Addition of Inotuzumab Ozogamicin Pre- and Post-Allogeneic Transplantation

Institution Study Number: **2018-0860**

Financial Support: Pfizer Pharmaceuticals

Sponsor: The University of Texas MD Anderson Cancer Center

IND Number: 142881

Principal Investigator: Issa F. Khouri, MD
The University of Texas MD Anderson Cancer Center
Stem Cell Transplantation and Cellular Therapy Department
1515 Holcombe Blvd, Unit 0423
Houston, TX 77030
Telephone: 713-745-0049
Fax: 713-794-4902
ikhouri@mdanderson.org

Co-Investigators: Richard E. Champlin, MD[1]
Alison M. Gulbis, PharmD[2]
Jin Seon Im, MD, PhD[1]
Elias J. Jabbour, MD[3]
Partow Kebriaei, MD[1]
David Marin, MD[1]
Amanda L. Olson, MD[1]
Uday R. Popat, MD[1]
Samer Srour, MD[1]
Priti Tewari, MD[4]

Statistician: Roland L. Bassett, Jr., MS[5]

[1] The University of Texas MD Anderson Cancer Center, Stem Cell Transplantation and Cellular Therapy Department
[2] The University of Texas MD Anderson Cancer Center, Pharmacy Clinical Programs
[3] The University of Texas MD Anderson Cancer Center, Leukemia Medicine Department
[4] The University of Texas MD Anderson Cancer Center, Pediatrics Department
[5] The University of Texas MD Anderson Cancer Center, Biostatistics Department

Table of Contents

1.0 OBJECTIVES 3

2.0 BACKGROUND 3

3.0 PATIENT ELIGIBILITY 5

3.1 Inclusion Criteria 5
3.2 Exclusion criteria 6

4.0 TREATMENT PLAN 6

4.1 Chemotherapy Agent Doses and Administration for Acute Lymphoblastic Leukemia, Aggressive Lymphoma Patients (based on WHO Classification), also indolent lymphoma in transformation, or those who have failed ≥ three small molecule inhibitors 6
4.2 Chemotherapy Agent Doses and Administration for patients with Indolent Lymphomas (based on WHO Classification) 8
4.3 Chemotherapy Agent Doses and Administration for Haploidentical or Mismatched Stem Cell Transplant Recipients 9
4.4 Supportive Care 11
4.5 Post-transplant 13

5.0 EVALUATION DURING STUDY 14

5.1 Pre-Treatment Evaluations 14
5.2 Evaluations During Study 15
5.3 Optional Procedure 16

6.0 STATISTICAL CONSIDERATIONS 16

6.1 Overview 16
6.2 FM Cohort Safety 17
6.3 Safety Monitoring 17
6.4 Analysis Plan 21
6.5 Safety Monitoring Plan 22

7.0 CRITERIA FOR REMOVAL FROM THE STUDY 23

8.0 ADVERSE EVENTS AND REPORTING REQUIREMENTS 23

8.1 Adverse Events and Data Collection 23
8.2 Serious Adverse Event Reporting (SAE) Reporting 25

9.0 BACKGROUND DRUG INFORMATION 27

9.1 Bendamustine 27
9.2 Melphalan 29
9.3 Fludarabine 29
9.4 Inotuzumab Ozogamicin 30
9.5 Rituximab 31
9.6 Cyclophosphamide 31
9.7 MESNA 32

10.0 DATA SECURITY/CONFIDENTIALITY 32

10.1 Access to Study Records 32
10.2 Methods of Storage of Study Records 33
10.3 Duration of Study Record Storage 33
10.4 Sharing of Study Records 33
10.5 Consent Process and Documentation 33

11.0 REFERENCES 35

Protocol Body

1.0 Objectives

The primary objective of this study will be to assess the safety of the addition of Inotuzumab Ozogamicin pre- and post- allogeneic transplantation in patients with CD22-positive hematological malignancies.

Secondary objectives include assessing:
1. Overall survival, progression-free survival and relapse rates.
2. Treatment-related mortality
3. Cumulative incidence of acute and chronic graft-versus-host disease (GVHD).

