a 2 hour intravenous infusion two weeks apart (Larson, et al 2005). The initial two doses of 9mg/m² has largely been abandoned because of hepatotoxicity in favor of single doses of either 3-6mg/m² (Burnett, et al

2012) or fractionated doses of 3mg/m² on days 1, 4, and 7 (Castaigne, et al 2012). Interestingly some of the strongest data for the addition of GO to standard induction chemotherapy comes from the fractionated dosing where both 2 year event free survival (41% vs. 17%) and 2 year overall survival (52% vs. 43%) were improved in the GO + standard induction group compared to standard induction alone (Castaigne, et al 2012). Most recently a meta-analysis and randomized trial has supported a GO dose of 3mg/m², albeit when combined with induction chemotherapy, moving forward based on a decreased early mortality with similar clinical efficacy (Burnett, *et al* 2016, Hills, *et al* 2014).

Over the years we have developed a model of hematopoietic stem cell biology termed the continuum model (Quesenberry, et al 2012). This model shows that primitive hematopoietic stem cells are actively cycling and when passing through cell cycle continually changing their phenotype. We have already shown that c-kit and Sca-1 surface molecules change over time as stem cell progress through cell cycle. We hypothesize that CD33 will show similar changes on leukemic cells and that at any one point in time only a percentage of the leukemic cells will be expressing or strongly expressing CD33.

Growth and progression of cancer cells requires continued evasion of the host immune system. An increasing number of cancer immunomodulatory mechanisms have been discovered and have led to approaches that overcome these barriers thereby permitting the host immune system to once again recognize and attack the cancer. For decades in hematologic malignancies the standard immune mediated therapy has been allogeneic stem cell transplantation (Thomas, et al 1977). Successful hematopoietic stem cell transplantation traditionally requires donor cell engraftment. Evolutionarily, a conserved property of the immune system is its ability to recognize and to rapidly and strongly reject cells from other individuals. This allogeneic effect is a major obstacle for transplantation that can cause graft rejection. Allogeneic stem cell transplantation removes this obstacle through the use of conditioning regimens that significantly weaken the recipient's immune system in order to prevent donor cell rejection and allow for engraftment. The consequence is that donor lymphocytes present in the transplanted cells generate alloreactive responses toward the recipient, attacking organs like the skin, liver and gut in a response termed graft-versus-host disease (GVHD). While GVHD can be severe enough to cause the death of the recipient, it was also observed that GVHD is linked to graft versus tumor effect (GVT)(Weiden, et al 1979, Weiden, et al 1981). A major goal of allogeneic stem cell transplantation research is to separate the beneficial GVT effect from deleterious GVHD.

Our non-engraftment donor leukocyte infusion (DLI) protocol is an alternative approach to activating the immune system of patients with refractory hematologic malignancies. Rather than donor cell engraftment and a subsequent GVT, non-engraftment DLI relies on allogeneic donor cell rejection and a host versus tumor effect. Responses occur in association with fever development and a cytokine release that mimics the pro-inflammatory cytokine release syndrome seen following the infusion of CAR-T cells or bi-specific antibodies (Lee, et al 2014). Non-engraftment DLI cells require no post collection modification and need only minimal pre-infusion chemotherapy or radiation to display efficacy (Colvin, *et al* 2009, Guo, *et al* 2012, Guo, *et al* 2011, Medina, *et al* 2008). The relative low toxicity and widespread potential application make non-engraftment DLI a viable treatment option for most patients with AML. We hypothesize that the addition of prolonged fractionated gemtuzumab ozogamicin to non-engraftment DLI will provide leukemia specific cell kill that will allow for further antigen presentation to reactivated host T cells and, in the process, provide durable clinical benefit for AML patients that can be administered at most treatment centers.

2.1 Cellular Immune Therapy: Investigations From Our Laboratory:

2.1.1 Murine Studies and Infusion of

HLA Identical Blood: We initially studied the capacity of murine marrow cells to engraft into non irradiated mice (Quesenberry 1997).

Interestingly, engraftment was possible in these studies without myeloablation. Based on the experimental data we obtained, donor cell engraftment is quantitative in

nature and results from competition between host and donor cells (Stewart, *et al* 1993). The more donor cells that are infused, the higher the levels of engraftment. However, non-myeloablative engraftment is not feasible in the clinical setting due to the high number of donor cells that would be required. Therefore, we next examined syngeneic murine engraftment in minimal myeloablation. Utilizing small doses of radiation (50-100cGy) we were able to demonstrate significant engraftment (Stewart, *et al* 1998). The rationale behind the efficacy of minimal myeloablation was that the radiation dose used was very stem cell toxic but not myelotoxic (Stewart, *et al* 2001). Initial attempts by our group to translate these findings to the allogeneic setting were unsuccessful secondary to immune barriers. However, costimulator blockade with anti-CD40 ligand antibody in the setting of multiple infusions of stems cells gave a durable engraftment in the nonmyeloablative setting (Lambert, *et al* 2002).

Table 1: Summary of responses seen in 26 patients with refractory hematological malignancies treated with haploidentical PBSC infusions

	Complete Response	Partial Response	Transient Response	Total Response
AML	3/13 (23%)	0/13 (0%)	7/13 (54%)	10/13 (77%)

2.1.2 Infusion of HLA Identical Pheresed Cells

We utilized these murine studies in part to develop a clinical approach for patients with refractory neoplasia, infusing graded doses of allogeneic T cells into 100 cGy treated patients with the end goal of engraftment. We determined the safety and efficacy of infusing 1×10^8 T-cells/kg along with a median of 5×10^4 CD34+ cells per kg from non-mobilized HLA identical blood in 11 patients with refractory hematologic malignancies after 100 cGy total body irradiation (TBI) (Ballen, *et al* 2002). Nine patients achieved mixed or complete chimerism. There were 4 complete responses of which 2 are of long duration. Complete responses were achieved in the single patient treated for refractory AML, in 2 patients with non-Hodgkin's lymphoma and in 1 patient with multiple myeloma. Five patients developed significant acute graft-versus-host disease (GVHD), resulting in one death. Of the complete responses, three developed 100% chimerism. The fourth patient in CR had only a transient 5% chimerism for one week but interestingly had a sustained CR of over 42 months. Another patient with chronic lymphocytic leukemia showed a 75% reduction in lymphadenopathy despite no evidence for chimerism suggesting that the cellular infusion may have activated the patient's own immune system against their hematologic malignancy.

2.1.3 Infusion of HLA Haploidentical Pheresed Cells In order to increase the number of patients eligible for cellular infusion, we next evaluated the infusion of haploidentical peripheral blood cells into 26 patients with refractory hematologic malignancies (Colvin, *et al* 2009). Patients were infused with haplo-identical leukocytes at a dose of $1-2 \times 10^8$ cells/kg following 100cGy total body irradiation (TBI). Donors were mobilized using G-CSF prior to leukapheresis. In this trial over half (14/26) of patients with refractory hematological malignancies generated responses including complete and partial remissions in AML and non-Hodgkin lymphoma patients (Table 1). These responses were associated with elimination of the donor cells with no detectable donor chimerism and included rapid onset of a pro-inflammatory response (median time of onset 14 hours) characterized by high levels of circulating IL-6 (>3000 pg/mL) and high persisting fevers along with other symptoms such as diarrhea, malaise, rash and elevated liver enzymes (Colvin, *et al* 2009).

Subsequently a second clinical trial was re-opened without the use of G-CSF mobilization and 100 cGy TBI. Although donor cells were effectively eliminated, reduced pro-inflammatory responses reflected by less IL-6 release and lower non-persisting fevers were observed in this trial and corresponded with minimal anti-leukemic responses. Interestingly in this study we did see an up-regulation of PD-1 on host T cells and PD-1 ligands on leukemic blasts following donor cell infusion thereby suggesting a possible mechanism of tumor immune evasion (Reagan, *et al* 2015). The lack of response underscores the need for some form of leukemia directed therapy prior to non-engraftment DLI infusion.

The clinical efficacy of nonengraftment DLI for AML treatment has been replicated by others, most notably Ai and colleagues (Guo, *et al* 2012, Guo, *et al* 2011). Thus far they have shown clinical efficacy for nonengraftment DLI in patients receiving both induction and consolidation therapy for AML. In their initial study in patients over 60 years of age with AML, Guo et al. administered either induction chemotherapy (mitoxantrone and cytarabine) alone or in combination with partially HLA matched G-CSF mobilized peripheral blood stem cells (PBSC). Donors underwent G-CSF mobilization with G-CSF 5mcg/kg subq twice daily for 5 days. In the chemotherapy alone group, the complete remission (CR) rate was 43% while the CR rate in the chemotherapy and PBSC group was 80%. Furthermore, the 2-year progression free survival (PFS) with chemotherapy alone was 10% in contrast to a 2-year PFS of 39% in the chemotherapy and PBSC cohort. These results show clear activity for cellular therapy in a patient population with a notoriously dismal prognosis. In a later study, Guo et al. infused HLA-mismatched donor G-CSF mobilized PBSC following 3 cycles of cytarabine for AML patients who attained CR after induction chemotherapy. In 101 treated AML patients, the 6 year overall survivals ranged from 65-89%, which is much greater than the 5 year overall survival of 24-55% seen in historical controls (Byrd, *et al* 2002). Of note, in contrast to our data, the responses reported by Ai and colleagues have all occurred with chemotherapy prior to donor cell infusion. Furthermore, responders typically received multiple doses of DLI as opposed to only one dose of DLI in our previous work. Our data and that reported by Ai and colleagues suggest a dose effect with improved response in patients who received a high dose of donor CD3+ cells ($\geq 1.1 \times 10^8$ /kg).

2.1.4 Current Proposal: Fractionated gemtuzumab ozogamicin followed by nonengraftment donor leukocyte infusions

Our previous work has established that HLA-matched peripheral blood cells with 1×10^8 T cells/kg can engraft into 100 cGy treated patients and result in clinical responses, some complete and long-term, but at a cost of graft-versus-host disease which can be fatal (Ballen, *et al* 2002). Subsequent studies evaluated infusion of haploidentical peripheral blood cells into 100 cGy treated patients with lymphoma or leukemia (Colvin, *et al* 2009). In this setting the patients developed a unique syndrome termed haploimmunostorm in which there was always fever and variably diarrhea, liver function abnormalities, skin rash and at times pulmonary symptoms. With haploidentical infusion dramatic and sometimes durable responses were seen. Remarkably chimerism was not demonstrated. This suggests the activity in haploidentical blood cell infusion is likely due to activation of the recipient's immune system against leukemia/lymphoma and not due to graft versus tumor. The underlying mechanism behind this phenomenon has not been fully elucidated but is thought to involve a complex interaction between interferon γ , CD8 T cells, NK cells, and antigen presenting cells. Most recently we tested infusion of haploidentical donor cells alone in patients with refractory acute myeloid leukemia without total body irradiation (BrUOG 273 NCT01685606). This study showed only mild transient responses without the previously observed cytokine release syndrome. We conclude that some form of leukemic cell DNA damage is required to facilitate leukemic antigen presentation. In this proposal we will administer fractionated gemtuzumab

ozogamicin (GO) on days 1, 4, and 7 over approximately 2 hours in order to selectively target leukemia cells and, we believe, enhance the response of nonengraftment donor leukocyte infusion.

This protocol will build upon these previous observations as follows:

- 0/6-3/6 G-CSF mobilized HLA matched peripheral blood pheresed cells from first or second degree relatives will be used at $1-2 \times 10^7$ CD3 cells/kg or $1-2 \times 10^8$ CD3 cells/kg.
- Fractionated gemtuzumab ozogamicin will be administered days 1, 4, and 7 over approximately 2 hours and will be completed prior to nonengraftment donor leukocyte infusion. The leukocyte infusion is to be administered at least 24 hours after completion of GO day 7 (see section 4.1.5 for dosing windows).

It is important to note that the proposed study is not a stem cell transplant study. In the situation of stem cell transplants, the goal of the procedure is to have engraftment, or sustainable donor chimerism in the marrow to provide hematopoietic reconstitution as well as immunologic reconstitution. In this study, we are evaluating the use of donor leukocytes (not stem cells) to stimulate an immune response of the recipients' immune system.

The current trial is a single-arm phase 1/2 non-randomized study designed to evaluate the safety and efficacy of infusional gemtuzumab ozogamicin followed by nonengraftment donor leukocyte infusions in patients with refractory/relapsed acute myeloid leukemia. The trial is designed to evaluate sequential cohorts based on fever, cytokine release profiles, response, and toxicities. Additional laboratory correlative studies will be performed in conjunction with the clinical trial to determine an underlying mechanism of action. All patients 18 years of age or older, with relapsed acute myeloid leukemia with at least one prior therapy and no curative options are eligible. HLA mismatched donors 18 years of age or older whom are healthy and meet criteria of blood donation are eligible. Additionally, donors must be 1st or 2nd degree relatives and a 0/6-3/6 match at HLA loci A, B, and DR.

Gemtuzumab Ozogamicin will be given at a $9\text{mg}/\text{m}^2$ total dose for patients <70 years of age and $6\text{mg}/\text{m}^2$ in patients ≥ 70 years on Day 1, 4, and 7 as a fractionated dose of either $3\text{mg}/\text{m}^2$ or $2\text{mg}/\text{m}^2$ over approximately 2 hours on each day capped at a 4.5mg daily dose. Meanwhile, donors will undergo five-day G-CSF mobilization starting day 3 with leukapheresis to occur the day post GO completion. The final product will be analyzed for CD3+ and CD34+ content via flow cytometry. The product will be administered unprocessed at least 24 hours post GO (the day post GO completion) (same day as leukapheresis). Two dose DLI dose levels will be examined.

DLI Dose Level 1: $1-2 \times 10^7$ CD3+ cells per kg irrespective of the number of CD34+.

DLI Dose Level 2: $1-2 \times 10^8$ CD3+ cells per kg irrespective of the number of CD34+.

No specific viral or bacterial prophylaxis is required. The infusion of HLA-mismatched peripheral blood cells must be initiated within 8 hours of product collection and completed within 24 hours.

Acetaminophen 650 mg PO and diphenhydramine 50 mg IV will be administered 30 minutes prior to cellular infusion. During the infusion, patient will be monitored for blood pressure, temperature and oxygen saturation. This monitoring will continue for 2 hours after infusion at the following time points; every 15-30 minutes the first hour post infusion and every 30-60 minutes the second hour post infusion.

The infusion will be stopped should the patient develop grade 3 or 4 infusion-related reactions.

Following infusion, patients will be further monitored in either the outpatient or inpatient setting for the development of cytokine release syndrome (CRS), which occurred at a median time of 14 hours post cellular infusion. CRS was universally associated with fever in addition to other symptoms such as rash,

diarrhea, liver function test abnormalities, and respiratory difficulty. Patients will be seen at a minimum of twice weekly with blood work (Complete blood count, electrolytes, renal/hepatic function, ferritin) performed for the first month post infusion. CRS will be observed only provided there is no respiratory compromise or hemodynamic instability. In the event of respiratory compromise or hemodynamic instability the suggestion is to give tocilizumab 4mg/kg once every 24-48 hours. Alternatively, dexamethasone 20mg IV (or equivalent steroid) every 8 hours may be administered until the toxicity improves to Grade 2 or less. Patients will then be placed on a rapid steroid taper.

Patients who show a complete response (CR) or complete response with incomplete count recovery (CRi) to therapy can receive up to two additional donor leukocyte infusions with GO 6mg/m² for all patients regardless of age administered via fractionated dosing no sooner than 35 days and no later than 56 days status post their last cellular infusion to allow adequate time between infusions to ensure no engraftment occurs. The inclusion of CRi as a marker of response was first identified in the initial GO studies and has been used to determine the single agent response rate of GO (Bross *et al*, 2001). All treatment must be given during a 6-month period. Once patients are assigned to a DLI dose level they will be given that same DLI dose for each infusion: there will be no dose reductions or increases.

2.1.5 Proposed Laboratory Correlative Studies

As part of this clinical trial, we will study cells from patients before and after cell infusions to determine if the key tumor killing mechanism(s) are generated by donor or recipient leukocytes and include effector responses by T cells, NK cells, monocytes or “other” cells. We will also determine cytokine and granzyme levels in these patients. Of particular interest will be the levels of IL-6 and IFN γ . Chimerism will be assessed at day 2 and 14 after donor cell infusion by STR analysis. If chimerism persists beyond day 14 it will be reassessed every 14 days until resolution. Alternatively the use of donor specific anti-HLA antibodies (provided by Arend Mulder), will be used to stain the donor cells present in the samples (Reagan, *et al* 2015).

Blood samples will be obtained from the patient prior to GO administration (one day before initiation, d-8), before cell infusion (d-1), and 0-4 ,8-24, 34-48, 72-96, and 168 hours after infusion (+/- 24 hours for all time points except 168 hours which can correlate with day 7 lab work with a +/- 2 day window). After the plasma has been collected, the peripheral blood mononuclear cells will be obtained from the blood samples by Ficoll Hypaque discontinuous centrifugation and the cells will be frozen down. When all samples have been obtained from a patient, all samples will be thawed and stained in a single experiment to reduce variability from day to day. The cells will be stained with panels of antibodies. One panel will define leukemic cells, using anti-CD13, CD33, CD34 and CD117 to define leukemic cells as well as measuring their expression of ligands such as PD-1 ligands (CD273, CD274) or markers expressed upon cell death such as CD47 and calreticulin. Additional panels will determine the frequencies of T cell subsets (CD3, CD4, CD8), the expression of activation antigens (CD137, PD-1, CTLA-4, LAG3, TIGIT), the expression of cytokines such as IFN- γ , granzyme A and B, exhaustion antigens such as CD39, expression of FoxP3 as a marker of T regulatory cells as well markers of naïve and memory subsets (CD45RA, CD127). Another panel will examine the frequency of NK and NKT cells, B cells, and macrophages as well as the state of activation of the macrophages.