2.0 Background

The cell-surface glycoprotein CD22 is expressed in more than 90% of patients with b-cell lymphoid malignancies, and has emerged as an attractive therapeutic target for b-cell cancers.[1] Inotuzumab ozogamicin (IO) is a humanized anti-CD22 monoclonal antibody conjugated to calicheamicin, a cytotoxic antibiotic agent. After the conjugate binds to CD22, the CD22-conjugate complex is rapidly internalized, and calicheamicin is released. Calicheamicin binds to the minor groove of DNA and thus induces double-strand cleavage and subsequent apoptosis.[1]

Recent studies have suggested that IO is associated with a high risk of veno-occlusive disease (VOD) in patients receiving allogeneic stem cell transplantation (alloSCT).[2] Multivariate analysis using stepwise selection confirmed that conditioning regimens containing two alkylating agents (especially if busulfan and thiotepa are involved) and last available pre-alloSCT bilirubin concentration more than or equal to the ULN might increase the risk of sinusoidal obstruction syndrome.[2]

Initial reports from MD Anderson Cancer Center using IO in relapsed/refractory B-ALL in both pediatric and adult patients showed promising results with overall response rate (ORR) of 57%.[3]The phase II Children's Oncology Group study (AALL1621) using inotuzumab in treating younger patients with relapsed/refractory B-ALL (NCT02981628) showed an ORR of 58% among the 48 patients enrolled, an MRD negativity rate of 65% among responders.[4]

A retrospective study using IO on a compassionate use program in pediatric patients reported on 51 heavily pretreated children with B-ALL who received the fractionated dosing schedule of IO: 67% achieved CR with most (71%) achieving MRD-negative status, and 41% undergoing alloSCT after IO. Notably VOD developed in 52% of patients who received alloSCT. Patients who developed VOD received dual alkylators, busulfan containing regimens, TBI based myeloablative regimens, or had history of one or more alloSCT prior to IO therapy. The 12 months EFS and OS for the entire group were 23.4%

and 36.3%, respectively.[5]

We have prospectively studied the safety of IO when added to our standard nonmyeloablative conditioning regimen, bendamustine-fludarabine and rituximab.[6,74] IO was infused intravenously (IV) on day -13 outpatient, with a dose cohort of 0.6, 1.2 or 1.8 mg/m^2, to determine the maximum tolerated dose. Bendamustine 130 mg/m2 IV daily on days -5 to -3 together with 30 mg/m2 IV of fludarabine on days -5 to -3 were given prior to transplantation. Rituximab was given at a dose of 375 mg/m2 IV on days -6, +1, and +8. Tacrolimus and mini-methotrexate were used for graft versus host disease (GvHD) prophylaxis. In addition, thymoglobulin 1 mg/kg IV was given on days -2, and -1 in patients receiving an unrelated donor transplant. This study included 21 patients (CLL=9; 3 with 17p- and 1 Richter's), mantle cell=7, follicular=3, and diffuse large cell=2; including 1 double-expresser). Median age was 59 (range, 31-70) years. Median prior treatments was 3 (range, 1-6); Ten (48%) received their transplants from HLA-compatible siblings and 11 (52%) from unrelated donors**.** The number of patients who received the 0.6, 1.2 or 1.8 mg/m^2 of IO were 4, 2 and 15 patients, respectively. Fifteen patients (71%) never experienced an absolute neutrophil count < 0.5 x 10^9/L nor required platelet transfusions. All patients engrafted donor cells and no secondary graft failure occurred. By day 30, median donor myeloid and T-cells were 89% and 99%, respectively. Both increased to 100% by day 90. The cumulative incidence of acute grade 2-4 graft-versus-host disease (GvHD) and chronic extensive GvHD were 29% (5% of grade 3, and 0% of grade 4) and 35%, respectively. One patient with underlying cholelithiasis developed acute cholecystitis with IO and was able to proceed with alloSCT after recovery. No dose-limiting toxicities or VOD were observed. With a median follow-up time of 23.5 (range, 3-54) months, the overall survival (OS) rate was 89% (90% CLL/follicular, 86% mantle cell and 100% in diffuse large cell; also 100% for siblings, 81% for unrelated) and the progression-free survival (PFS) rate was 78%.

A more intense chemotherapy conditioning is needed in acute lymphoblastic leukemia (ALL). In order to avoid the commonly used drugs of busulfan and thiotepa that are associated with VOD, we propose the use of fludarabine and mephalan (FM). The efficacy of reduced intensity conditioning (RIC) of FM in b-ALL has been studied in two retrospective studies.5,6 Indications for this conditioning at the City of Hope[8] were: (1) aged 50 years or older (42%), (2) compromised organ function (54%), or (3) recipient of a previous alloSCT (37.5%). Patients had a median age of 47.5 years and the median follow-up was 28.5 months for living patients. Both OS and disease-free survival rates at 2 years were 61.5%.[8]These results were recently confirmed by Kawamura and colleagues, in using the same conditioning in ALL[9]

A study by the CIBMTR (Center for International Bone Marrow Transplant Research),[10]analyzed the intertwining role of the intensity of the conditioning and minimal residual disease (MRD) status by flow-cytometry pre-alloSCT in 197 adults with Ph+ ALL in first complete remission. Sixty-seven patients receiving RIC were matched with 130 receiving myeloablative conditioning (MAC) for age, donor type and year of transplant. At a median 4.5 years follow-up, 1-year transplant-related mortality (TRM)

was lower in RIC (13%) than MAC (36%; P=0.001) while the 3-year relapse rate was 49% in RIC and 28% in MAC (P=0.058). OS was similar (RIC 39% vs 35%; P=0.62). Patients MRD + pre-alloSCT had higher risk of relapse with RIC vs MAC [hazard ratio (HR) 1.97; P=0.026]. However, patients who were MRD (-) pre-RIC SCT had superior OS (55%) compared with a similar MRD population after MAC (33%; P=0.0042). This suggests that although RIC is associated with a lower TRM, additional non-toxic strategies are especially needed in b-ALL patients receiving RIC regimen.

In this study, we propose to extend our experience with IO in the transplant setting and to treat more patients with lymphomas and to also include patients with ALL. In order to decrease the risk of toxicity and VOD, we propose to split the IO we have previously used into pre- and post-transplant components. This is justified by the more intense RIC regimens we are using. This strategy is also extrapolated from the conventional non-transplant hyper-CVAD+IO studies done at MD Anderson, where there has been a significant reduction of VOD with a split dose of IO.[11]

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Patient age 12 to 75.
3.1.2 English and non-English speaking patients are eligible.
3.1.3 CD22+ lymphoid malignancies including B-ALL
3.1.4 Eligible to receive a reduced-intensity alloSCT
3.1.5 Patients with:
  a. Indolent lymphoma patients who failed conventional treatment; or,
  b. Acute lymphoblastic leukemia (ALL), aggressive lymphoma, indolent lymphoma in transformation, or those who have failed ≥ three small molecule inhibitors
3.1.6 Donor: HLA compatible (8/8 match) related or matched unrelated donor (HLA-A, B, C, DRB1) or mismatched MUD (7/8 match) or haploidentical[16]
3.1.7 Performance status of 0 to 2, Lansky ≥ 80 for < 16 years and Karnofsky ≥ 80 for ≥ 16 years of age.
3.1.8 Adequate organ function at time of study entry
  a. Creatinine less than or equal to 1.6 mg/dL
  b. Bilirubin less than 1.6 mg/dL
  c. SGPT < 2 x UL
  d. Ejection fraction >/= 40%
  e. FEV1, FVC and cDLCO >/= 40%
3.1.9 Negative Beta HCG test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization) or currently breast-feeding. Pregnancy testing is not required for post-menopausal or surgically sterilized women.