The plasma obtained will be used to measure levels of proinflammatory cytokines/chemokines such as IL-6, IL-10, IL-12, IL-15, IL-18, IFN- γ , TNF, IL-1 β , MIP-1 α , MIP-1 β , MCP.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria of Recipient (Patient)

- 3.1.1 Histologic confirmation of acute myeloid leukemia (AML)
- 3.1.2 Recurrence or progression (including refractory disease defined as disease confirmed to have not responded to prior treatment) of AML after at least 1 prior standard treatment with progression within 6 months from last treatment. Please note that patient must have received at least one cycle of a standard treatment for their disease. Patients who have relapsed or progressed > 6 months post their last treatment are not eligible. See 3.1.8, as patients must be > 6 months post autologous stem cell infusion, if applicable.
- 3.1.3 ≥ 4 -weeks since prior chemotherapy or radiation to cellular therapy infusion. (Hydroxyurea may be utilized up to 48 hours prior to initiation of treatment on this protocol and end date must be sent to BrUOG at time of registration. Hydroxyurea can resume at the discretion of the treating physician post cellular infusion and must be documented on concomitant medication log.)
- 3.1.4 Age equal to or greater than 18 years.
- 3.1.5 Patients with a history of invasive second malignancy who are disease free for ≥ 2 years. Patients with a history of invasive second malignancy who are not disease free for at least 2 years are excluded. Patients with ductal carcinoma in situ of the breast and/or squamous cell/basal cell cancer of the skin will be allowed on trial.
- 3.1.6 Patients must have an expected life expectancy of at least 2 months at the time of initiation of treatment, as documented by treating physician.
- 3.1.7 No active systemic infections allowed. Minor infection that can be controlled with a 2 week course of antibiotics/antivirals is acceptable. Patient with such infection must have begun antibiotics at least 2 days prior to drug treatment.
- 3.1.8 Patients who have relapsed after standard autologous stem cell infusion are eligible as long as they meet all inclusion criteria and no exclusion criteria. These patients must be out more than 6 months from cell infusion to be eligible for enrollment.
- 3.1.9 DLCO Hb $\geq 40\%$ with no symptomatic pulmonary disease.
- 3.1.10 LVEF $\geq 40\%$ by MUGA or echocardiogram.
- 3.1.11 Creatinine $< 1.5 \times$ ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥ 40 mL/min, AST and ALT $< 2.5 \times$ ULN, Total Bilirubin $< 1.5 \times$ ULN
- 3.1.12 Women of childbearing potential and all males must use 2 highly effective methods of contraception from time of consent through 6 months after completing treatment (whether last treatment is infusion or drug). If a man has a history of vasectomy, condom use will still be required. Documentation of this being discussed is required to also note types of contraception.
- 3.1.13 Not pregnant or nursing. Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to beginning of treatment (drug). Post-menopausal women (surgical menopause or lack of menses ≥ 12 months) do not need to have a pregnancy test, please document status.
- 3.1.14 Performance status ECOG ≤ 2 (or KPS 70)

3.2 Exclusion Criteria of Recipient (Patient)

- 3.2.1 Evidence of HIV infection.
- 3.2.2 Any uncontrolled severe, concurrent illness which in the opinion of the treating physician would make this protocol treatment unreasonably hazardous for the patient.
- 3.2.3 Oxygen dependent obstructive pulmonary disease.
- 3.2.4 Previous history of Veno-occlusive disease/Sinusoidal Obstruction Syndrome

- 3.2.5 Failure to demonstrate adequate compliance with medical therapy and follow-up as documented by treating physician.
- 3.2.6 Significant medical or psychiatric illness that would impair the ability to participate in protocol therapy.
- 3.2.7 Previous allogeneic stem cell transplant
- 3.2.8 Eligibility for allogeneic stem cell transplant
- 3.2.9 Patients who have had previous purine analog (fludarabine, pentostatin, 2-CDA) treatment or treatment with alemtuzumab within 1 year of entering the study
- 3.2.10 Active hepatitis B or C
- 3.2.11 Patients with known active central nervous system leukemia
- 3.2.12 Patients with prior treatment of gemtuzumab ozogamicin
- 3.2.13 Patients with allergy to latex.

3.3 Donor Eligibility Criteria * donor eligibility must be documented and assessed by a separate participating physician other than the treating physician of the recipient. In order to confirm donor eligibility section 3.3, section 6.2 and appendix D must be used.

If the same donor is used for subsequent leukocyte infusions, then 3.3.7-3.3.11 and all exclusion requirements must be re-assessed along with HLA testing within 7 days and submitted to BrUOG to confirm prior to collection. If a new donor is used then all inclusion/exclusion (3.3.1-3.3.11 and 3.4.1-3.4.12), must be confirmed and submitted, with source to BrUOG for registration prior to any collection. Each donor will be registered with their own number and this must occur before any collection. BrUOG must be made aware that the recipient will undergo a 2nd or 3rd infusion for planning purposes to review and register the donor. If the same donor is used for more than one infusion the same donor number will be used but a new registration will be sent confirming eligibility for the 2nd or 3rd collection.

Subsequent DLIs can be performed no sooner than 35 days status post the last cellular infusion to allow adequate time between infusions to ensure no engraftment occurs. All treatment must be given during a 6-month period.

- 3.3.1 Donors agree to up to 3 donor leukocyte collections as documented by assessing physician (although it is not required that the same donor is used for all leukocyte infusions it is preferable, therefore agreement is important at screening). This must be documented in writing by treating physician.
- 3.3.2 Typing is required at the following loci: HLA A, B, C, and DRB1.
- 3.3.3 Patients with a HLA 0/6 to 3/6(using loci A, B, DR) donor match will be able to participate in this protocol.
- 3.3.4 Donors must be a first or second degree relative.
- 3.3.5 If the patient/recipient is CMV negative, only CMV negative donors are eligible. If the patient/recipient is CMV positive, CMV testing is not required for the donor.
- 3.3.6 Although ABO blood type matching is not required given use of apheresis product preference will be made to ABO compatible donors
- 3.3.7 Donors must be ≥ 18 years of age to donate.
- 3.3.8 Donor with a history of malignancy other than non-melanoma skin cancers are eligible only if they had a history of a solid tumor malignancy more than five years prior to lymphocyte donation, and are considered to be in longstanding complete remission as documented by a physician. The donor must be healthy and have all testing criteria completed and meet all criteria

for stem cell donation. Testing criteria: normal CBC and negative testing for: HIV-1, HIV-2, syphilis, hepatitis, HTLV 1 and 2, CMV (CMV negative is not a requirement see 3.3.5), Chagas, and West Nile Virus by the Rhode Island Blood Center. The Rhode Island Blood Center will perform nucleic acid testing (NAT) for WNV, HIV-1, HCV and HBV. They will perform surface and core antigen for HBV. All testing by the Rhode Island Blood center will be with FDA-licensed, approved or cleared tests for donor screening.

- 3.3.9 The donor will also be assessed by physician who will document behavioral risk for exposure to infectious agents and diseases. Donors determined by the treating physician to be at risk for exposure to infectious agents and diseases will be excluded. Testing will include the following:
 - 3.3.9.1 Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease: this will exclude the donor
 - 3.3.9.2 Communicable disease risks associated with xenotransplantation: this will exclude the donor
 - 3.3.9.3 *Chlamydia trachomatis* and for *Neisseria gonorrhea* (see schedule of evaluations for required testing). Must use FDA-licensed, approved, or cleared tests labeled for the detection of those organisms in an asymptomatic, low-prevalence population. Required testing under this section must be performed by a laboratory that either is certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493, or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services. This will exclude the donor
 - 3.3.9.4 *Treponema pallidum (syphilis)*. This will exclude the donor
- 3.3.10 The donor must be in good general health and not have significant cardiopulmonary, renal, endocrine, or hepatic disease as documented in writing by physician.
- 3.3.11 β -HCG urine or serum negative if donor is of childbearing potential within 7 days of PBMC procurement. Not applicable for donors who are Post-menopausal (surgical menopause or lack of menses ≥ 12 months). Menopausal status must be documented to BrUOG
- 3.3.12 Donors must have adequate venous access so leukapheresis can be performed via standard peripheral IV without the need for placement of a central venous catheter. Required to be documented by physician post assessment by treating physician

3.4 Donor Exclusion Criteria

- 3.4.1 Evidence of infection for HIV-1, HIV-2, syphilis, hepatitis B or C, HTLV 1 or 2, WNV, Chagas.
- 3.4.2 Uncontrolled diabetes mellitus. If donor has controlled diabetes this must be documented by physician.
- 3.4.3 Active or congestive heart failure syndrome from any cause per donor medical history. Approval for participation by Cardiologist required to be sent to BrUOG.
- 3.4.4 Full cardiac workup by a Cardiologist is required for any history of congestive heart failure syndrome, conduction abnormalities or history of arrhythmia other than treated atrial fibrillation.
- 3.4.5 Active angina pectoris. To be documented by physician
- 3.4.6 Oxygen dependent pulmonary disease. To be documented by physician
- 3.4.7 History of any lymphoid, myeloid or other non-solid malignancy. To be documented by physician
- 3.4.8 Failure to receive full informed consent.
- 3.4.9 Inadequate renal and/or hepatic function per medical history. To be documented by physician
- 3.4.10 Known history of cirrhosis or active liver disease per medical history. To be documented by physician
- 3.4.11 History of transplantation. To be documented by physician.

- 3.4.12 Allergy to latex. To be documented by physician.
- 3.4.13 A donor in whom plasma dilution sufficient to affect the results of communicable disease testing is suspected, unless:
- (A) You test a specimen taken from the donor before transfusion or infusion and up to 7 days before recovery of cells or tissue; or
 - (B) You use an appropriate algorithm designed to evaluate volumes administered in the 48 hours before specimen collection, and the algorithm shows that plasma dilution sufficient to affect the results of communicable disease testing has not occurred.
- 3.4.15 Clinical situations in which you must suspect plasma dilution sufficient to affect the results of communicable disease testing will exclude the donor. Such situations include, but are not limited to the following:
- (A) Blood loss is known or suspected in a donor over 12 years of age, and the donor has received a transfusion or infusion of any of the following, alone or in combination:
 - (1) More than 2,000 milliliters (mL) of blood (e.g., whole blood, red blood cells) or colloids within 48 hours before death or specimen collection, whichever occurred earlier, or
 - (2) More than 2,000 mL of crystalloids within 1 hour before death or specimen collection, whichever occurred earlier.
- See section 6.2: *Donor labs must be drawn within 7 days of collection + 24 hours and final test results available for eligibility. Once donor is registered, labs must continue to be redrawn to ensure labs and results are within 7 days (+24 hours) of each collection. Pre-collection labs will occur Day 3 (-1 Day). Results will be required prior to collection. If when re-drawn the result aligns with an exclusion criterion (i.e. a result of a test now deems the donor ineligible), the donor is disqualified from DLI collection and will be labeled as a screen failure. BrUOG is required to receive all donor testing and lab results.

4. TREATMENT PLAN

After both recipient and donor are consented and the donor is successfully evaluated, BrUOG will review registration and if acceptable, both recipient and donor will be registered. After registration study treatment including donor collection and recipient infusion will occur.

If more than one infusion is used, please refer to donor eligibility section above on requirements.

The study will utilize a 3+3 design to determine if $1-2 \times 10^8$ CD3 cells/kg can be safely administered with GO. Two DLI dose levels will be assessed:

- DLI Dose Level 1: $1-2 \times 10^7$ CD3+ cells/kg
- DLI Dose Level 2: $1-2 \times 10^8$ CD3+ cells/kg

Three patients will be accrued to DLI dose level 1. All patients will be assessed for dose limiting toxicities (DLTs) through 35 days post the last dose of GO. If no DLTs are observed during this assessment time period, then accrual to level 2 will proceed.

Patients who experience a DLT will not be eligible to receive any additional DLI or GO on study.

Patients who do not experience a DLT, and who remain on study to receive DLI/GO #2 or DLI/GO #3, will remain on the DLI dose level received during infusion #1, for the remainder of their infusions.

If a DLT is observed in one of the first 3 patients in a dose level, then accrual for that level will be expanded to 6 patients. Two or more instances of DLT in a cohort of 6 patients will result in the preceding dose level being defined as the maximum tolerated dose (MTD). If 2 or more DLTs are observed in dose level 1, the study will be closed.

Depending on DLTs observed, 6-12 patients may be included in the Phase 1 portion of this study.

The Phase 2 part of the study will apply a Simon Two-Stage Design and enroll a total of 15 patients. At least six patients will be treated as part of the phase I. If there are no DLTs observed, twelve additional patients for up to a total of 15 will be enrolled and treated at the recommended phase 2 dose (MTD). Patients enrolled and treated in the phase 1 MTD portion will be included in the Simon Two-Stage design assessment, which could include up to 6 patients. Patients in the phase 2 study, who experience an event defined as a DLT will be taken off of study. Total enrollment for the study will be 18-21 patients depending on DLT experienced in the dose escalation phase.

All evaluable patients included in the Phase 1 portion will be followed for 30 days post the patient's final DLI to ensure all safety information and treatment is captured.

As described in the Section 5, Dose limiting toxicities as defined below.

Adverse events will be scored according to the NCI CTCAE version 5.0 criteria.

All AEs will be considered relevant to determine DLTs unless the event can be determined to be completely unrelated to treatment. All adverse events will be assessed for causality and relationship to DLI and GO.

Dose limiting toxicity (DLT) will be defined as any of the following events

- IBMTR Severity Index C graft versus host disease of any duration
- IBMTR Severity Index D graft versus host disease of any duration
- Grade 3 or 4 infusion related reaction of any duration
- Any grade 3 non-hematological toxicities not directly resulting from patient's disease
- Excluding nausea, vomiting and diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization (a grade 3 nausea, vomiting or diarrhea that requires tube feeding, TPN, or which requires hospitalization or prolongs hospitalization is a DLT). Additional exclusions: fatigue, fever, or grade 3 hypokalemia that resolves to baseline within 72 hours.
- Any grade 4 related or unrelated non-hematological toxicity not directly resulting from patient's disease
- Development of SOS
- Discontinuation of treatment due to an adverse event of any grade is considered a DLT unless the AE is clearly and solely related to the underlying disease.

All Grade 5 toxicities are considered DLTs unless clearly and solely related to the underlying disease. Fractionated gemtuzumab ozogamicin will be administered days 1, 4, and 7 over approximately 2 hours and will be completed prior to nonengraftment donor leukocyte infusion. The leukocyte infusion is to be administered at least 24 hours after completion of GO.

4.1 Recipient (Patient) Treatment

- 4.1.1** For standard of care in this patient population of relapsed/refractory acute myeloid leukemia, patients may be admitted to the hospital for administration of gemtuzumab ozogamicin. This is typically done to ensure patient oversight for possible administration

of blood products as needed as well as monitoring for potential toxicities, especially neutropenic fever. Therefore to align with standard of care practices patients may be admitted for gemtuzumab ozogamicin administration as part of this study. Patient's will likely remain admitted for the infusion of donor leukocytes and observed post administration of gemtuzumab ozogamicin.

- 4.1.2** Patients <70 years of age will be given gemtuzumab ozogamicin 3mg/m² (each day for days 1,4,7) and patients ≥ 70 years of age will be given gemtuzumab ozogamicin 2mg/m² (each day for days 1,4,7), over approximately 2 hours capped at 4.5mg individual doses. 9mg/m² and 6mg/m² will be the total doses respectively capped at a total dose of 13.5mg. Fractionated Gemtuzumab Ozogamicin will be administered days 1,4 and 7 over approximately 2 hours and will be completed prior to nonengraftment donor leukocyte infusion. The leukocyte infusion is to be administered at least 24 hours after completion of GO day 7 (see section 4.1.5 for dosing windows).
- 4.1.3** All patients will be placed on ursodiol 300mg twice daily beginning day 1 of GO through 4 weeks after the last dose of GO for sinusoidal obstruction syndrome prophylaxis of the day before GO administration. For patients who receive additional GO administrations, patients will remain on ursodiol until 4 weeks post the final GO administration.
- 4.1.4** Patients will receive G-CSF 5mcg/kg if their absolute neutrophil count is less than 0.5x10⁹/L starting the day after DLI until their ANC is over 1.0x10⁹/L.

4.1.5 Day 4 and Day 7 Dosing:

Dosing days 4, 7 will have a +1 day window. All GO treatment in a cycle must be completed in 8 days.

Cytopenias are an expected side effect of this treatment regimen. GO dosing will not be held for cytopenias nor should it be listed as a serious adverse event if cytopenias require hospital admission for transfusion support.

Day 4 and Day 7 GO should be delayed for the following:

- Creatinine ≥ 2.0 mg/dl
- Total bilirubin > than 1.5x the upper limit of normal (ULN),
- AST and ALT > 2.5x ULN
- All treatment related (to GO and DLI treatment) non-heme toxicities must be confirmed as being ≤ grade 2 (except alopecia and weight loss)

Infusional GO must be completed in 8 days. The following medications will be given approximately 1 hour prior to infusional GO:

1. Acetaminophen 650mg PO once
2. Famotidine 20mg IV once
3. Dexamethasone 10mg IV once

4.1.6 Infusion Reactions GO:

GO infusion will be stopped should the patient develop Grade 3 or 4 infusion related reactions. Permanently discontinue GO upon occurrence of a severe (grade 3) infusion reaction or for any life-threatening (grade 4) infusion reactions. Furthermore GO will be permanently discontinued for any episode of SOS, see section 5.2

For Grade 2 infusion related reactions the following protocol will be followed:

1st occurrence of Grade 2 infusion related reaction

1. Infusion placed on hold
2. Acetaminophen 650mg PO x 1
3. Diphenhydramine 50mg IV x 1
4. Famotidine 20mg IV x1
5. Infusion restarted following improvement in symptoms to Grade 1 or less. Once symptoms resolve, consider resuming the infusion at no more than half the rate at which the reaction occurred. Repeat the procedure above in the event of recurrence of symptoms.
6. Monitor patients during and for at least 1 hour after the end of the infusion or until signs and symptoms completely resolve.

2nd occurrence of Grade 2 infusion related reaction

1. Infusion placed on hold
2. Methylprednisone 100mg IV x 1
3. Infusion restarted following improvement in symptoms to Grade 1 or less. Once symptoms resolve, consider resuming the infusion at no more than half the rate at which the reaction occurred. Repeat the procedure above in the event of recurrence of symptoms.
4. Monitor patients during and for at least 1 hour after the end of the infusion or until signs and symptoms completely resolve.

4.1.7 DLI:

The product will be administered unprocessed at least 24 hours post GO (the day post GO completion and same day as leukapheresis) at the following dose levels:

DLI dose level 1: minimum of 1×10^7 CD3+ cells/kg and maximum of 2×10^7 CD3+ cells/kg irrespective of the number of CD34+ cells.

DLI dose level 2: minimum of 1×10^8 CD3+ cells/kg and maximum of 2×10^8 CD3+ cells/kg irrespective of the number of CD34+ cells.