3.2 Exclusion criteria

3.2.1 HIV positive
3.2.2 Prior autologous transplant less than 1 year prior to consent.
3.2.3 Active and uncontrolled disease/infection
3.2.4 Unable or unwilling to sign consent
3.2.5 Current active hepatic or biliary disease (with exception of Gilbert's syndrome)
3.2.6 Active hepatitis B or C
3.2.7 Recent systemic chemotherapy or radiation within 3 weeks of study entry (intrathecal therapy is allowed). Standard biological agents such as rituximab, TKIs such as ibrutinib, and venetoclax are allowed to be given within 3 days prior to receiving inotuzumab ozogamicin. Blinatumomab is allowed to be given until 1 week prior to Day -13 inotuzumab ozogamicin on study.
3.2.8 Prior Inotuzumab Ozogamicin within 3 weeks of study entry.
3.2.9 Peripheral blast count of greater than 10 K/mL.
3.2.10 QTcF interval > 470 ms.
3.2.11 Patients with cognitive impairments and/or any serious unstable pre-existing medical condition or psychiatric disorder that can interfere with safety or with obtaining informed consent or compliance with study procedures.

4.0 Treatment Plan

The transplant day is referred as day zero (D0), treatment plan activities prior or after D0 are denominated as day minus (D-) or day plus (D+).

Obtain ECGs and electrolytes prior to the start of IO treatment and periodically monitor as clinically indicated during treatment.

Within 3 weeks prior to start treatment, D-13, patients must be off any prior systemic biological therapy, chemotherapy, radiotherapy, or other investigational therapy (intrathecal therapy is allowed). Blinatumomab is allowed to be given until 1 week prior to Day -13 inotuzumab ozogamicin on study.

4.1 Chemotherapy Agent Doses and Administration for Acute Lymphoblastic Leukemia, Aggressive Lymphoma Patients (based on WHO Classification), also indolent lymphoma in transformation, or those who have failed ≥ three small molecule inhibitors

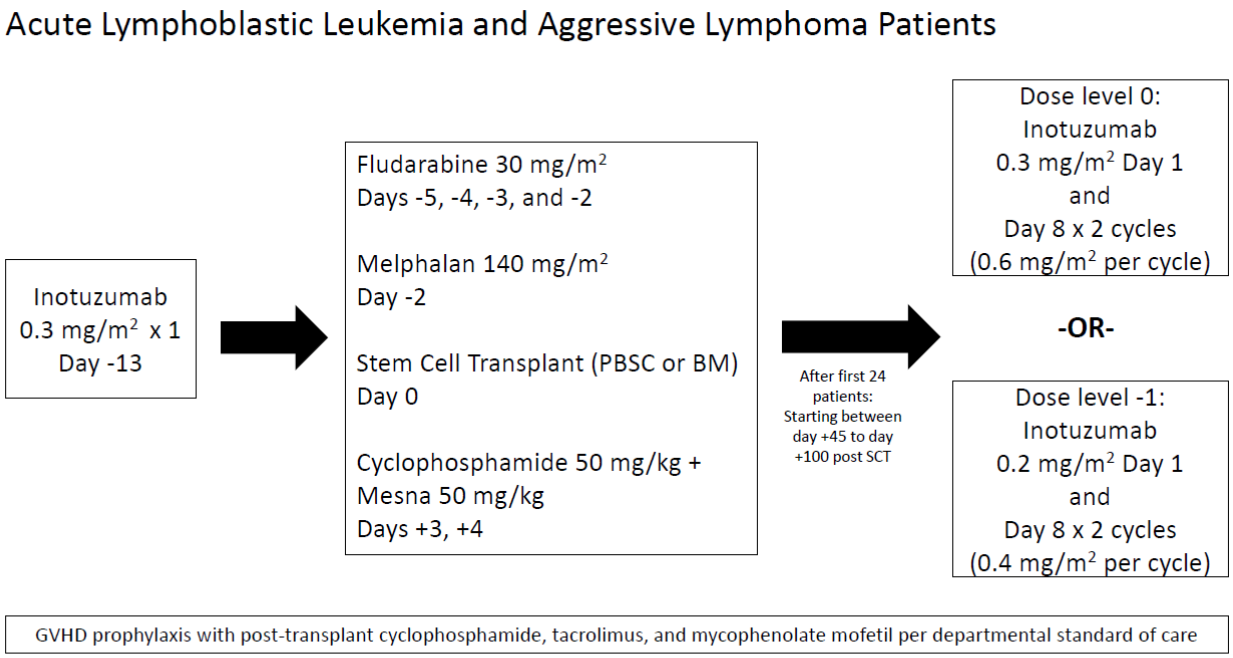
Day -13: Patients will receive IO on day -13 of conditioning at dose levels: 0.3 mg/m^2 intravenously (IV). Dose is based on actual body weight/body surface area. Patients will receive premedication with diphenhydramine and hydrocortisone (or equivalent corticosteroid) as follows before IO infusion:

- **Adults ≥ 18 years:** diphenhydramine 25 mg orally or IV and hydrocortisone 50 mg IV
- **Pediatric patients 12 – 17 years old: diphenhydramine 0.5 mg/kg (max 25 mg) orally or IV and hydrocortisone 1 mg/kg (max 50 mg) IV**
- For pediatric patients, adjusted body weight will be calculated using pediatric standards.

Day -5, -4, -3, -2: Fludarabine and Melphalan will be administered IV following SCTCT department standard practice.[12,13] Fludarabine will be administered at a dose of 30 mg/m2 IV on days -5, -4, -3, and -2. Melphalan will be administered at a dose of 140 mg/m^2 on day -2. On day -2, fludarabine should be administered prior to melphalan. Fludarabine doses will be based on actual body weight/actual body surface area. Melphalan doses will be dosed per adjusted body weight for patients weighing > 20% above their ideal body weight. For patients less than or equal to 20% above their ideal body weight, the actual body weight is used. Formula to calculate adjusted body weight for melphalan as follows: Adjusted BW (kg) = IBW + 0.5 (Actual body weight-IBW).

Day 0 –Transplant

Fresh or cryopreserved bone marrow or peripheral blood progenitor cells (bone marrow preferred) will be infused on day 0. Depending on arrival time, patients who receive a graft from an unrelated donor might have one day delayed from D0.



Please note: Patients enrolled prior to protocol Version 18.0 received thymoglobulin and standard GVHD prophylaxis with tacrolimus and mini methotrexate.

4.2 Chemotherapy Agent Doses and Administration for patients with Indolent Lymphomas (based on WHO Classification)

Day -13: Patients will receive IO on day -13 of conditioning at dose levels: 0.6 mg/m^2 or 0.3 mg/m^2 intravenously (IV) (if necessary. Please see statistical design). Dose is based on actual body weight/body surface area. Patients will receive premedication with diphenhydramine and hydrocortisone (or equivalent corticosteroid) as follows before IO infusion:

- **Adults ≥ 18 years:** diphenhydramine 25 mg orally or IV and hydrocortisone 50 mg IV
- **Pediatric patients 12 – 17 years old: diphenhydramine 0.5 mg/kg (max 25 mg) orally or IV and hydrocortisone 1 mg/kg (max 50 mg) IV**
- For pediatric patients, adjusted body weight will be calculated using pediatric standards.

D-5, -4 and -3: Fludarabine will be administrated at a dose of 30 mg/m2 IV followed by Bendamustine at a dose of 130 mg/m^2 IV.

Fludarabine and Bendamustine will be administered IV following SCTCT department standard practice. Fludarabine will be based on actual body weight/actual body surface. Bendamustine will be dosed per adjusted body