All product dose levels (kg) refer to recipient weight not donor weight. Failure to collect either 1×10^7 CD3+ cells/kg or 1×10^8 CD3+ cells/kg will disqualify the recipient from the study. Both recipient and donor will then be taken off study. Please refer to section 4.2.9 for complete details.

The infusion of HLA haploidentical peripheral blood cells infusion must be initiated within 8 hours of product collection at least 24 hours post GO (the day post GO completion) and completed within 24 hours. Pretreatment prior to haploidentical infusion will be as follows:

1. Acetaminophen 650mg PO 30 minutes prior to cellular infusion
2. Diphenhydramine 50mg IV 30 minutes prior to cellular infusion

No specific viral or bacterial prophylaxis is required. During the infusion, patient will be monitored for blood pressure, temperature and oxygen saturation. This monitoring will continue for 2 hours after infusion at the following time points; q15-30 minutes the first hour post infusion, q30-60 minutes the second hour post infusion.

The infusion will be stopped should the patient develop Grade 3 or 4 infusion related reactions. For Grade 2 infusion related reactions the following protocol will be followed:

1st occurrence of Grade 2 infusion related reaction

1. Infusion placed on hold
2. Acetaminophen 650mg PO x 1
3. Diphenhydramine 50mg IV x 1
4. Famotidine 20mg IV x1
5. Infusion restarted following improvement in symptoms to Grade 1 or less

2nd occurrence of Grade 2 infusion related reaction

1. Infusion placed on hold
2. Methylprednisone 100mg IV x 1
3. Infusion restarted following improvement in symptoms to Grade 1 or less

4.2 Donor Collection (to be completed with all DLI infusions) (4.2.1-4.2.8)

See section 6.2: *Donor labs must be drawn within 7 days of collection + 24 hours and final test results available for eligibility. Once donor is registered, labs must continue to be redrawn to ensure labs and results are within 7 days (+24 hours) of each collection. Pre-collection labs will occur Day 3 (-1 Day). Results will be required prior to collection. If when re-drawn the result aligns with an exclusion criterion (i.e. a result of a test now deems the donor ineligible), the donor is disqualified from DLI collection and will be labeled as a screen failure. BrUOG is required to receive all donor testing and lab results.

- 4.2.1** Collection and separation of leukocytes of donor via apheresis by The Rhode Island Blood Center at Rhode Island Hospital
- 4.2.2** Donors will undergo G-CSF mobilization with 5mcg/kg subq twice daily of G-CSF for 5 days prior to leukapheresis on days 3-7. Donors will be instructed on G-CSF administration during their pre-collection lab visit on day 3 (-1 day) and will self-administer G-CSF. See section 6.2.
- 4.2.3** Donors will have vein-to-vein leukapheresis 24 hours after completion of GO
- 4.2.4** Donors will have documented 0-3/6 HLA matching to patient. If a new donor is used for the second or third infusions they must have HLA typing verified. Infectious testing is required prior to each infusion even if the same donor is used. Each donor must be confirmed to meet eligibility requirements and must be registered by BrUOG before any collection.
- 4.2.5** Peripheral mononuclear cells will be removed while other blood components will be returned. Prior to collection donors will undergo a complete blood count along with CD3+ assessment. Apheresis collection is performed over approximately 5 hours. Blood volume to be collected will be determined based on the CBC and CD3+ percent at the time of collection initiation. A cell count of the product is performed at approximately 2.5 hours. After this assessment, the collection time is adjusted as needed.
- 4.2.6** At least 24 hours post GO (the day post GO completion), the donor will undergo leukapheresis for peripheral blood mononuclear cells.
- 4.2.7** Leukapheresis product will be labeled with the donor's name and date of birth at this time. The cellular product will be labeled with the product name, name of donor, medical record number of donor, recipient name and Medical record number, date of collection, time, and volumes of product, and anticoagulant, and a unique donation identification number, and the tag "Caution: New Drug- Limited by Federal law for Investigational Use." Either two copies of this label shall be created or the label off the bag will be removed once the product is infused, so that a copy of the label can be kept in the recipient's shadow chart.

- 4.2.8** At the time of product collection, two sample aliquots will be collected.
- 4.2.8.1** One sample will be sent to microbiology for a stat gram stain as well as a 14-day microbial culture to assess final product sterility. In the event of a positive extended microbial culture, the attending physician and the patient will be notified. Patients will be monitored immediately for clinical symptoms, additional blood cultures will be drawn, speciation/sensitivity testing of detected microbial organisms will be performed, an investigation will be undertaken to determine root cause, and corrective actions will be performed to prevent future recurrences.
- 4.2.8.2** The second sample will be sent for a complete blood cell count to determine the total nucleated cell (TNC) count, and sent to the lab of Dr. Peter Quesenberry. Here, cell viability will be determined through trypan blue staining and FACS. Release of the final product is contingent upon a negative gram stain and total cell viability of the sample of $\geq 70\%$. Final cell product will be analyzed for CD3+ and CD34+ content via FACS. Using the TNC and CD3+ percentage, the number of CD3+ cells will be calculated to ensure collection of a minimum of 1×10^7 CD3+ cells/kg or 1×10^8 CD3+ cells/kg and maximum of 2×10^7 CD3+ cells/kg or 2×10^8 CD3+ cells/kg are collected. These tests will be performed immediately at completion of leukapheresis to facilitate same day infusion of cellular product.

Patient treatment with DLI (4.2.9-4.2.13)

- 4.2.9** The product will be administered unprocessed at least 24 hours post GO (the day post GO completion) (same day as leukapheresis) with a minimum of 1×10^7 CD3+ cells/kg and maximum of 2×10^7 CD3+ cells/kg irrespective of the number of CD34+ cells (DL1) or a minimum of 1×10^8 CD3+ cells and maximum of 2×10^8 CD3+ cells/kg irrespective of the number of CD34+ cells/kg (DL2). Failure to collect 1×10^7 CD3+ cells/kg or 1×10^8 CD3+ cells/kg (depending on DL) will disqualify the donor from the study. Red blood cell reduction by the apheresis machine will be performed as indicated by ABO typing of donor and recipient. At the RIBC, approximately 10ml of donor RBC is present in the final donor leukapheresis product. This value may be slightly more or less depending on if there are access issues during pheresis. RBC reduction is performed automatically by the apheresis machine, as the nurses aim for hematocrits of 2-4% by visual inspection using colorgrams during collection provided by the manufacturer. The infusion of the cellular product must be initiated within 8 hours of completion of collection and the infusion must be completed within 24 hours of collection.
- 4.2.10** Prior to cellular product infusion into the patient, the appropriate sections of the Quality Assurance checklist (Appendix B) will be completed by a member of the Oncology research team. A second review of the Quality Assurance checklist will be performed by either another member of the Oncology research team or a member of the Lifespan Oncology Clinical Research (LOCR) office. After completion and review of the Quality Assurance checklist both parties will sign off on the Quality Assurance checklist in the appropriate location. Collection and infusion will occur at Rhode Island Hospital or The Miriam Hospital. The Quality Assurance checklist is required to be sent to BrUOG.
- 4.2.11** The cellular product will be infused on the same day as collection so there will be no storage. A member of the research team will transport the cellular product directly to the infusion suite or inpatient unit. The suggested rate of infusion rate is 100ml/hr. This rate is suggested but not required. The infusion rate can be increased secondary to time

constraints. It is required that an infusion pump be utilized. Infusion will generally last 4 hours or less.

4.2.11.1 Administer with a Y-Type Blood/Solution set with blood filter. Prime with normal saline. Calculate how much normal saline to prime line by either referencing the manufacturer guidance for Priming Volume or preferred method prime. Deplete prime line into a measuring device, repeating twice to confirm volume. Prepare patient for blood products, performing pre-dose vital signs. Calculate the total administration volume, which would be the DLI desired volume plus the prime volume. Administer DLI as close to dose level as feasible following institutional guidelines. DLI must be completed no more than 24 hours from end of collection. At conclusion of Total Volume Administration, clamp cells, and open normal saline Y tubing. Flush for at least prime volume to ensure all cells desired have been received.

4.2.12 Residual, unused donor CD34+ cells and CD3 positive cells may be retained for laboratory research purposes. This will only include extra cells from the initial apheresis.

4.2.13 Patients who do not receive the initial DLI for any reason will be deemed unevaluable and replaced.

Additional DLI and GO treatment

4.2.14 Patients who show a CR or CRi to therapy can receive up to two additional donor leukocyte infusions with GO 6mg/m² (administered as 2mg/m² on days 1, 4, and 7 and capped at 4.5mg individual doses) for all patients regardless of age no sooner than 35 days status post their last cellular infusion to allow adequate time between infusions to ensure no engraftment occurs. All treatment must be given during a 6 month period. If patients are determined to not have a response and thus not go forward to receive any additional GO+ DLI this information will be submitted to BrUOG and the patient will be assessed for safety through 30 days post last treatment. DLTs will be assessed in the first 6 patients through 30 days post the last infusion.

4.2.14.1 Required prior to 2nd and 3rd GO+ DLI treatment:

4.2.14.1.1 The following must be confirmed within 7 days prior to a 2nd and 3rd GO infusion AND within 72 hours of the 2nd of 3rd DLI infusion:

- ANC > 500
- PLT > 100
- Creatinine ≤ 2.0 mg/dl
- Total bilirubin less than 1.5x the upper limit of normal (ULN),
- AST and ALT < 2.5x ULN
- All treatment related (to prior GO and DLI treatment) non-heme toxicities must be confirmed as being ≤ grade 2 (except alopecia and weight loss)
- PE (inclusive of vitals and PS) confirming treating physician feels patient is suitable and a good candidate to receive 2nd or 3rd GO+DLI
- ID Testing of Patient and Donor
- HLA and HLA antibody testing

4.3 Toxicities of Non-Engraftment Donor Collection and Patient (recipient) Leukocyte Infusion

Potential donor toxicities include splenic rupture from G-CSF administration (Rare, <5%). More common side (>20%) effects of G-CSF administration are fever, headache, and back pain. During leukapheresis donors may experience perioral tingling and muscle cramping from citrate reactions. To mitigate against

this all donors will receive 5 grams of calcium carbonate in 250 normal saline given over 50ml/hour during collection, for approximately 1 gram per hour (IV).

Potential patient toxicities of infusion of haploidentical leukocytes include the following common toxicities (>20%): Fever, rash, diarrhea, hepatotoxicity, pulmonary edema, dyspnea, signs and symptoms of volume overload and noncardiogenic peripheral edema. In addition to the acute toxicities of cellular infusion syndrome, graft versus host disease may occur. Graft versus host disease is expected to be less common (1-10%). Graft versus host disease could develop weeks to months or even years after infusion of donor leukocytes and could include skin rash, pancytopenia, diarrhea, infection, pleural and pericardial effusion, congestive heart failure and death.

4.4 Quality Control:

A member of the Oncology research team and either a member of LOCR or the Hematology/Oncology attending will sign complete and both sign off on Appendix B, the Quality Assurance Checklist, prior to infusion of the cellular therapy product into the patient.

5. TOXICITIES AND MANAGEMENT

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (CTCAE) version 5.0 (Appendix D). Serious and non-serious adverse events will be captured from the time the patient signs consent until 30 days post the last infusion or GO (whichever is last). If a laboratory abnormality is directly related to active leukemia, it is not considered an AE. If a patient receives another treatment off study prior to the 30 days SAE collection will end. Serious adverse events occurring more than 30 days after study discontinuation need only be reported if a relationship to donor leukocyte infusion is suspected. DLTs will be assessed in the first 6 patients through 30 days post the last infusion.

Subjects that discontinue the protocol for any reason (including completion of treatment) will be followed for survival. At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days (+1 week) post the last donor leukocyte infusion.

If a subject does start another therapy, then SAEs will no longer be required to be reported, unless the SAE is thought to be related to the leukocyte infusion.

The study will utilize a 3+3 design to determine if $1-2 \times 10^8$ CD3 cells/kg can be safely administered with GO. Two DLI dose levels will be assessed:

DLI Dose Level 1: $1-2 \times 10^7$ CD3+ cells/kg

DLI Dose Level 2: $1-2 \times 10^8$ CD3+ cells/kg

Three patients will be accrued to DLI dose level 1. All patients will be assessed for dose limiting toxicities (DLTs) through 35 days post the last dose of GO. If no DLTs are observed during this assessment time period, then accrual to level 2 will proceed.

Patients who experience a DLT will not be eligible to receive any additional DLI or GO on study.

Patients who do not experience a DLT, and who remain on study to receive DLI/GO #2 or DLI/GO #3, will remain on the DLI dose level received during infusion #1, for the remainder of their infusions.

If a DLT is observed in one of the first 3 patients in a dose level, then accrual for that level will be expanded to 6 patients. Two or more instances of DLT in a cohort of 6 patients will result in the preceding dose level being defined as the maximum tolerated dose (MTD). If 2 or more DLTs are observed in dose level 1, the study will be closed.

Depending on DLTs observed, 6-12 patients may be included in the Phase 1 portion of this study.

The Phase 2 part of the study will apply a Simon Two-Stage Design and enroll a total of 15 patients. At least six patients will be treated as part of the phase 1. If there are no DLTs observed, twelve additional patients for up to a total of 15 will be enrolled and treated at the recommended phase 2 dose (MTD). Patients enrolled and treated in the phase 1 MTD portion will be included in the Simon Two-Stage design assessment, which could include up to 6 patients. Patients in the phase 2 study, who experience an event defined as a DLT will be taken off of study. Total enrollment for the study will be 18-21 patients depending on DLT experienced in the dose escalation phase.

All evaluable patients included in the Phase 1 portion will be followed for 30 days post the patient's final DLI to ensure all safety information and treatment is captured.

All AEs will be considered relevant to determine DLTs unless the event can be determined to be unrelated to treatment. All adverse events will be assessed for causality and relationship to DLI and GO.

All AEs will be considered relevant to determine DLTs unless the event can be determined to be completely unrelated to treatment. All adverse events will be assessed for causality and relationship to DLI and GO.

Dose limiting toxicity (DLT) will be defined as any of the following events

- IBMTR Severity Index C graft versus host disease of any duration
 - IBMTR Severity Index D graft versus host disease of any duration
 - Grade 3 or 4 infusion related reaction of any duration
 - Any grade 3 non-hematological toxicities not directly resulting from patient's disease
 - Excluding nausea, vomiting and diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization (a grade 3 nausea, vomiting or diarrhea that requires tube feeding, TPN, or which requires hospitalization or prolongs hospitalization is a DLT). Additional exclusions: fatigue, grade 3 hypokalemia that resolves to baseline within 72 hours, or fever.
 - Any grade 4 non-hematological toxicity not directly resulting from patient's disease
 - Development of SOS
- All Grade 5 toxicities are considered DLTs unless clearly and solely related to the underlying disease.
- Discontinuation of treatment due to an adverse event of any grade is considered a DLT unless the AE is clearly and solely related to the underlying disease.

Adverse event evaluation for the donor will occur from the day of collection to 2 weeks post apheresis (+ 2 weeks). Donor AEs will be documented and reported in the same manner as AEs for the recipient.

5.1 Cytokine Release Syndrome Treatment (Previously identified as “Haplo-immunostorm”)

Our previous phase I study (BrUOG 273) that used haploidentical cellular infusions saw the development of hyperpyrexia at a median time of 14 hours after cellular infusion. Patients that develop Cytokine Release Syndrome are to receive treatment with the following (Neelapu, *et al* 2018):

Treatment of CRS CRS Severity Management Prodromal Syndrome: Low-grade fever, fatigue, anorexia CRS requiring mild intervention (one or more of the following): -High fever -Hypoxia -Mild hypotension CRS requiring moderate to aggressive intervention (one or more of the following): –Hemodynamic instability despite intravenous fluids and vasopressor support –Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation –Rapid clinical deterioration	-Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support. -Administer antipyretics, oxygen, intravenous fluids and/or low dose vasopressors as needed. -Administer high dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. -Administer tocilizumab 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. -If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS. -Limit to a maximum total of 4 tocilizumab doses. -If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high flow oxygen are no longer needed, then taper.
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5.2 Sinusoidal Obstruction Syndrome

Previous use of gemtuzumab ozogamicin has been associated with development of Sinusoidal Obstruction Syndrome (SOS). All patients will be placed on ursodiol for SOS prophylaxis. Patients will have daily weights recorded the first week following GO treatment followed by weekly measurement thereafter. LFTs will be monitored weekly. Patients will be scored for SOS using the following criteria (Baltimore Criteria)(Richardson, *et al* 2017):

1. Bilirubin ≥ 2 mg/dL AND
2. At least 2 of the following:
 - a. ascites (on radiographic or physical examination),
 - b. weight gain $\geq 5\%$ above baseline,
 - c. and hepatomegaly increased over baseline

Patients who develop SOS will have GO permanently discontinued and will be treated with defibrotide at the following doses:

1. Defibrotide 6.25mg/kg every 6 hours infused IV over 2 hours. The dose should be based on the patient's pre-GO infusion weight
2. Continue defibrotide for a minimum of 21 days. If after 21 days SOS has not resolved defibrotide should be continued for up to 60 days or resolution of SOS.

Prophylaxis: Patients will be started on ursodiol 300mg twice daily beginning day 1 of GO, which continue through 4 weeks post the last GO administration. Patients who receive more than one GO administration will remain on ursodiol through 4 weeks post the final GO dose.