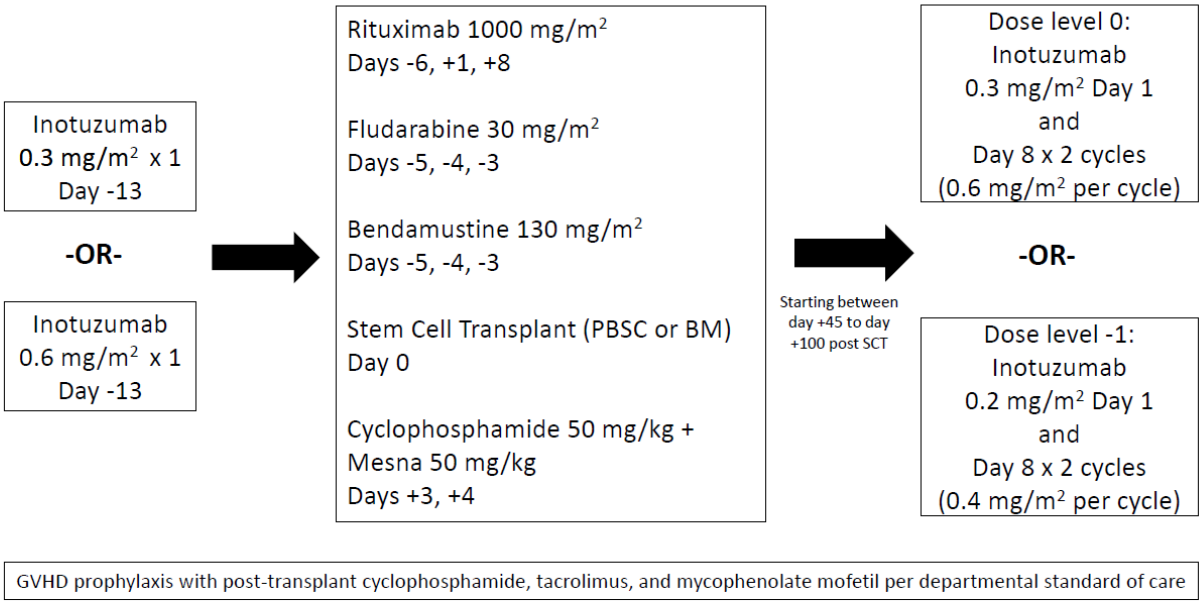
weight for patients weighing > 20% above their ideal body weight. For patients less than or equal to 20% above their ideal body weight, the actual body weight is used. Formula to calculate adjusted body weight for bendamustine is as follows: Adjusted BW (kg) = IBW + 0.5 (Actual body weight-IBW).

Lymphoma patients will also receive rituximab IV at 1,000 mg/m^2 IV (based on actual body weight) on D-6, D+1 and D+8. Rituximab infusion will follow SCTCT department standard practice. A rituximab biosimilar may be used based on institutional formulary and/or if required by insurance.

Day 0 –Transplant

Fresh or cryopreserved bone marrow or peripheral blood progenitor cells (bone marrow preferred) will be infused on day 0. Depending on arrival time, patients who receive a graft from an unrelated donor might have one day delayed from D0.

Indolent Lymphoma Patients



Please note: Patients enrolled prior to protocol Version 18.0 received thymoglobulin and standard GVHD prophylaxis with tacrolimus and mini methotrexate.

4.3 Chemotherapy Agent Doses and Administration for Haploidentical or Mismatched Stem Cell Transplant Recipients

Day -13: Patients will receive IO on day -13 of conditioning at dose level 0.3 mg/m^2 intravenously (IV). Dose is based on actual body weight/body surface area. Patients will receive premedication with diphenhydramine and hydrocortisone (or equivalent corticosteroid) as follows before IO infusion:

- **Adults ≥ 18 years:** diphenhydramine 25 mg orally or IV and hydrocortisone 50 mg IV
- **Pediatric patients 12 – 17 years old: diphenhydramine 0.5 mg/kg (max 25 mg) orally or IV and hydrocortisone 1 mg/kg (max 50 mg) IV**
- For pediatric patients, adjusted body weight will be calculated using pediatric standards.

D-5, and -4: Fludarabine will be administrated at a dose of 40 mg/m2 IV.

D-3, and -2: Fludarabine will be administrated at a dose of 40 mg/m2 IV followed by melphalan 50 mg/m2 IV.