5.3 Graft versus Host Disease

We do not expect donor engraftment and therefore should not have acute or chronic GVHD. However, we will monitor for this utilizing the International Bone Marrow Transplant Registry (IBMTR) grading system (Rowlings, Przepiorka *et al.* 1997):

Organ Severity Stage	IBMTR criteria
Skin	
0	No rash
1	Rash < 25% of BSA
2	Rash 25% to 50% of BSA
3	Rash > 50% of BSA
4	Generalized erythroderma with bullous formation
Liver	
0	Total serum bilirubin < 2 mg/dL
1	Total serum bilirubin 2 to 3 mg/dL
2	Total serum bilirubin 3.1 to 6 mg/dL
3	Total serum bilirubin 6.1 to 15 mg/dL
4	Total serum bilirubin > 15 mg/dL
Upper GI	
0	No persistent nausea and no histologic evidence of GvHD in the stomach or duodenum
1	Persistent nausea with histologic evidence of GvHD in the stomach or duodenum
Lower GI	
0	Diarrhea < 500 mL/day
1	Diarrhea > 500 mL/day
2	Diarrhea > 1000 mL/day
3	Diarrhea > 1500 mL/day
4	Severe abdominal pain with or without ileus

International Bone Marrow Transplant Registry Severity Index
A – Stage 1 skin involvement; no liver or gut involvement
B – Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement
C – Stage 3 skin, liver, or gut involvement

D – Stage 4 skin, liver, or gut involvement

6. STUDY CALENDARS FOR RECIPIENT

Table 1: SCREENING

TESTS & Observation	≤ 28 days of study treatment	≤ 14 days of study treatment	≤ 7 days of study treatment
Informed Consent (If signed ICF is from >30 days prior to infusion patient must be re-consented prior to infusion)	X ^a		
History and Physical ^b			X
Demographics	X		
Physical Exam			X
Temperature, Blood Pressure, Heart Rate, Respiratory Rate, O ₂ , Height & Weight			X
Performance Status (Karnofsky or ECOG)			X
Toxicity Assessment		X	
Conmed log		X	
Chest X-ray			X
EKG		X	
Urine analysis			X
MUGA or Echocardiogram			X
Pulmonary Function Tests		X	
CBC, Differential, Platelets			X
Serum Creatinine, BUN, Na, K, Cl, HCO ₃ , Glucose, AST, ALT, Total Bilirubin, LDH, ALK Phos, Uric Acid, Total Protein, Albumin, Magnesium, Phosphorus, Calcium, Ferritin			X
CD4 count			X
HIV 1/2			X
Hepatitis B and C, CMV Ab, CMV Ag or PCR			X
HTLV-1/2 Syphilis	X		
Chagas	X		
β-HCG urine or Serum ^c			X ^c
ABO type, Rh type	X		
HLA Type	X		
Bone Marrow Asp & Biopsy	X		
Chimerism Samples ^d	X (Peripheral blood at this time)		

a. ICF can be within 30 days of treatment.

b. History includes documenting behavioral risk for exposure to infectious agents and disease being tested.

- c. ≤ 7 days of study treatment (GO) + 24 hours, pregnancy test not required if female recipient is post-menopausal (surgical menopause or lack of menses ≥ 12 months). This must be documented however.
- d. Peripheral blood will be collected at baseline to be used for chimerism testing, see section 6.3. Submit confirmation sample was drawn and submitted.

Table 2: Treatment*

TESTS & Observation	Cycle 1 GO+DLI #1 GO: D1 (- 7 days) ^a , D4 (-24 hrs) D7 (-24 hrs)	Cycle 2: GO + DLI #2 ^f Cycle 3: GO + DLI #3 ^f GO: D1(-7 days) AND DLI (≤ 72 hrs) ^f	Cycle 1/2/3: Day of DLI ^f	For 1-month <i>post</i> DLI 2x/week (weeks 1,2,3,4) ^b
Physical Exam	X	X	X	X
Performance Status (Karnofsky or ECOG)	X	X	X	X
Temperature**, Blood Pressure, Heart Rate, Respiratory Rate, O ₂ , Weight**	X	X	X	X
Toxicity Assessment	X	X	X	X ^g
Conmed Log	X	X	X	X ^g
CBC, Differential, Platelets	X	X	X	X
Serum Creatinine, BUN	X	X	X	X ^c
Na, K, Cl, HCO ₃ , Glucose	X		X	X ^c
AST, ALT, Total Bilirubin, LDH, ALK Phos,Uric Acid	X	X	X	X ^c
Total Protein, Albumin	X		X	X ^c
Mg, Phosphorus, Calcium	X		X	X ^c
Ferritin	X		X	X ^c
HIV 1/2		X		
Hepatitis B and C CMV Ab, CMV Ag or PCR		X		
HTLV-1/2 Syphilis		X		
Chagas		X		
β -HCG urine or Serum		X		
HLA antibody screening		X		
HLA Type		X		
Bone Marrow Asp & Biopsy				X ^d
Chimerism Samples			X (See section 6.3) ^e	X (See section 6.3) ^e

Cytokine Release Syndrome/Immunologic Samples			X (See section 6.4)	X (See section 6.4)
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- Screening assessments can be used for Cycle 1 Day 1 (dose 1 GO) if completed in last 7 days (7 days from day 1), otherwise, assessments must be re-done.
- For all GO+DLI cycles: assessments 1 month post DLI 2x/week (weeks 1,2,3,4) there must be > 48 hrs between visits). Patients who come off study prior to 1 month post DLI, will only require the 30 days (+1 week) toxicity assessment. Visits can be done virtually, at discretion of the investigator in order to minimize the risks of coronavirus exposure to both study participants and staff.
- During weeks 2-4 the following lab work only needs to be drawn each week: serum Cr, BUN, serum electrolytes, Glu, AST, ALT, Bili, LDH, ALK, Uric acid, T protein, Albumin, Mg, Phos, Ca, Ferritin. However, CBC w/ diff and PLT required twice weekly even weeks 2-4
- BMBX is required at time points post baseline for all patients who are thought to have a response to treatment. BMBX to be collected at 2 weeks and approximately 4 weeks (+ 2 weeks) after DLI. BMBX confirming at minimum a complete response or complete response with incomplete count recovery is required to be documented via both time-points to confirm patient is eligible for additional 2nd and or 3rd GO+DLI treatment. BMBX pathology report must be sent to BrUOG any time it is performed. After initial GO+DLI if patient is not thought to have responded and BMBX is not to be done, then information is to be sent to BrUOG confirming a 2nd and 3rd GO+DLI will not be scheduled. This will start the toxicity review time-frame.
- Peripheral blood will be collected post infusion (see section 6.3) to be used for chimerism testing. If chimerism continues then peripheral blood must be drawn every 14 days +/- 5 days until chimerism is ≤2%
- If applicable. If DLI#2 or #3 is not applicable, submit documentation patient not getting #2 or #3 to BrUOG and begin safety evaluation and follow-up.
- Toxicity assessment to be done 30 days (+1 week) post last infusion (DLI or GO whichever is last). SAEs are to be recorded from time patient signs consent to 30 days post last infusion or GO infusion (whichever is last) unless patient begins a new therapy. (AE evaluation if believed to be attributed to study treatment will continue even if on new treatment). SAEs post 30 days are still to be reported if suspected to be related to leukocyte infusion or GO. Conmed assessment to end at 30 days post last treatment.

*** Please submit Quality Assurance Checklist-Appendix B to BrUOG with treatment data.**

**** Please refer to protocol section 6.1.1 & 6.1.2 regarding additional temperature and weight timepoints.**

Table 3: Follow-up

TESTS & Observation	Begins post last treatment (end of treatment) Month 2 1x/week (weeks 5,6,7,8)*	Follow-up Month 3-24 (EVERY 28 DAYS) ^{a*} (+/- 7 Days)	End of 2 year follow-up ^{a*} (+/- 8 weeks)
Physical Exam	X	X	X
Performance Status (Karnofsky or ECOG)	X	X	X
Temperature, Blood Pressure, Heart Rate, Respiratory Rate, Weight	X	X	
Toxicity Assessment	X ^b	X ^b	

CBC, Differential, Platelets	X	X	X
Serum Creatinine, BUN	X	X	
Na, K, Cl, HCO ₃ , Glucose	X	X	
AST, ALT, Total Bilirubin, LDH, ALK Phos, Uric Acid	X	Every 4 months	
Total Protein, Albumin	X	Every 4 months	
Mg, Phosphorus, Calcium	Month 2	Every 4 months	
Bone Marrow Asp & Biopsy		X ^c	X ^c
Chimerism Samples	X ^d		
Survival		X	X

- Post coming off study (once treatment is done) patients will be followed for survival q 3 months (3 months from date off study). Survival can be collected via phone call, visit or note from another treating physician. Survival and death to be reported to BrUOG
- Toxicity assessment to be done 30 days (+1 week) post last infusion (DLI or GO whichever is last). SAEs are to be recorded from time patient signs consent to 30 days post last infusion or GO infusion (whichever is last) unless patient begins a new therapy. (AE evaluation will continue even if on new treatment). SAEs post 30 days are still to be reported if suspected to be related to leukocyte infusion or GO.
- BMBX is required at time points post baseline for all patients who are thought to have a response to treatment. BMBX is required at time points post baseline for all patients who are thought to have a response to treatment. BMBX to be collected at 3, 6, 12 and 24 months post last DLI infusion. BMBX pathology report must be sent to BrUOG any time it is performed.
- If chimerism continues post end of treatment then peripheral blood must be drawn every 14 days +/- 5 days until chimerism is $\leq 2\%$

*The study treatment period will be completed at 2 years or after patient has progression of their leukemia or received other treatments, whichever comes first. All patients will be followed post the 30-Day safety visit for chimerism (if observed), AE's (if believed to be attributable to study treatment) and overall survival until death regardless of starting new treatments or progression.

6.1.1: **Temperature Table to be used after each DLI.

Temperature	Time Point
	Prior to DLI
	0-4 hours POST DLI
	8-24 hours POST DLI
	34-48 hours post DLI
	72-96 hours post DLI
	168 hours +/- 2 days post DLI

6.1.2: ***Daily Weight Table to be used the first week following GO treatment.

Weight	Time Point
	Day 0 post GO treatment
	Day 1 post GO treatment
	Day 2 post GO treatment

	Day 3 post GO treatment
	Day 4 post GO treatment
	Day 5 post GO treatment
	Day 6 post GO treatment
	Day 7 post GO treatment

6.2 Study Calendar for Donor **required along with eligibility for each donor (if a different one is used) and simplified eligibility needed to be confirmed even if the same donor is used again- see section above)

Donor Screening/Registration:

TESTS & OBSERVATION	PRIOR TO REGISTRATION (WITH RESULTS)
Informed Consent	X ^c
History and Physical (physician note) (to be sent to RIBC)	X ^{ac}
Physical Exam	X ^a
Demographics	X ^c
Cardiac Exam ^d	X ^a
Vital Signs	X ^a
Performance Status (Karnofsky or ECOG)	X ^a
Chest X-ray	X ^b
EKG	X ^a
Urine analysis	X ^a
Vein assessment	X ^g
Conmed log	X ^a
CBC, Differential, Platelets	X ^b
HIV1/2	X ^b
Hepatitis B and C	X ^b
CMV Ab, CMV Ag or PCR	X ^b
HTLV-1/2	X ^b
Syphilis	X ^b
Chagas	X ^b
West Nile Virus	X ^b
Chlamydia & Gonorrhea	X ^b
β-HCG urine or Serum	X ^a
ABO type	X ^c
Rh type	X ^c
HLA Type	X ^c
HLA Antibody screen	X ^c

Chimerism Samples	X ^f
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^a ≤ 7 days of registration, Pregnancy test is not required for female donor if post-menopausal (surgical menopause or lack of menses ≥12 months), however this must be documented.

^b ≤14 days of registration.

^c Tests and Observations ≤ 28 days of registration; ICF ≤30 days of collection or donor is to be re-consented.

^d Full cardiac workup by a Cardiologist is only required for any history of congestive heart failure syndrome, conduction abnormalities or history of arrhythmia other than treated atrial fibrillation.

^e History includes documenting behavioral risk for exposure to infectious agents and disease being tested-see section 3.3.9 as well.

^f Peripheral blood will be collected at baseline to be used for chimerism testing, see section 6.3

^g treating physician to confirm vein access and confirmation to be sent with registration to BrUOG

Donor On Study:

ASSESSMENTS	Confirmation Labs (Day 1 GCSF/Recipient Day 3 (-1)) ^c	2 Weeks (+2wks) Post Apheresis
CBC, Differential, Platelets	X	
HIV1/2*	X ^a	
Hepatitis B and C *	X ^a	
CMV Ab, CMV Ag or PCR*	X ^a	
HTLV-1/2 *	X ^a	
Syphilis*	X ^a	
Chagas*	X ^a	
West Nile Virus*	X ^a	
Chlamydia & Gonorrhea*	X ^a	
β-HCG urine or Serum*	X ^a	
Adverse Event evaluation		X ^b
Conmed log		X ^b

^a ≤ 7 days of collection + 24 hours, Pregnancy test is not required for female donor if post-menopausal (surgical menopause or lack of menses ≥12 months), however this must be documented.

^b See section 9.2 for event evaluation for donor 2 weeks (+2 weeks) post apheresis. Donor does not need to come into clinic for evaluation, phone call can suffice. For conmed assessment: conmeds should only include medications given secondary to the collection or post collection AEs.

^c Confirmation Labs required prior to collection. CBC, Differential, Platelets must be drawn on Donor Day 1 GCSF/Recipient Day 3 (-1 Day), and results must be submitted to BrUOG. If previous labs for Infectious Disease are within window, labs do not need to be redrawn.

*Donor labs must be drawn within 7 days of collection + 24 hours and final test results available for eligibility. Once donor is registered, labs must continue to be redrawn to ensure labs and results are within

7 days (+24 hours) of each collection. Pre-collection labs will be drawn on Donor Day 1/Recipient Day 3 (-1 Day). Results will be required prior to leukocyte collection. If when re-drawn the result aligns with an exclusion criterion (i.e. a result of a test now deems the donor ineligible), the donor is disqualified from DLI collection and will be labeled as a screen failure. BrUOG is required to receive all donor testing and lab results.

CHIMERISM AND IMMUNOLOGIC SAMPLE SUBMISSION

6.3 Chimerism Sample Procurement

6.3.1 Prior to cell infusion, collect peripheral blood samples from ***BOTH*** donor and recipient. If WBC>2000 then send one 10ml EDTA sample. If WBC<2000 send two 10ml EDTA samples. Samples are sent to the Rhode Island Blood Center for short tandem repeat (STR) genotyping

6.3.2 Post cell infusion, collect four peripheral blood samples from recipient only at the following time points to the Rhode Island Blood Center for STR chimerism analysis (one sample at each time point):

- 48 hours (2 days) after cell infusion
- 14 days after cell infusion, +/- 2 days
- Every 14 days (+/- 5 days) if chimerism persists beyond the initial 14 days. This will continue to be performed until chimerism is $\leq 2\%$.

6.4 Immunologic Sample Procurement

Peripheral blood samples will be collected from the recipient in 2- 6mL purple top tubes at the following time points and sent to the lab of Dr. Peter Quesenberry to study the Cytokine Release Syndrome (CRS) and Effector Cell proportions:

- prior to GO administration (one day before initiation, d-8)
- before cell infusion (d-1)
- 0-4 hours post cell infusion

If CRS is observed:

- 8-24 hours post infusion (Onset of CRS)
- 34-48 hours post infusion (Midpoint of CRS)
- 72-96 hours post infusion (End of CRS)
- 168 hours post infusion (with Day 7 scheduled blood work) +/- 2 days

Samples may be batch processed.

7. CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

7.1 Criteria for AML (adapted from (Cheson, *et al* 2003))

Definitions of Response

Complete remission (CR) is defined as the presence of all of the following

- Peripheral blood
 - No leukemic blasts present.
- No extramedullary findings of leukemia or disappearance of such (i.e. CNS or soft tissue involvement)
- Bone marrow
 - Cellularity >20% with baseline maturation.
 - No Auer rods

- Less than 5% blast cells.
- Complete blood counts and bone marrow normalization criteria must be met within one week of each other. Hematopoietic recovery is an ANC $> 1.0 \times 10^9/L$ and platelet count $> 100 \times 10^9/L$. No specific hemoglobin or hematocrit level is specified but the patient must be transfusion free.

Complete remission with incomplete recovery (CRi) is defined as the following:

- Meets criteria for CR except
- ANC $< 1.0 \times 10^9/L$ or platelet count $< 100 \times 10^9/L$

Progressive Disease

- Failure to achieve a CR or CRi.
- Failed to achieve remission as determined by peripheral blood and bone marrow aspirate and biopsy.

Treatment failure due to patient death

- Patient died within 60 days of therapy completion (infusion of leukocytes)
- Record whether the patient died with or without evidence of persistent leukemia as determined by peripheral blood and bone marrow aspirate and biopsy.

Relapse

- Any of the following, occurring after either CR or CRi:
- The reappearance of circulating blast cells not attributable to “overshoot” following recovery from myelosuppressive therapy.
- More than 5% blasts in the marrow, not attributable to another cause (e.g., bone marrow regeneration).
- If there are no circulating blasts, but the marrow contains 5-20% blasts, a repeat bone marrow at least 1 week later with more than 5% blasts is necessary to meet the criteria for relapse.
- The detection of the development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.

Event

- **Progressive disease, relapse after CR or CRi or death**

Event Free Survival

- Time from study entry to event development

Overall Survival

- Time from study entry to death

8. PATIENT REGISTRATION

All volunteers will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Volunteer Consent Form must be emailed to the BrUOG Central Office, BrUOG@brown.edu, at the time of registration and prior to volunteer treatment.

Details of patient’s study participation should be documented in clinic/file notes. This project will leverage the Lifespan REDCap instance for making electronic health data accessible for research purposes. REDCap was developed by Vanderbilt University with collaboration from a consortium of

institutional partners as a software toolset and workflow methodology for electronic collection and management of research and clinical trial data.¹⁵ The REDCap platform is a secure, web-based application flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data, and enforces real time validation rules (with automated data type and range checks) at the time of entry. This platform provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, and real-time data monitoring/querying of participant records. REDCap has multiple data export options to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The investigator will electronically sign the REDCap case reports prior to DSMB review and at the end of follow-up to indicate that, to his/her knowledge, they are complete and accurate.

Sites are to be sure that elements to support all inclusion and exclusion criteria are submitted and that all assessments from the schedule of evaluations (Section 9) are submitted for registration.

This protocol will allow for enrollment of patients remotely. All patients will require a signed informed consent and that visit will be conducted by a member of the Research Team at BrUOG remotely via telehealth according to BrUOG Standard Operating Procedures. For patients undergoing protocol treatment and not able to travel to the Investigator's institution, data will be collected by the Research Team using locally obtained data.

9. SERIOUS ADVERSE EVENT REPORTING PROCEDURES

BrUOG considers the SAE reporting period to begin when the subject signs the study specific informed consent.

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Gemtuzumab ozogamicin ® whether or not considered related to Gemtuzumab ozogamicin ®. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial. If a laboratory abnormality is directly related to active leukemia, it is not considered an AE.

Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Suspected adverse reaction:

BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected.

As per 21 CFR 312.32 (a), the FDA has defined a suspected adverse reaction as any adverse event where there is reasonable possibility that the drug may have caused the adverse event. A reasonable possibility means there is evidence suggesting a causal relationship between the drug and the adverse event.

A suspected adverse reaction outlines the possibility of the causal relationship between the event and the drug, whereas an adverse reaction means the drug caused the event.

9.1 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious adverse event (SAE)

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Persistent or significant disability or incapacity, congenital anomaly / birth defect
- Cytopenias are an expected side effect of this treatment regimen. GO dosing will not be held for cytopenias nor should it be listed as a serious adverse event if cytopenias require hospital admission for transfusion support.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 1. Study drug administration and donor cell infusion (GO may be administered on an inpatient basis and if patients are admitted for GO administration this will be secondary to observation or for standard of care. Patients who are admitted for drug administration will likely not be discharged before DLI),
 2. transfusional support,
 3. disease staging/re-staging procedures,
 4. concomitant radiotherapy,
 5. thoracentesis / paracentesis,
 6. placement of an indwelling catheter, unless associated with other serious events.

7. Hospitalization for observation without an associated AE will not be a SAE nor will the admission for treatment of a pre-existing condition not associated with the development of a new AE or worsening of the pre-existing condition (i.e. for work-up of persistent pre-treatment lab abnormality).
 8. An emergency room visit should not be considered a SAE unless the patient is formally admitted to the hospital even if <24 hours. For an ER visit, the event leading to the ER visit should be assessed for medical importance.
- The hospitalization for the GO administration or DLI is not a SAE for this trial. An event which meets serious or important medication event criteria that occurs during the planned admission for the GO or DLI will be considered a SAE however.

The definition of serious adverse event (experience) also includes important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of “related” being that there is a reasonable possibility that the drug caused the adverse experience.

Unexpected adverse event

An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

9.2 Any adverse event, whether serious or non-serious, occurring after the patient has provided informed consent and until 30 days after the patient has received final cell infusion or GO infusion (whichever is last) must be reported unless the subject has already begun another treatment, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first. Non-serious AE evaluation will continue for the full 30 days.

Serious adverse events occurring more than 30 days after study discontinuation (final DLI or GO infusion, whichever is last) need only be reported if a relationship to the cell infusion is suspected.

Adverse event evaluation for the donor will occur from the day of collection to 2 weeks (+2 weeks) post apheresis. Donor AEs will be documented and reported in the same manner as AEs for the recipient.

9.3 Pregnancies

Pregnancies occurring while the subject is on study or within 4 weeks after the recipient's infusion or GO (whichever is last) are considered expedited reportable events. If the recipient is found to be pregnant

prior to infusion they are to be taken off study immediately and not receive infusion. The pregnancy must be reported to the Brown University Oncology Research Group, by the site, immediately (within 24 hours), via the site completed and signed 3500A MedWatch form and the Pfizer Pregnancy Form (site to submit to BrUOG), and BrUOG will in turn report to the FDA. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 4 weeks (30 days) of the recipient's infusion or GO infusion (whichever is last), are considered immediately reportable events.

Examples of other pregnancy outcomes that require SAE reporting:

- Spontaneous abortion (includes miscarriage and missed abortion)
- Stillbirth
- Congenital anomaly (including in an aborted fetus, a stillborn infant, or neonate that dies shortly after birth)
- Neonatal death

In the case of **neonatal death**:

Any neonatal death that occurs within 1 month of birth should be reported, without regard to causality, as an SAE

In the case of **infant death**: Any infant death that is assessed as possibly related to the in utero exposure to the Pfizer product or blinded therapy should be reported as an SAE

If a female partner of a male subject taking investigational product becomes pregnant, the male subject should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

9.4 Otherwise reportable events (reported as an important medical event)

Certain types of events, as identified below, are reportable under the reporting processes and requirements for SAEs, even if there is no associated adverse event. These are considered “otherwise reportable events” and generally reflect circumstances that could lead to an increased risk of an adverse event. **Like an SAE, an otherwise reportable event is to be reported to within the SAE time frames and followed up to determine outcome, including the later occurrence of an associated SAE.**

- 1) Hy's Law: Subjects who present with the following laboratory abnormalities should be evaluated further as potential Drug induced liver injury (DILI) (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:
 - Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
 - For subjects with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which value(s) are above the ULN at baseline.
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).
 - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ or if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

- Rises in AST/ALT and TBili separated by more than a few weeks are assessed individually based on clinical judgment; any case where uncertainty remains as to whether it might represent a potential DILI case is reviewed.

2) Lack of Efficacy (LOE) (reported as an important medical event) For clinical study reporting purposes, lack of efficacy is defined as: Failure of expected pharmacological action or therapeutic benefit

LOE should be reported to Pfizer when one or more of the following conditions are met:

- It is associated with an SAE *OR*
- The product is used for the treatment of a life-threatening condition (e.g. anti-infectives*) with the exclusion of HIV and anti-cancer products, which are discussed below
 - A life-threatening infection where lack of efficacy seems to be due to the development of a newly resistant strain of bacterium/virus/fungus previously regarded as susceptible should be reported
 - A life-threatening situation where the medicinal product was not in fact appropriate for the infectious agent should not be reported, unless the report contain an SAE
- Progression of disease if the patient expires secondary to their disease during the reporting time period
- Exposure during breast feeding
- Exposure during pregnancy (See pregnancy section)

Reporting requirements and procedures depend upon:

- Whether haploidentical cellular or GO infusion is suspected of causing toxicity;
- Whether the possibility of such a toxicity was reported in the protocol or consent form; and
- The severity of grade of the toxicity. All reactions in a “reportable” category must be reported unless it is documented on flow sheets and/or follow-up forms that the treatment is definitely not responsible for the toxicity.

9.5 Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

9.6 Types of Report:

Telephone report:

For SAEs contact BrUOG Central Office (401) 863-3000 within 24 hours of event to alert BrUOG. BrUOG must also receive 24-hour- notice prior to a SAE report being sent.

Written report: Send the copy of the completed and signed MedWatch 3500A form within 5 business days of being made aware of the event to the BrUOG Central Office by email. If the SAE is a pregnancy or suspected pregnancy, follow instructions above.

Brown University Oncology Research Group

Fax: (401) 863-3820

Phone: (401) 863-3000

BrUOG@brown.edu

All deaths or life threatening events during treatment (during time patient is received GO or DLI) or within 30 days post final infusion must be reported within 5 business days (from being made aware of the event) or as soon as the investigator is made aware of the event. If the death or life threatening event is thought to be related to the study infusion, the SAE must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (donor infusion)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to GO and donor leukocyte infusion.
- Action taken with GO and DLI infusions
- Site must be clear about what events are being reported as being serious
- Must be typed
- **It is required that you put the following numbers on the MedWatch form for tracking:**
 - **WI231684**
 - **BrUOG 345**

A final report to document resolution of the SAE (such as discharge from hospital) is required

9.7 Follow-up information:

Additional Info maybe added to a previously submitted report by any of the following methods.

- When submitting a follow-up SAE use a new MedWatch form to provide follow-up information and do not cross out or add to the prior MedWatch.

Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect treatment, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report).

9.8 BrUOG Responsibility Regarding Reporting:

The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 5 business days after initial receipt of signed MedWatch. BrUOG will alert Pfizer to an SAE immediately or within 24 hours/1 business day, of being made aware of the event and only when in receipt of the signed documentation via the site submitted MedWatch.

BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected (21 CFR 312.32 (c)(1)(i)). It is required that events that are suspected, serious and unexpected, be reported to the FDA via an IND safety report as per requirements in 21CFR 312.

BrUOG will fax reports to the FDA for IND Safety Reports: to the CDER DHP Division fax number.

Fax: (301) 796-9845.

SAEs will be reported as an amendment to the IND (if applicable) within 15 days of sponsor notification. The FDA will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA (which will be sent to the division fax). A copy of the form will be kept by the BrUOG Central Office.

- “IND safety report” for 15-day reports
- “Follow-up IND safety report” for follow-up information
- “7-day IND safety report” for unexpected fatal or life-threatening adverse reaction reports

All SAEs will be sent to Pfizer within 1 business day as noted above (fax) : 1-866-997-8322 or via email to SAEFaxmailbox@Pfizer.com

9.9 Safety Reporting for IND Holders

In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with safety-reporting requirements.

9.10 IND Annual Reports, for IND study only

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CFR 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Novartis as a supporter of this study.

9.11 Adverse event updates/IND safety reports External

Pfizer shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

10. AGENT ACCOUNTABILITY

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from manufacturer using a Drug Accountability Record Form.

10.1 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be reviewed by BrUOG and BrUOG will route drug accountability logs to Pfizer.

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

Investigational gemtuzumab ozogamicin (expired or end of study) should be destroyed on site according to the institution's standard operating procedure only once approved by BrUOG (who will obtain approval from Pfizer). Drug remaining from an infusion can be destroyed as per institutional standard operating procedure without approval. Be sure to document destruction on drug accountability logs (do not need to document used drug remaining from infusion on the log).

Drug orders should be placed via the Pfizer portal and cc'd to BrUOG@brown.edu

Temperature excursions should be emailed to GCSTempExcursionSupport@pfizer.com and be cc'd to BrUOG@brown.edu

Storage excursion:

Include the following in the body of the email for temperature excursions:

Study number (BrUOG 345)

Site number (1)

Completed RF07 form (Template)

Temperature recorder data of monitoring log showing the date and duration of excursion (data should include previous acceptable reading and reading showing return to acceptable conditions)

Shipment excursion:

Include the following in the body of the email:

Study number (BrUOG 345)

Site number (1)

Shipment number

Temperature recorder data of monitoring log showing the date and duration of excursion (data should include previous acceptable reading and reading showing return to acceptable conditions)

10.2 PHARMACEUTICAL INFORMATION

Pfizer Pharmaceuticals will supply Gemtuzumab Ozogamicin for this study.

10.2.1 Drug Supply and Storage

Mylotarg (gemtuzumab ozogamicin) 4.5 mg/vial is supplied as a white to off-white, preservative free, lyophilized cake or powder. The drug product is supplied in a 20 mL amber vial with a butyl rubber stopper and crimp seal with flip-off cap. It must be stored in the refrigerator at 2 to 8°C (36 to 46°F), and is for single-use only.

10.2.2 Instructions for Reconstitution

Reconstitute the contents of each vial with 5 mL of Sterile Water for Injection. Gently invert or swirl the vial(s) several times before use. To avoid foaming, do not shake or agitate vigorously. The light exposure of vials and dosing solutions should be minimized.

Always refer to the most up to date Investigator Brochure for details on reconstitution.

10.2.3 Instructions for Dilution

Prepare an admixture solution of Mylotarg by diluting the reconstituted solution into 0.9% sodium chloride injection solution. Depending on the dose, the dilution can be performed in latex-free polypropylene syringes or in an infusion bag composed of PVC with DEHP or polyolefin (polypropylene and/or polyethylene). Mylotarg should only be diluted with 0.9% sodium chloride solution. Mylotarg should not be diluted with any other solution or mixed with other drugs.

Doses must be mixed to a concentration between 0.075 mg/mL to 0.234 mg/mL according to the following instructions:

- Doses less than 3.9 mg must be prepared for administration in a 25 mL NS IV bag in an appropriate volume of 0.9% Sodium Chloride Injection to a final concentration between 0.075 mg/mL to 0.234 mg/mL immediately before infuse, using BAXTER set. PROTECT FROM LIGHT.
- Doses greater than or equal to 3.9 mg are to be diluted in a 50 mL NS IV bag in an appropriate volume of 0.9% Sodium Chloride Injection to ensure a final concentration between 0.075 mg/mL to 0.234 mg/mL. PROTECT FROM LIGHT

Following dilution with 0.9% (w/v) sodium chloride, gemtuzumab ozogamicin solution should be infused immediately. Protect the reconstituted and diluted GO solutions from light. The solutions should be used immediately. Do not freeze the reconstituted or diluted solution. If the product can't be used immediately, the diluted product may be stored up to 6 hours at room temperature (15-25°C; 59-77°F), including the infusion step, with an additional 12 hours storage at 2-8°C (36-46°F).

Always refer to the most up to date Investigator Brochure for details on dilution.

10.2.4 Instructions for Administration

Gemtuzumab ozogamicin should never be administered as an IV push or bolus. Use an in-line 0.2 micron polyethersulfone (PES) filter for infusion of MYLOTARG. Protect the intravenous bag from light using a light blocking cover during infusion. The infusion line does not need to be protected from light. Do not mix MYLOTARG with, or administer as an infusion with, other medicinal products.

Flush all lines with NS to ensure all drug is delivered.

Dose 1: Patients <70 years of age will be given gemtuzumab ozogamicin 9mg/m² total dose and patients ≥70 years of age will be given gemtuzumab ozogamicin 6mg/m² on days 1, 4, and 7 as a fractionated infusion over approximately 2 hours at a dose of either 3mg/m² or 2mg/m² capped at 4.5mg individual dose. Gemtuzumab Ozogamicin will be given prior to donor leukocyte infusion, which will be given at least 24 hours post GO (the day post GO completion).

Patients who show at minimum a CR or CRi to therapy can receive up to two additional donor leukocyte infusions with GO 6mg/m² (fractionated infusion dosing of 2mg/m² on days 1, 4, and 7) capped at 4.5mg individual dose for a total capped dose of 13.5mg for all patients regardless of age administered day 1, 4, 7 (see treatment section for details on windows) no sooner than 35 days status post their last cellular

infusion to allow adequate time between infusions to ensure no engraftment occurs. All treatment must be given during a 6 month period.

10.2.5 Instructions for Safe Use, Handling, and Disposal

All opened (i.e. aluminum over-seal broken) vials (full, partially used, and empty) may be destroyed at the site by the appropriate site personnel (e.g. Pharmacist; Study Nurse/Coordinator) following local environmental requirements and institutional policies.

All destruction of unused drug must be fully documented at the time of destruction on the drug accountability log at the time of destruction.

All unused, unopened and rejected supplies will need to be approved by Pfizer for destruction prior to any drug being destroyed. BrUOG will obtain Pfizer approval to destroy. Documentation of all destruction is required on the drug accountability log.

Discarded volumes of active solutions should be disposed of as pharmaceutical waste according to local site procedures.

Normal saline may be disposed of according to local site procedures. Other items used in the dose preparation and administration should be disposed of according to local site procedures.

Mylotarg is considered a hazardous substance, therefore sites must follow local practices for the storage, handling and disposal of Mylotarg.

10.2.6 Safety:

As documented in section 6.2.3.4.3 of the Investigator Brochure: The most frequently reported fatal SAEs (≥ 12 events [$\geq 1.0\%$ of the events]) in patients receiving single agent GO were disease/AML progression (333 events), sepsis (76 events), pneumonia (43 events), thrombocytopenia (30), Multiple organ dysfunction syndrome and respiratory failure (29 events each), neoplasm malignant (25 events), renal failure (17 events), neutropenia, acute respiratory distress syndrome and acute kidney injury (16 events each), febrile neutropenia (15 events), cerebral hemorrhage 13 events), graft versus host disease (13 events), liver disorder (11 events), pancytopenia, hemorrhage intracranial, gastrointestinal hemorrhage, and veno-occlusive liver disease (12 events each).

11. REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.

1. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
2. The physician feels it is in the best interest of the patient to stop the treatment.

3. Intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
4. Non protocol chemotherapy or immunotherapy is administered during the study
5. Noncompliance with protocol or treatment—major violation
6. Suspected Pregnancy
7. Patient is lost to follow-up
8. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
9. Patient request
10. General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
11. Progressive disease at any time
12. At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.
13. Death
14. Grade 3 and 4 infusion reactions to GO
15. Sinusoidal Obstruction Syndrome

In this event notify:
Brown University Oncology Research Group (BrUOG) Central Office
Phone: (401) 863-3000
Fax: (401) 863-3820
Cell: (401) 413-5844

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol. Follow-up after withdrawal forms are to be sent to BrUOG.**

12. FOLLOW-UP

Subjects that discontinue the protocol for any reason will be followed for survival for 2 years. At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days post the final donor leukocyte infusion or final GO infusion whichever is last.

Serious adverse events will be captured from the time the patient signs consent to 30 days post final infusion (DLI or GO whichever is last) or until patient receives other treatment. Non-serious AEs will be captured regardless of if a patient begins a new treatment. Serious adverse events occurring more than 30 days after study discontinuation need only be reported if a relationship to donor leukocyte infusion is suspected. See AE section of the protocol for more details.

Adverse event evaluation for the donor will occur from the day of collection to 2 weeks (+2 weeks) post apheresis. Donor AEs will be documented and reported in the same manner as AEs for the recipient.

13. REGULATORY CONSIDERATIONS

13.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

13.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be provided by the Brown University Oncology Research Group. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

13.3 Protocol amendments or changes in study conduct:

Any change or addition to this protocol requires a written protocol amendment by The Brown University Oncology Research Group and the principal investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to the Brown University Oncology Research Group.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, the Brown University Oncology Research Group must be notified and the IRB at the center must be informed immediately.

14. DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

14.1 Good Clinical Practice:

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be

thoroughly familiar with the appropriate use of the study procedures, drug and cell therapy as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Patient Confidentiality:

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the Brown University Oncology Research Group or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.3 Protocol Compliance:

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority (ies). Changes to the protocol will require approval from the Brown University Oncology Research Group and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. Any departures from the protocol must be fully documented in the source documents. Deviations will be reviewed via BrUOG standard operating procedures.

14.4 On-site Audits:

Regulatory authorities, the IEC/IRB and/or the Brown University Oncology Research Group clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14.5 Premature Closure of the Study:

This study may be prematurely terminated, if in the opinion of the investigator or The Brown University Oncology Research Group, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided by the Brown University Oncology Research Group.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data

14.6 Record Retention:

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigator (John Reagan, M.D.) and Brown University Oncology

Research Group will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c]) require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified.

The site and PI must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest.

All records for this trial are required to be kept until site and PI obtains approval from BrUOG.

15. DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB reviews trial performance information such as accrual information.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

16. STATISTICS

16.1 Statistical Design

The study will utilize a 3+3 design to determine if $1-2 \times 10^8$ CD3 cells/kg can be safely administered with GO. Two DLI dose levels will be assessed:

DLI Dose Level 1: $1-2 \times 10^7$ CD3+ cells/kg

DLI Dose Level 2: $1-2 \times 10^8$ CD3+ cells/kg

Three patients will be accrued to DLI dose level 1. All patients will be assessed for dose limiting toxicities (DLTs) through 35 days post the last dose of GO. If no DLTs are observed during this assessment time period, then accrual to level 2 will proceed.

Patients who experience a DLT will not be eligible to receive any additional DLI or GO on study.

Patients who do not experience a DLT, and who remain on study to receive DLI/GO #2 or DLI/GO #3, will remain on the DLI dose level received during infusion #1, for the remainder of their infusions.

If a DLT is observed in one of the first 3 patients in a dose level, then accrual for that level will be expanded to 6 patients. Two or more instances of DLT in a cohort of 6 patients will result in the preceding dose level being defined as the maximum tolerated dose (MTD). If 2 or more DLTs are observed in dose level 1, the study will be closed and terminated early.

Depending on DLTs observed, 6-12 patients may be included in the Phase 1 portion of this study.

All evaluable patients included in the Phase 1 portion will be followed for 30 days post the patient's final DLI to ensure all safety information and treatment is captured.

Patients who do not receive the first nonengraftment DLI will be considered unevaluable and will be replaced for statistical assessment. If a donor is found to be ineligible post registration and once the patient has begun GO, the patient will complete GO and then be taken off study and considered not evaluable. If the donor is found to be ineligible post registration and before the patient has begun GO, the patient is to be screen failed unless another donor can be found and assessed for inclusion.

A total of 18-21 patients in the Phase 1 and 2 parts of this study with relapsed/refractory AML may be accrued to this study.

The Phase 2 part of the study will apply a Simon Two-Stage Design and enroll a total of 15 patients. At least six patients will be treated as part of the phase 1. If there are no DLTs observed, twelve additional patients for up to a total of 15 will be enrolled and treated at the recommended phase 2 dose (MTD). Patients enrolled and treated in the phase 1 MTD portion will be included in the Simon Two-Stage design assessment, which could include up to 6 patients. Patients in the phase 2 study, who experience an event defined as a DLT will be taken off of study. Total enrollment for the study will be 18-21 patients depending on DLT experienced in the dose escalation phase.

A Simon two-stage design will be used for the Phase 2 portion. The primary objective of the phase 1 portion is to determine the MTD of DLI in combination with GO while the primary objective of Phase 2 portion is to assess the response rate after one cycle of infusional GO followed by nonengraftment DLI in patients with relapsed/refractory acute myeloid leukemia. Prior studies have shown that a response rate with GO alone in relapsed/refractory AML is 26%. The hypothesis in the current study is that the combination of GO with DLI will provide a response rate higher than that baseline, and the study will target a response rate of 57% considered to be interesting enough to warrant further study in a randomized setting.

With this hypothesis in mind, the phase 2 portion of the study will use Simon's two-stage design. The null hypothesis that the true response rate (complete remission and complete remission with incomplete count recovery) is only 29% will be tested against a one-sided alternative. In the first stage, 9 subjects will be accrued. Patients treated at MTD in the Phase 1 portion of the study will be included in this cohort. If there are 3 or fewer responses in these 9 patients, the study will be stopped for futility. Otherwise, 6 additional subjects will be accrued for a total of 15. The null hypothesis will be rejected if 7 or more responses are observed in 15 patients. This design yields a type I error rate of 0.1 and power of 80% if the true response rate is 57%.

Overall and event free survival will be determined by the Kaplan Meier method (from the time of study enrollment).

Patients who do not receive the first nonengraftment DLI will be considered unevaluable and will be replaced for statistical assessment.

A continuous assessment of toxicity will be utilized for the Phase 2 portion of this study for either 9 or 12 patients since either the initial 3 or 6 patients included in the Phase 2 portion will be assessed for DLT based on the 3+3 design. Sequential boundaries will be used to monitor dose-limiting toxicity rate for these remaining 9 or 12 patients. The accrual will be halted if excessive numbers of dose-limiting toxicities are seen, that is, if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients with full follow-up (see table).

Number of Patients, n	1	2	3	4	5	6	7	8	9
Boundary, b_n	-	-	3	3	4	4	5	5	5

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12
Boundary, b_n	-	-	3	3	4	4	5	5	5	6	6	6

This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 5% when the rate of dose-limiting toxicity is equal to the acceptable rate of 20%.

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Appendix A; Patient Consent Form

Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information

Committee #

Name of Study Volunteer

Fractionated Gemtuzumab Ozogamicin Followed by Non-engraftment Donor Leukoocyte Infusions for Relapsed/Refractory Acute Myeloid Leukemia : BrUOG 345

You are being asked to take part in a research study. All research studies carried out at <INSERT HOSPITAL> institutions are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPITAL>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement, which states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these

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BrUOG 345: 6/19/17, 6/20/17, 6/21/17, 6/23/17, 7/5/17, 9/21/17, 10/20/17, 10/31/17, 11/3/17, 11/6/17, 11/7/17, 11/8/17, 11/9/17, 1/17/18, 1/26/18, 1/29/18, 2/4/18, 2/6/18, 2/9/18, 2/12/18, 2/13/18, 2/14/18, 2/15/18, 2/20/18, 2/26/18, 2/27/18, 3/9/18, 3/18/18, 3/19/18, 4/12/18 approved Pfizer 4/13/18 for FDA, 4/17/18, Edits per FDA 5/8/18, 5/14/18, Withdrawal 5/21/18, 6/11/18, 6/15/18, 6/18/18, 6/20/18, 6/25/18, 6/29/18, 7/3/18, 7/4/18, 7/5/18, 7/6/18, 8/10/18, 8/14/18, 8/17/18, 9/5/18, 9/6/18, 12/13/18, 1/3/19, 1/22/19, 2/22/19 to align with FDA comments, 2/25/19, 2/26/19. 3/5/19, 3/6/19, 3-7-19, AM #1 6/4/2020, AM #2 9/1/2021, Edits per FDA 1/10/2022

things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

1. Nature and Purpose of the Study

Your doctors are conducting a research study sponsored by the Principal Investigator, Dr. John Reagan, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

You are being asked to participate in this study because you have relapsed (cancer that has come back) or refractory (cancer that has not responded to prior treatment) acute leukemia. You have previously been treated with standard treatment but your leukemia is still present and there is no curative treatment option available. Your doctors are studying whether the drug Gemtuzumab Ozogamicin, followed by an infusion of blood cells called leukocytes from a donor, can stimulate the immune system to potentially fight your leukemia. Gemtuzumab ozogamicin is a class of drugs known as an antibody drug conjugate. The drug is given intravenously approximately on days 1, 4, and 7 of a treatment cycle. It is infused, attaches to cells with a certain marker on the surface (the majority of which would be leukemia cells). The drug is then internalized and the chemotherapy drug becomes activated. Gemtuzumab is currently FDA approved for the treatment of acute myeloid leukemia. This is the FDA approved infusion time. You may be forgoing (giving up or delaying) potentially curative therapy and therefore may be choosing not to receive targeted therapies that are approved for the treatment of relapsed/refractory AML, such as gemtuzumab ozogamicin, enasidenib, ivosidenib, and gilteritinib, in order to participate in this trial.

The infusion of leukocytes to stimulate the immune system to fight your leukemia is investigational and has not been proven to cure your cancer. This combination of Gemtuzumab Ozogamicin and donor leukocytes is not an FDA approved treatment and is investigational.

Initially a total of 6 patients with a condition similar to your own will be included in the study to study the safety of the treatment. Once 6 patients have been treated and no unacceptable toxicities are seen, more patients will be enrolled. The study will treat up to 18 patients on the study.

2. Explanation of Procedures

A potential donor of leukocytes will be selected for you. Your donor must be a first or second degree relative. The leukocytes from your donor have been chosen since they share no more than half of the common features (HLA antigens) with your leukocytes. That donor will have had blood tests to make sure that he or she doesn't have certain infections including hepatitis and AIDS that could be transmitted to you by the leukocytes.

You will receive an IV (by vein) infusion of Gemtuzumab Ozogamicin on approximately days 1, 4, and 7. You may receive this infusion as an inpatient in the hospital as this can be considered standard of care.

Twenty-Four hours after the completion of the Gemtuzumab Ozogamicin, the donor will undergo a procedure called leukapheresis which uses a machine to separate and collect some of the leukocytes. The

leukapheresis will be performed by the Rhode Island Blood Center at Rhode Island Hospital or The Miriam Hospital. Your donor will be connected to the machine to collect their leukocytes for approximately 5 hours.

The same day the cells are collected from the donor, the leukocytes from the donor will be infused by vein into your blood stream over about 4 hours. You may receive this infusion while you remain in the hospital if you have not yet been discharged or if you are being observed after the Gemtuzumab Ozogamicin infusion. However, if you are not still in the hospital, you will receive the leukocyte infusion at the outpatient clinic at the Rhode Island Hospital or The Miriam Hospital Comprehensive Cancer Center. You will be given acetaminophen (Tylenol) and diphenhydramine (Benadryl) prior to the leukocyte infusion to try to prevent a fever or allergic symptoms. The treatment component of this study, when you receive the cellular therapy, will last only 4 hours.

If you show a response to the treatment, you may receive up to 2 additional treatments with Gemtuzumab Ozogamicin and donor leukocyte infusions. Your doctor will assess how well you did with the first treatment to make this decision. If you do receive additional treatments, the second treatment will be given at least 35 days after the first leukocyte infusion and all treatment must be completed in a 6-month period.

If you do receive more than one leukocyte infusion it is not required that the same donor be used. The donor, whether or not it is the same person, will be screened prior to each leukocyte collection.

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical Examination (including your performance status)
- Chest x-ray
- Blood tests (about 7 tablespoons, to evaluate your blood counts, electrolytes, liver and kidney tests, measure your immune system, your blood type and the HLA blood type of your leukocytes, and evaluation for certain viruses including HIV, hepatitis B, CMV and hepatitis C. Blood will also be taken for baseline testing for chimerism, which means your DNA will be examined prior to the infusion as a way for your doctors to see if the infusion works.)
- Electrocardiogram (EKG)
- Evaluation of your heart function by a MUGA test or echocardiogram
- Evaluation of your lungs by pulmonary function (breathing) tests
- Bone marrow biopsy (within 28 days of entry into study)

During the study treatment month 1 (twice a week during weeks 1, 2, 3, 4): These assessments will be repeated again for 1 month after each full treatment (days 1,4,7) of Gemtuzumab Ozogamicin and donor leukocyte infusion.

- Physical examination (including your performance status), with vital signs, and an assessment of any side effects you may be experiencing Temperature: your temperature will be recorded at the following time points after each leukocyte infusion to look for a Cytokine release syndrome (a syndrome which is described below in the risk section): 0-4 hours, 8-24 hours, 34-48 hours, 72-96 hours, approximately day 7. If you are not still admitted in the hospital during these times the temperatures will be collected in the outpatient clinic at the Rhode Island Hospital or The Miriam

Hospital Comprehensive Cancer Center

- Blood tests (about 3 tablespoons) to evaluate your blood counts, electrolytes, liver and kidney tests, measure your immune system
- Blood tests (about 3 tablespoons), which will look at antibodies in your blood after the infusion, 0-4 hours post infusion. If you experience what is called Cytokine release syndrome (a syndrome which is described below in the risk section), you will also have blood drawn at 8-24 hours post infusion, 34-48 hours, 72-96 hours, and approximately 168 hours (day 7).
- Blood (one tube of blood approximately 2 teaspoons) for DNA testing will be taken approximately 2 days and approximately 14 days after the leukocyte infusion.
- Bone marrow biopsy: for patients who are thought to have responded to treatment, this will be done at 2 and approximately 4 weeks after you receive the donor leukocytes then at 3, 6 and 12 and 24 months post infusion.

Month 2 (once a weeks, weeks 5,6,7,8): These assessments will be repeated again for month 2 after each full treatment (days 1,4,7) of Gemtuzumab Ozogamicin and donor leukocyte infusion, Months 3-24 (once a month)

- Physical examination (including your performance status), with vital signs, and an assessment of any side effects you may be experiencing.
- Blood tests (about 3 tablespoons) to evaluate your blood counts, electrolytes, liver and kidney tests, measure your immune system.
- Bone marrow biopsy: for patients who are thought to have responded to treatment, this will be done at 3, 6 and 12 and 24 months post infusion.
- Survival and disease status (if your cancer has progressed or if it has improved)

The day you begin Gemtuzumab Ozogamicin, you will be started on a drug called ursodiol. Ursodiol is a naturally occurring bile acid made by the liver, that helps to break down gallstones. You will receive this because there is a rare risk of the drug, described later on, called sinusoidal obstruction syndrome (veno-occlusive disease), which is when the veins of the liver are blocked, leading to liver damage. This drug will be given in hopes of preventing this from happening.

- You will begin taking the drug ursodiol, day 1 of Gemtuzumab Ozogamicin and you will stay on the drug ursodiol, until approximately 4 weeks after your last dose of Gemtuzumab Ozogamicin.
- You will take ursodiol 300mg twice a day, preferably in the morning and night. 300mg in the morning and 300mg at night. This is 600mg total each day.
- If you miss a dose you should not make it up.
- Never take a double dose at one time (do not take 600mg at one time)

How long will I be in the study?

All treatment will be completed in 6 months. If you only have one infusion of Gemtuzumab Ozogamicin and one leukocyte infusion treatment will be completed approximately 24 hours later (the day after Gemtuzumab Ozogamicin is completed). The active period of the trial is potential 2.5 years, during which time you will be required to have physical examination, blood work and bone marrow biopsies. You will then be followed for survival.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping study related follow-up including blood tests, bone marrow evaluation and physical examination. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these ‘research only’ services include the following which will be paid for by the study and will not be billed to you or your health insurance company.

- The testing of your leukocytes and donor leukocytes
- The evaluation of your genetic profile in your blood for “chimerism” to determine if any of the blood cells of the donor are still in your blood stream or bone marrow. This will occur on days 2 and 14. If chimerism is still present at day 14, the test will be repeated every 14 days until chimerism is lost. The evaluation for “chimerism” will also be performed on cells removed at the bone marrow done 2 months after you receive the donor leukocytes.
- Monitoring blood samples pre and post fever development to determine cytokine release syndrome (CRS) profiles.
- The costs and charges associated with handling and infusing the donor leukocytes.
- Gemtuzumab ozogamicin will be provided at no cost to you by Pfizer, the maker of the drug

In addition, there are other services you will receive during this research study which are considered to be “routine clinical” services, meaning that you might have received even if you were not participating and/or being screened for participation in the research study, but were going to receive treatment for your disease. These “routine clinical” services include inpatient hospitalization, x-ray studies, physical examinations, EKG, evaluation of your heart and lungs, blood tests and bone marrow tests performed for leukemia assessments at baseline and during active follow-up until your disease progresses, as well as any other tests, procedures, assessments, or interventions that your doctor feels are medically necessary, including routine medications, such as those given to you to help alleviate or prevent undesired side effects (including ursodiol), required hospitalizations, and any additional doctor’s visits that your study doctor feels are necessary, like additional visits performed as part of follow-up or sick visits that you may need. The routine services listed in this paragraph will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

You will not be paid any money for participating in this study.

Contact Information:

If you have any questions regarding the study or your participation in this study, concerns about side effects, problems, or if you feel you have experienced a research-related injury or a reaction to the study product, you may contact your study doctor at the number provided to you or the Principal Investigator, Dr. John L. Reagan at (401) 444-6217. You may also reach your research nurse through the <INSERT HOSPITAL> Oncology Clinical Research Office at RI Hospital, at <INSERT >, at <INSERT >, at <INSERT >,, or you may call the direct number provided to you by the nurse on their business card. If you require immediate medical attention after business hours, please call <INSERT >, at (<INSERT >, or

<INSERT >, at <INSERT >, and ask for the hematologist/oncologist on-call. Of course, you may always seek medical attention at an emergency room or urgent care clinic at anytime, if necessary. If you seek emergency care, and/or if hospitalization is required, please inform the treating doctor that you are participating in this clinical research study.

3. Discomforts and Risks

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or can cause death. In some cases, side effects can be serious, long-lasting, or may never go away.

Taking part in this study may lead to time away from work.

Infusion of Donor Leukocytes (Common > 20%):

After infusion of donor leukocytes the following side effects are expected to occur immediately or develop within 24-48 hours. These side effects could be severe and may require hospitalization. There is a chance the side effects could be fatal. Side effects may include:

- Fever
- Rash
- Diarrhea
- Liver dysfunction
- Fluid around the lungs and heart
- Shortness of breath or other breathing abnormalities such as cough
- Swelling of the extremities
- Low blood pressure (hypotension) or changes in heart rate
- Lightheadedness/dizziness
- Hives
- Itching
- Abdominal pain
- Infusion related reactions including flushing or local or diffuse erythema (redness of skin)
- Rigors (shaking, chills, and shivering)
- Feeling unwell with muscle or joint aches and pains
- Headache and dizziness
- Nausea and vomiting
- There may be other potential unknown side effects

The following is a list of the most medically significant or most common side effects reported in studies using Gemtuzumab Ozogamicin. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/therapy and some may never go away. The study doctor may give you medicines to help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

There is a small risk of death

Infusion of Gemtuzumab Ozogamicin

Common > 20%

- Shortness of breath
- Fatigue
- Constipation
- Nausea and vomiting
- Hemorrhage (bleeding)
- Liver inflammation and toxicity
- Increased liver enzymes
- Fever
- Cardiotoxicity: this includes damage to the heart muscle which makes it more difficult for your heart to pump blood and abnormal EKGs
- Hypertension (High blood pressure)
- Hyperglycemia
- Hyperbilirubinemia (higher levels of bilirubin in the blood, this can cause yellowing of the skin, fatigue, weight loss, abdominal pain)
- Blood Lactate Dehydrogenase increased
- Headache
- Mucositis (inflammation and ulceration of the mucous membranes in the lining of the digestive tract and mouth)
- Infection
- Lack of enough red blood cells (anemia which may make you short of breath, weak, fatigued, or tired)
- Reduced white blood cells which can cause infection
- Reduced platelets which can cause bleeding. Hemorrhage may be life threatening and due to prolonged low platelet count.
- Infusion reaction: This includes symptoms of fever and chills, and less commonly hypotension and dyspnea (difficulty breathing). This usually occurs in the first 24 hours after infusion.
- Decreased appetite
- Diarrhea
- Abdominal pain
- Edema (swelling)

Less common (<20%-10%)

- Skin rash
- Febrile neutropenia: a fever with other signs of infections with abnormally low neutrophils (a type of white blood cell)

Rare (<10%)

- Nephrotoxicity: Toxicity of the kidneys, including acute kidney injury

- Dyspepsia (indigestion)
- Ascites (fluid buildup)
- Erythema (reddening of the skin)
- Pruritus (itchy skin)
- Hepatomegaly
- Multi-Organ Failure

Rare and serious: (<1%)

- Veno-occlusive disease: liver toxicity when small veins in the liver are obstructed. This is a complication of chemotherapy and may include weight gain, ascites, yellowing of the skin. It is often associated with kidney failure and can be severe and fatal. This risk has been associated with single use Gemtuzumab Ozogamicin and in combination with other drugs. Your doctor will frequently monitor you for any signs or symptoms of this toxicity. You will be given a drug called ursodiol, described earlier in the consent, to try to prevent this from happening.
- Bacterial infection
- Urinary tract symptoms that include bleeding and irritation. This can result in damage to the bladder.
- Interstitial pneumonitis (scarring of the of the lung tissue). This can cause dry non-productive cough and weight loss.
- Neutropenic enterocolitis, which is a life threatening condition which often includes inflammation of the cecum (a part of the colon) in patients who are myelosuppressed (have decreased red and white cells and platelets)
- Lung infection, Pneumonia
- Tumor lysis: Rapid death of cancer cells that may let large amounts of the cells into the blood that injures organs, such as kidneys is referred to as tumor lysis syndrome.
- Aesthenia (weakness or lack of energy)
- Sepsis
- Melena (dark stool)

If you develop these side affects you will be treated with a steroid such as solumedrol that should help these side effects to get better in a few hours or days.

Graft Versus Host Disease (Less Common 1-10%)

The donor leukocytes could recognize your normal body tissues as foreign and attack them, which is called graft versus host disease. Graft versus host disease can occur in patients who receive bone marrow transplants, even if that person is a full HLA match for the patient. This can develop days, weeks, months, or even years after donor leukocytes are infused. We believe that the chance that you will develop graft versus host disease is very low in your treatment. Your treatment differs from a bone marrow transplant in that you will not be given high-risk chemotherapy or radiation immediately just before to the donor leukocyte infusion. Therefore, your body's immune system will not be weakened and should reject the infused cells and not allow them to take over blood cell production in your body. However, the following graft versus host disease side effects could still occur:

- Skin rash
- Very low blood counts
- Diarrhea (which could be chronic)
- Liver dysfunction

- Fluid around the lungs and heart
- Shortness of breath
- Increased risk of infections
- Death

Chest X-Ray

If you take part in this research, you will have a chest x-ray that involves a small amount of radiation. To give you an idea about how much radiation you will get, we will compare it to the amounts that people encounter in daily life. There is radiation that naturally occurs from space and from rocks in the soil. This natural radiation is greater at higher altitudes. This research gives you about the same amount of radiation as you would get from living in a high altitude city such as Denver for 12 days, or taking 4 airplane flights from New York to Los Angeles. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests.

Reproductive Risks

Chemotherapy may decrease the sperm count. This is usually temporary but is infrequently permanent, which would result in sterility. Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study. Ask your study doctor for more information regarding preventing pregnancy during the study treatments. You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

Females: You cannot take part in this study if you are pregnant or breast-feeding. Because of the possible risks to an unborn child, if you are a female who can become pregnant, you will be asked to take a pregnancy test within 7 days prior to starting study drug treatment.

If you decide to take part in this study, you should avoid becoming pregnant while receiving study medication. You must commit to using 2 effective methods of contraception throughout the study without interruption; while receiving study medication or for a longer period if required by local regulations. If you become pregnant while receiving study medication or within 6 months after your last treatment, you must tell the study doctor right away. If this happens, study treatment will be discontinued. The study doctor will follow you and your pregnancy to completion.

Males:

If you have a partner of childbearing potential, you should avoid fathering a child and agree to using 2 effective methods contraception while receiving treatment on the study and for 6 months after the last treatment. If your partner becomes pregnant while you are receiving study medication, you must tell the study doctor right away.

By signing this document you are acknowledging that you understand and agree to the information presented in the Reproductive Risk section above.

4. Benefits

It is hoped that the infusion of donor leukocytes may help treat your leukemia but it is not known if this will be helpful. You may not have any benefit from this treatment.

5. Alternative Therapies

You could choose not to participate in this study. You should speak with your doctor about other alternative therapies. You may be able to receive other chemotherapy or other types of therapy. You may choose to only receive supportive care including blood transfusions as needed for low blood counts and antibiotics if you get an infection. You may also choose to have no further therapy at all and just receive comfort measures.

6. Refusal/Withdrawal

You decide whether or not you want to be in the study. Participation is voluntary. If you decide now to participate, you can change your mind later and quit the study. If you decide not to participate, or if you quit the study, it will not affect the health care services that you normally receive. If the researcher or your doctor feels it is in your best interest, they may choose to take you out of the study at any time before you complete the study.

As soon as it becomes available, the researcher will give you new information about the study that may or may not affect your decision to stay in the research study.

If you decide to withdraw from this study you will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

7. Medical Treatment/Payment in Case of Injury

If you experience a research injury <INSERT HOSPITAL>, or the study doctor, will arrange for medical treatment at no cost to you. The cost of your treatment will be paid for as described below. A research injury is any physical injury or illness caused by your participation in the study. If you are injured by a medical treatment or procedure that you would have received even if you were not in the study, that is not a research injury. To help avoid injury, it is very important to follow all study directions.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. John Reagan, the sponsor of the study, nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you suffer a research injury and you are covered by insurance, it is possible that some or all of the costs of treating your condition could appropriately be billed to your insurance company. If such costs are not covered either by health insurance or the study sponsor, <INSERT HOSPITAL> will pay for what it considers fair and proper treatment. <INSERT HOSPITAL> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Signing this form does not lessen or take away any of your lawful rights. For more facts, please contact <INSERT>, in the <INSERT HOSPITAL> Office of Research Administration, at <INSERT>

8. Rights and Complaints

If you have any complaints about your taking part in this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies, you may contact <INSERT>, in the <INSERT HOSPITAL> Office of Research Administration, at <INSERT>

9. Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies/ might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor John Reagan, MD, the Brown University Oncology Research Group (BrUOG) and their affiliates, Pfizer, the maker of the drug Gemtuzumab Ozogamicin
- Doctors, nurses, laboratories and others who provide services to you in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL >, to release your health information without your permission. For example, Rhode Island law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

This study involves ‘genetic testing’ as defined by the Genetic Information Nondiscrimination Act of 2008 (GINA). GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. There are some limitations to GINA’s protections (it does not apply to all insurers or employers, nor does it apply to all genetic information, such as information related to a genetic disease that you already have). In addition to GINA’s protections regarding the ultimate use to which your genetic information is put, <INSERT HOSPITAL>’s privacy policies generally protect the privacy of such information and restrict its release outside of <INSET HOSPITAL>, unless you specifically authorize its disclosure or unless disclosure without your authorization is permitted under applicable privacy laws.

Additionally, a description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT>, in the Office of Research Administration, <INSERT>.

For more detail about your privacy rights see the <INSERT HOSPITAL> Joint Privacy Notice which has or will be given to you.

10. **Research authorization for use and disclosure of information**

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. **If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.**

Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write Dr. John Reagan, MD c/o the Lifespan Oncology Clinical Research Office at Rhode Island Hospital, 593 Eddy Street, APC Building Rm. 131, Providence, RI 02903.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT>, in the Office of Research Administration, <INSERT>

Uses and releases covered by this authorization (permission)

Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

- ☒ Every research site for this study, including this hospital, and including each site's research staff and medical staff
- ☒ Health care providers who provide services to you in connection with this study
- ☒ Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol
- ☒ The following research sponsors and the people and companies that they use to oversee, administer, or conduct the research: The PI and sponsor John Reagan, MD, The Brown University Oncology Research Group (BrUOG), Rhode Island Blood Center, Pfizer, the maker of the drug Gemtuzumab Ozogamicin
- ☒ The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights.
- ☒ The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study
- ☒ Principal Investigator and other Investigators
- ☒ Study Coordinator
- ☒ Additional members of the Research Team
- ☐ The Patient Advocate or Research Volunteer Protector: _____
- ☒ Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
- ☐ Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)
- ☒ Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee
- ☒ The members and staff of the hospitals affiliated Privacy Board (if such a board is used)
- ☐ Others (as described below)_____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

☒ The entire research record and any medical records held by the hospital may be used and released.

☐ The following information:

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL >, Privacy notice*

This informed consent document expires on _____.
DO NOT sign this document after this expiration date

Signature of study volunteer/authorized representative* _____ Date and _____ Time when signed

I was present during the consent PROCESS AND signing of this agreement above by the study volunteer or authorized representative

Signature of witness (required if consent is presented orally or at the request of the IRB) _____ Date

I ASSURE THAT I HAVE FULLY EXPLAINED TO THE ABOVE STUDY VOLUNTEER/AUTHORIZED REPRESENTATIVE, THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH STUDY.

Signature of researcher or designate _____ Date and _____ Time when signed

* If signed by agent other than study volunteer, please explain below.

Documentation that a copy of this Informed Consent was given to the research participant is a Federal requirement. Prior to making a copy of the signed and dated Informed Consent please check appropriate box(es) as applicable to indicate copy provided to:

☐ Study Volunteer ☐ Medical Record ☐ Researcher ☐ Other (Specify)

Patient Consent Form For Donor:

Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information

Committee #

Name of Study Volunteer

Fractionated Gemtuzumab Ozogamicin Followed by Non-engraftment Donor Leukocyte Infusions for Relapsed/Refractory Acute Myeloid Leukemia: BrUOG 345

DONOR CONSENT

You are being asked to take part in a research study. All research studies carried out at <INSERT HOSPITAL> are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPITAL>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement, which states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

Nature and Purpose of the Study

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. John Reagan in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

You are being asked to donate some of your white blood cells (leukocytes) so they can be collected and infused into the bloodstream of your first or second degree family member with leukemia. Leukocytes are a type of immune blood cells. The infusion of your leukocytes may stimulate the your family member's immune system to fight their leukemia. Your leukocytes also may help to directly fight your family member's leukemia.

In this study we are studying whether the drug Gemtuzumab Ozogamicin, followed by an infusion of donor mismatched blood cells called leukocytes can stimulate your family member's immune system to potentially fight your family member's leukemia.

We expect to enroll 36 subjects into this study at Lifespan, 18 patients and 18 donors. This study is only

taking place at Lifespan. In Phase I of the study, a total of 6 patients with leukemia and 6 donors will be included in the study to study the safety of the treatment. Phase 1 will look for unacceptable toxicities. If no unacceptable toxicities are seen in Phase 1, we will start Phase 2, which will enroll 12 more patients and 12 more donors.

Explanation of Procedures

To donate your leukocytes you will need to undergo a procedure at Rhode Island Hospital or The Miriam Hospital called leukapheresis which collects some of your leukocytes. After donation, your body will replace most of the white blood cells collected by 4 weeks post collection. The decrease in your white blood cells over this time period should have no effect on your health.

Before you begin the study...

You will have testing to determine that you are a healthy donor, including blood tests, urinalysis, chest x-ray, electrocardiogram, and physical examination (including your performance status). You will be asked to fill out a questionnaire that asks about your exposure to various infections, including HIV, the virus that causes AIDS. If you are pregnant you can not donate leukocytes. **A pregnancy test will be run if you are a woman of childbearing potential.** Your blood type will be tested to see if it is matched or mismatched with your family member's blood. Your blood also will be tested for various infections including hepatitis and HIV. If the hepatitis and/or HIV blood tests are positive, they will be reported to the Rhode Island Department of Health as required by State law. The research investigator will notify you or your physician of the positive hepatitis and/or HIV test results and recommend next steps for you and your healthcare providers to take. All test results will remain confidential, except for the required reporting of positive hepatitis and/or HIV test results. You have the right to review the results of all your tests. These tests are performed to see if you are a healthy donor, if your blood type is mismatched with your family member's and to protect the health of your family member (the patient with AML). All of the tests will be done at Rhode Island Hospital or The Miriam Hospital and are not part of your standard care. If the test results are satisfactory, you will be eligible to undergo the leukapheresis procedure. Your blood will be drawn for testing a second time 7 days before your leukapheresis procedure to re-confirm your results and see if you remain eligible. The total amount of blood drawn over those two times will be about 7 tablespoons.

Five days prior to your leukapheresis, you will also receive granulocyte-colony stimulating factor (GCSF), a drug that stimulates your bone marrow to produce more white blood cells so there will be more to collect. You will be asked to give this drug to yourself at home via self-injection (give yourself a shot). You will be trained how to do this and be given all the necessary supplies. You will be asked to give this drug to yourself two times a day (approximately 12 hours apart) for 5 days, for a total of 10 doses.

Day of Leukapheresis

Leukapheresis consists of drawing blood from you into a machine, which will separate and collect some of your leukocytes and return your other blood cells to you. The Rhode Island Blood Center personnel will perform the procedure in the outpatient setting at Rhode Island Hospital over about 5 hours, using temporary needles in your veins that will be removed after the procedure. After collection of the leukocytes, the leukocytes will be sampled in the laboratory, and then given intravenously to your family member on the same day. Not all of the leukocytes collected will be used for your family member. The ones that are left over ("biospecimens") may be used for research procedures. You will be asked below to allow the use of these biospecimens for research purposes. If you do not consent to the future use of these

leftover biospecimens, they will be discarded.

There is a potential for you to have leukapheresis two more times on different days (for a total of 3 times on 3 different days) if your family member's leukemia goes into remission. There would be a minimum of 35 days between the days of leukapheresis in order for your body to make more white blood cells. It is not required that you donate your white blood cells a second or third time since you can decline donation at any time. modified screening to see if the results are still satisfactory. If they are satisfactory, then you will have the leukapheresis procedure.

You will have an opportunity to ask questions. You have the choice to refuse to donate your leukocytes.

Your identifiable private health information may be used for future research studies or distributed to another researcher for future research studies without additional informed consent. If your private health information is used in the future, all identifiers will be removed (“de-identified”) before using or distributing them.

Costs for participating in this study

All of the services you will receive are being performed only because you are participating in this research study. These “research only” services include bloodwork, chest x-ray, urinalysis, electrocardiogram, physical exam, G-CSF and G-CSF administration, and the leukapheresis procedure. There will be no costs to you for participating in this study. All costs will be paid by the research study.

You will not be paid for your participation in this study.

Contact Information: If you have any questions regarding this study, you may contact the Principal Investigator, John Reagan, MD at (401) 444-6217.

Discomforts and Risks

Prior to the leukapheresis procedure you will have an injection of G-CSF twice daily for 5 days.

Risks associated with Granulocyte-colony stimulating factor (G-CSF)

Common >10%

- Changes in your liver. These changes are usually mild and monitored with laboratory tests. Once treatment is complete, these changes usually go back to normal.
- Bone pain
- Headaches
- Fatigue
- Back pain
- Bruising
- Nosebleeds or bleeding from your gums
- Diarrhea
- Fever

Occasional <10%

- Enlarged spleen
- Inflammation around the injection site
- Tummy (abdominal) pain
- Swollen hands and feet (oedema)
- Skin rash
- Constipation
- Difficulty sleeping (insomnia)
- Breathlessness and cough
- Pain passing urine

Rare Approximately 1%

- Allergic reaction
- Capillary leak syndrome

A temporary needle will be placed in your vein to draw the blood sample. The leukapheresis procedure can be associated with numbness, tingling, or lightheadedness. Rarely, low blood pressure or an abnormal heart rhythm can occur. It is also possible that the procedure may lower the potassium and calcium levels in your body. If the levels drop too low it may be necessary for you to receive a supplement after the procedure to regulate these levels. Also rare is the occurrence of loss of blood or destruction of red cells. There may be movement of large volumes of fluid during the procedure. A similar procedure is used on a daily basis on platelet donors. Serious side effects have been extremely rare.

Other unanticipated side effects may occur rarely and will be treated as medically indicated.

You may have psychological distress from answering questions on the donor-screening questionnaire.

LEUKOCYTE STORAGE

Federal regulatory agencies require that the terms of leukocyte cell storage be discussed in this consent form. It is intended that the leukocytes collected (except for 2-3 teaspoons collected for quality control tests) be given to the patient with leukemia/lymphoma. If extra cells are collected, they will be provided to the research laboratory of Dr. Peter Quesenberry, a co-principal investigator of this study. Extra cells will not be stored for the purpose of infusing them at a later time into your family member.

As part of this study, the study doctors would like to keep any extra leukocytes to better understand how cellular therapy works and to learn more about leukemia within the laboratory, so that future treatments might be improved.

I agree that my extra leukocytes may be used for the purposes described above.

_____ Yes _____ No _____ Initials

Benefits

There are no health benefits to you for participating in this study. Your body's leukocytes may be helpful treating your family member's leukemia although this is not known.

Alternative Therapies

You could also choose not to donate leukocytes.

Refusal/Withdrawal

You decide whether or not you want to be in the study. Participation is voluntary. If you decide now to participate, you can change your mind later and quit the study. If you decide not to participate, or if you quit the study, it will not affect the health care services that you normally receive. If the researcher or your doctor feels it is in your best interest, they may choose to take you out of the study at any time before you complete the study.

As soon as it becomes available, the researcher will give you new information about the study that may or may not affect your decision to stay in the research study.

Reasons the researchers would take you out of the study even if you wanted to stay in:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers
- The study is suspended or canceled.

Medical Treatment/Payment in Case of Injury

If you experience a research injury <INSERT HOSPITAL>, or the study doctor, will arrange for medical treatment at no cost to you. The cost of your treatment will be paid for as described below. A research injury is any physical injury or illness caused by your participation in the study. If you are injured by a medical treatment or procedure that you would have received even if you were not in the study, that is not a research injury. To help avoid injury, it is very important to follow all study directions.

If you suffer a research injury and you are covered by insurance, it is possible that some or all of the costs of treating your condition could appropriately be billed to your insurance company. If such costs are not covered either by health insurance or the study sponsor, <INSERT HOSPITAL> will pay for what it considers fair and proper treatment. <INSERT HOSPITAL> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

The study will not pay for this medical treatment. Neither Dr. John Reagan, the sponsor of the study, nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

Signing this form does not lessen or take away any of your lawful rights. For more facts, please contact <INSERT> in the Office of Research Administration at <INSERT>

Rights and Complaints

If you have any complaints about your taking part in this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies, you may contact <INSERT>, in the <INSERT HOSPITAL> Office of Research Administration, <INSERT>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies/ might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor and PI John Reagan, MD, the central coordinating office and sponsor representative Brown University Oncology Research Group (BrUOG) and their affiliates, Rhode Island Blood Center, Pfizer, the maker of the drug
- Doctors, nurses, laboratories and others who provide services to you in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL >, to release your health information without your permission. For example, Rhode Island law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL>. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

This study involves 'genetic testing' as defined by the Genetic Information Nondiscrimination Act of 2008 (GINA). GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. There are some

limitations to GINA's protections (it does not apply to all insurers or employers, nor does it apply to all genetic information, such as information related to a genetic disease that you already have). In addition to GINA's protections regarding the ultimate use to which your genetic information is put, <INSERT HOSPITAL> privacy policies generally protect the privacy of such information and restrict its release outside of <INSERT HOSPITAL>, unless you specifically authorize its disclosure or unless disclosure without your authorization is permitted under applicable privacy laws.

Additionally, a description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT> in the Office of Research Administration, <INSERT>

For more detail about your privacy rights see the <INSERT HOSPITAL >, Joint Privacy Notice which has or will be given to you.

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL >, Privacy notice*

This informed consent document expires on _____.
DO NOT sign this document after this expiration date

Signature of study volunteer/authorized representative* _____ Date and _____ Time when signed

I was present during the consent PROCESS AND signing of this agreement above by the study volunteer or authorized representative

Signature of witness (required if consent is presented orally or at the request of the IRB) _____ Date

I ASSURE THAT I HAVE FULLY EXPLAINED TO THE ABOVE STUDY VOLUNTEER/AUTHORIZED REPRESENTATIVE, THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH STUDY.

Signature of researcher or designate _____ Date and _____ Time when signed

* If signed by agent other than study volunteer, please explain below.

Documentation that a copy of this Informed Consent was given to the research participant is a Federal requirement. Prior to making a copy of the signed and dated Informed Consent please check appropriate box(es) as applicable to indicate copy provided to:

☐ Study Volunteer ☐ Medical Record ☐ Researcher ☐ Other (Specify)

Appendix B:

Non-Engraftment Donor Leukocyte Infusion Quality Assurance Checklist (To be signed by a member of the Oncology research team and/or a LOCR staff member)Pre-Infusion	
Recipient Name	
BrUOG Study #	
Recipient Date of Birth	
Recipient Height (cm)	
Recipient Weight (kg)	
Donor Name	
Donor Date of Birth	
Informed Consent Documented for Patient (yes/no) and date	
Informed Consent Documented for Donor(yes/no) and date	
HLA typing for patient and date (document match)	
HLA typing for donor and date (document match)	
Infectious disease testing of donor and recipient within 7 days of product collection (yes/no)	
Recipient Chimerism blood sample collected, yes/no and date	
Sent to RIBC yes/no, date	
Donor Chimerism blood sample collected yes/no and date	
Sent to RIBC yes/no, date	
Donor received 10 doses of GCSF prior to product collection (yes/no)	
Number of CD3+ cells collected	
Negative Gram Stain (must be Yes)	
Percent Cell Viability (must be $\geq 70\%$)	
Infectious disease testing of product sent (Yes/No, Date)	
Date of Collection	
Time start	
Time stop	
Anti-coag	
Unique ID# for Donor Product	
Product Label or Tag with "Caution: New Drug- Limited by Federal Law for Investigational Use (Yes/No) *one label on product and one with source documents*	
Number of CD3+ cells/kg recipient weight (must be $1-2 \times 10^8$ cells/kg)	
Date of infusion	
# hours post GO	
Pre-meds given (Yes/No)	
Signature Pre-Infusion Reviewer 1:	Title:
Signature Pre-Infusion Reviewer 2:	Title
Infusion	
Date and Time start	

Time from collection to initiation of infusion (must be less than 8 hours)	
Date and Time Stop	
Time from collection to completion of infusion (must be less than 24 hours)	
Immunologic sample for CRS collected on recipient 0-4 hours post infusion and send to Dr. Quesenberry yes/no	
Vital signs taken per study and recorded on CRF Yes/No	
Signature Post-Infusion Reviewer 1:	Title:
Signature Post-Infusion Reviewer 2:	Title

Appendix C: PATIENT/RECIPIENT REGISTRATION Checklist: Please note it is required that the inclusion/exclusion from the protocol be used to assess eligibility. The below document is a tool only

Inclusion Criteria Patient

- _____ (y/n) Histologic confirmation of acute myeloid leukemia (AML)
- _____ (y/n) Recurrence or progression (including refractory disease defined as disease confirmed to have not responded to prior treatment) of AML after at least 1 prior standard treatment with progression within 6 months from last treatment. Please note that patient must have received at least one cycle of a standard treatment for their disease. Patients who have relapsed or progressed > 6 months post their last treatment are not eligible. See 3.1.8, as patients must be > 6 months post autologous stem cell infusion, if applicable.
- _____ (y/n) ≥ 4 -weeks since prior chemotherapy or radiation to cellular therapy infusion. (Hydroxyurea may be utilized up to 48 hours prior to initiation of treatment on this protocol and end date must be sent to BrUOG at time of registration. Hydroxyurea can resume at the discretion of the treating physician post cellular infusion and must be documented on concomitant medication log.)
- _____ (y/n) Age equal to or greater than 18 years.
- _____ (y/n) Patients with a history of invasive second malignancy who are disease free for ≥ 2 years. Patients with a history of invasive second malignancy who are not disease free for at least 2 years are excluded. Patients with ductal carcinoma in situ of the breast and/or squamous cell/basal cell cancer of the skin will be allowed on trial.
- _____ (y/n) Patients must have an expected life expectancy of at least 2 months at the time of initiation of treatment, as documented by treating physician.
- _____ (y/n) No active systemic infections allowed. Minor infection that can be controlled with a 2 week course of antibiotics/antivirals is acceptable. Patient with such infection must have begun antibiotics at least 2 days prior to drug treatment.
- _____ (y/n) Patients who have relapsed after standard autologous stem cell infusion are eligible as long as they meet all inclusion criteria and no exclusion criteria. These patients must be out more than 6 months from cell infusion to be eligible for enrollment.
- _____ (y/n) DLCO Hb $\geq 40\%$ with no symptomatic pulmonary disease.
- _____ (y/n) LVEF $\geq 40\%$ by MUGA or echocardiogram.
- _____ (y/n) Creatinine $< 1.5 \times$ ULN or any serum creatinine level associated with a measured or calculated creatinine clearance of ≥ 40 mL/min, AST and ALT $< 2.5 \times$ ULN, Total Bilirubin $< 1.5 \times$ ULN
- _____ (y/n) Women of childbearing potential and males must use 2 highly effective methods of contraception from time of consent through 6 months after completing treatment (whether last treatment is infusion or drug). If a man has a history of vasectomy condom use will still be required. Documentation of this being discussed is required to also note types of contraception.
- _____ (y/n) Not pregnant or nursing. Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to beginning of treatment (drug). Post-menopausal women (surgical menopause or lack of menses ≥ 12 months) do not need to have a pregnancy test, please document status.
- _____ (y/n) Performance status ECOG ≤ 2 (or KPS 70)

Exclusion Criteria of Recipient (Patient)

- _____ (y/n) Evidence of HIV infection.
- _____ (y/n) Any uncontrolled severe, concurrent illness which in the opinion of the treating physician would make this protocol treatment unreasonably hazardous for the patient.
- _____ (y/n) Oxygen dependent obstructive pulmonary disease.

_____ (y/n) Previous history of Veno-occlusive disease/Sinusoidal Obstruction Syndrome
 _____ (y/n) Failure to demonstrate adequate compliance with medical therapy and follow-up as documented by treating physician.
 _____ (y/n) Significant medical or psychiatric illness that would impair the ability to participate in protocol therapy.
 _____ (y/n) Previous allogeneic stem cell transplant
 _____ (y/n) Eligibility for allogeneic stem cell transplant
 _____ (y/n) Patients who have had previous purine analog (fludarabine, pentostatin, 2-CDA) treatment or treatment with alemtuzumab within 1 year of entering the study
 _____ (y/n) Active hepatitis B or C
 _____ (y/n) Patients with known active central nervous system leukemia
 _____ (y/n) Patients with prior treatment of Gemtuzumab ozogamicin
 _____ (y/n) Patients with allergy to latex.

REQUIRED:

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form	Enclosed	Not Enclosed	Not Applicable
2) Heme/Onc initial note	Enclosed	Not Enclosed	Not Applicable
3) Pathology Report(s)	Enclosed	Not Enclosed	Not Applicable
4) Chest X-ray	Enclosed	Not Enclosed	Not Applicable
5) EKG	Enclosed	Not Enclosed	Not Applicable
6) Adverse Event Evaluation	Enclosed	Not Enclosed	Not Applicable
7) ConMed	Enclosed	Not Enclosed	Not Applicable
8) H&P PE PS Dem & Vitals	Enclosed	Not Enclosed	Not Applicable
9) Lab Source Documents	Enclosed	Not Enclosed	Not Applicable
RIBC infectious testing	Enclosed	Not Enclosed	Not Applicable
Typing	Enclosed	Not Enclosed	Not Applicable
10) PFT and MUGA or ECHO	Enclosed	Not Enclosed	Not Applicable
11) BmBx	Enclosed	Not Enclosed	Not Applicable
12) Chimerism Samples	Enclosed	Not Enclosed	Not Applicable
10) ICF signature page			
11) Other documents, please list _____			

The below portion is to be completed and submitted to BrUOG prior to initial registration

IRB approval date of protocol (most recent IRB approval of amendment or CR): _____

Hospital where patient will be treated for GO: _____

Hospital where patient will receive DLI: _____

Date patient will receive day 1 GO: _____ Date patient will receive DLI: _____

Signature of physician who determined RECIPIENT eligibility:

Name: _____ Signature: _____

Date of determination of eligibility: _____

Your signature: _____

Appendix D: DONOR REGISTRATION Checklist: Please note it is required that the inclusion/exclusion from the protocol be used to assess eligibility. The below document is a tool only

Inclusion Donor

_____ (y/n) Donors agree to up to 3 donor leukocyte collections as documented by assessing physician (although it is not required that the same donor is used for all leukocyte infusions it is preferable, therefore agreement is important at screening). This must be documented in writing by treating physician.

_____ (y/n) Typing is required at the following loci: HLA A, B, C, and DRB1.

_____ (y/n) Patients with a HLA 0/6 to 3/6 (using loci A, B, DR) donor match will be able to participate in this protocol.

_____ (y/n) Donors must be a first or second degree relative

_____ (y/n) If the patient/recipient is CMV negative, only CMV negative donors are eligible. If the patient/recipient is CMV positive, CMV titer is not required for the donor.

_____ (y/n) Although ABO blood type matching is not required given use of apheresis product preference will be made to ABO compatible donors

_____ (y/n) Donors must be ≥ 18 years of age to donate.

_____ (y/n) Donor with a history of malignancy other than non-melanoma skin cancers are eligible only if they had a history of a solid tumor malignancy more than five years prior to lymphocyte donation, and are considered to be in longstanding complete remission as documented by a physician.

_____ (y/n) The donor must be healthy and meet all criteria for stem cell donation. Testing criteria: includes normal CBC and negative testing for HIV-1, HIV-2, syphilis, hepatitis, HTLV 1 and 2, CMV (CMV negative is not a requirement), Chagas, and West Nile Virus by the Rhode Island Blood Center. The Rhode Island Blood Center will perform nucleic acid testing (NAT) for WNV, HIV-1, HCV and HBV. They will perform surface and core antigen for HBV.

_____ (y/n) The donor will also be assessed by physician who will document behavioral risk for exposure to infectious agents and diseases being tested, including: (Check box to confirm this has been assessed by MD and submit source)

- ☐ Human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease
- ☐ Communicable disease risks associated with xenotransplantation
- ☐ FDA-licensed, approved, or cleared donor screening tests for *Chlamydia trachomatis* and for *Neisseria gonorrhea* (see schedule of evaluations for required testing)
- ☐ *Treponema pallidum* (syphilis).

_____ (y/n) The donor must be in good general health and not have significant cardiopulmonary, renal, endocrine, or hepatic disease as documented in writing by physician.

_____ (y/n) β -HCG urine or serum negative if donor is of childbearing potential within 7 days of PBMC procurement. Not applicable for donors who are Post-menopausal (surgical menopause or lack of menses ≥ 12 months). Menopausal status must be documented to BrUOG

_____ (y/n) Donors must have adequate venous access so leukapheresis can be performed via standard peripheral IV without the need for placement of a central venous catheter. Required to be documented by physician post assessment by treating physician

Donor Exclusion Criteria

_____ (y/n) Evidence of infection for HIV-1, HIV-2, syphilis, hepatitis B or C, HTLV 1 or 2, WNV, Chagas.

_____ (y/n) Uncontrolled diabetes mellitus. See 3.4.3

_____ (y/n) Active or congestive heart failure syndrome from any cause per donor medical history. Approval for participation by Cardiologist required to be sent to BrUOG.

- _____ (y/n) Full cardiac workup by a Cardiologist is required for any history of congestive heart failure syndrome, conduction abnormalities or history of arrhythmia other than treated atrial fibrillation.
- _____ (y/n) Active angina pectoris.
- _____ (y/n) Oxygen dependent pulmonary disease.
- _____ (y/n) History of any lymphoid, myeloid or other non-solid malignancy. To be documented by physician
- _____ (y/n) Failure to receive full informed consent.
- _____ (y/n) Inadequate renal and/or hepatic function per medical history.
- _____ (y/n) Known history of cirrhosis or active liver disease per medical history.
- _____ (y/n) History of transplantation.
- _____ (y/n) Allergy to latex. To be documented by physician.
- _____ (y/n) A donor in whom plasma dilution sufficient to affect the results of communicable disease testing is suspected, unless: (check box to note this has been confirmed to be not applicable and submit source from MD)
- ☐ (A) You test a specimen taken from the donor before transfusion or infusion and up to 7 days before recovery of cells or tissue; or
- ☐ (B) You use an appropriate algorithm designed to evaluate volumes administered in the 48 hours before specimen collection, and the algorithm shows that plasma dilution sufficient to affect the results of communicable disease testing has not occurred.
- _____ (y/n) Clinical situations in which you must suspect plasma dilution sufficient to affect the results of communicable disease testing include, but are not limited to the following:
- ☐ (A) Blood loss is known or suspected in a donor over 12 years of age, and the donor has received a transfusion or infusion of any of the following, alone or in combination:
- ☐ (1) More than 2,000 milliliters (mL) of blood (e.g., whole blood, red blood cells) or colloids within 48 hours before death or specimen collection, whichever occurred earlier, or
- ☐ (2) More than 2,000 mL of crystalloids within 1 hour before death or specimen collection, whichever occurred earlier.

REQUIRED:

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

- | | | | | |
|---------------------------------|----------|---------------------------------------|---|--------------------------|
| 1) Eligibility Form | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 2) MD note | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 3) Cardiac Exam | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 4) Chest X-ray | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 5) EKG | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 6) Adverse Event Evaluation | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 7) ConMed | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 8) H&P PE PS Dem & Vitals | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 5) Lab Source Documents | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| RIBC infectious testing | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| Typing | Enclosed | ☐ Not Enclosed | ☐ Not Applicable | ☐ |
| 6) ICF signature page | | | | |
| 7) Other documents, please list | _____ | | | |

The below portion is to be completed and submitted to BrUOG prior to initial registration and also with each submission of registration materials for infusion 2 and infusion 3:

Document if this submission is for DLI/GO #1 or for DLI/GO #2 or #3: _____

IRB approval date of protocol (most recent IRB approval of amendment or CR): _____

Date Donor scheduled for day 3 testing and GCSF day 1: _____

Confirm Donor assessed for adequate vein access (submit to BrUOG) _____ yes or no _____

Name and address of establishment that made donor-eligibility determination:

Signature of physician who determined DONOR eligibility:

Name: _____ **Signature:** _____

Date of determination of eligibility: _____

Your signature: _____

Appendix E:

NCI CTCAE Version 5

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: Grade the event using the NCI CTCAE Version 5.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is NOT listed in table below:

Appendix F:

NCI CTCAE Version 5.0

Definition of grades for infusion related reactions, and cytokine release syndrome

Adverse Event	1	2	3	4	5
Infusion related reaction ^A	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Cytokine Release Syndrome ^B	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to $< 40\%$ O ₂	Hypotension managed with one pressor; hypoxia requiring $\geq 40\%$ O ₂	Life-threatening consequences; urgent intervention indicated	Death

A: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.

B: Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. Navigational Note: Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache

Appendix G: **FDA MedWatch Reporting Checklist for site to complete at time of report**
The below document is a tool only

Patient #: _____ **Initials:** _____

- ☐ Initial SAE Report ☐ Follow-up #1 SAE Report ☐ Follow-up #2 SAE Report
- ☐ Report must be typed
- ☐ **Mfr Report #:** enter the Pfizer reference # **WI231684**
- ☐ **Section A** Include protocol #, patient initials, and patient number (if assigned) (i.e. Br345 initials #)

Section B Description of event:

- ☐ Include description of event (e.g. this is an initial SAE report to document pt X presented to the hospital on XX-XX-XXXX for X, X, X)
- ☐ Include protocol description (i.e. pt X began treatment on BrUOG 345 on X)
- ☐ Include treatment regimen (GO, Donor Infusion) - dates, etc. (i.e. patient received last dose of X on XX-XX-XX)
- ☐ Clearly outline which events are being reported as serious and non-serious (using CTCAE terms with Grade) (e.g. serious events are grade 3 fatigue and grade 3 nausea, non-serious events at time of hospitalization include grade 1 fever and grade 1 vomiting)
- ☐ Investigator's assessment of the relationship of the serious adverse event to GO and donor leukocyte infusion. (e.g. fatigue is not related to GO and not related to DLI, and is related to disease)
- ☐ Include treatment of event (i.e. patient received IV antibiotics and fluids for treatment of serious event X)
- ☐ Outcome of event, if known (i.e. grade 3 serious fatigue resolved upon discharge or grade 3 serious fatigue downgraded to non-serious grade 2 upon discharge)
- ☐ Action taken with treatment as a result of the SAE and expectedness (based on the IB and consent) if it is unknown at the time of submission, please indicate "at this time, treating MD is uncertain when treatment with XXX will resume"
- ☐ Indicate any supportive laboratory results and diagnostics (section B6)
- ☐ Create unscheduled event in REDCap and upload all supportive documents
- ☐ A final report to document resolution of the SAE (such as discharge from hospital) is required

Section C Suspect Products(s)

- ☐ site to complete if the initial reporter suspected the drug product was associated with the SAE. If the product was **not suspected** to be associated with the SAE, only C2 conmed section should be completed (lot # and expiration date must be included if applicable).