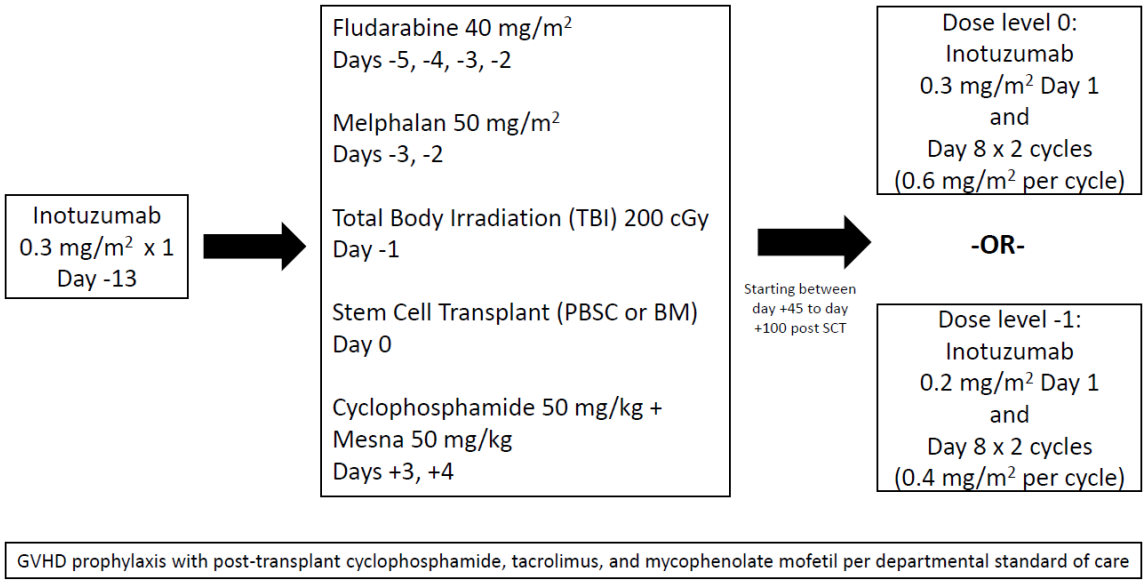
Fludarabine doses will be based on actual body weight/actual body surface area. Melphalan doses will be dosed per adjusted body weight for patients weighing > 20% above their ideal body weight. For patients less than or equal to 20% above their ideal body weight, the actual body weight is used. Formula to calculate adjusted body weight for melphalan as follows: Adjusted BW (kg) = IBW + 0.5 (Actual body weight-IBW).

Day -1
Total body irradiation (TBI) 200 cGy will be administered.

Day 0 –Transplant

Fresh or cryopreserved bone marrow or peripheral blood progenitor cells (bone marrow preferred) will be infused on day 0. Depending on arrival time, patients who receive a graft from an unrelated donor might have one day delayed from D0.

Haploidentical or Mismatched Stem Cell Transplant Recipients



Please note: Patients enrolled prior to protocol Version 18.0 received thymoglobulin and standard GVHD prophylaxis with tacrolimus and mini methotrexate.

4.4 Supportive Care

4.4.1 Prior to inotuzumab ozogamicin treatment, subjects should receive pretreatment medications to reduce the incidence and severity of an anticipated infusion syndrome characterized by fever and chills, and less commonly hypotension. Premedication before inotuzumab ozogamicin may also include antiemetics. Antiemetics that do not predispose patients to Torsade de Pointes, such as granisetron or palonosetron, are recommended. Subjects should be pretreated with hydrocortisone (or other corticosteroid) and antihistamine approximately 0.5 to 2 hours before each inotuzumab ozogamicin administration. In cases of infusion reactions, discontinue infusion and institute appropriate medical treatment as needed (e.g., corticosteroids, epinephrine, bronchodilators, or oxygen). Depending on the severity of the infusion reaction and interventions required, the investigator could consider restarting the infusion at a reduced rate.

4.4.2 All patients will receive Graft Versus Host Disease (GvHD) prophylaxis, infectious disease prophylaxis, growth factors, blood and platelet transfusion and other supportive treatment as per departmental standard practice in patients receiving allogeneic transplant. In order to avoid liver toxicity related to antifungal agents, patients should receive an echinocandin up until day +30 after which time therapy could be changed to an azole per SCT standard of care if LFTs are within normal limits.

Post-transplant cyclophosphamide (PTCy) administration[14]

PTCy will be administered on Days +3 and +4 as per dose level (50 mg/kg/dose) IV as per SOC guidelines unless otherwise indicated. PTCy dose is based on ideal body weight (IBW) unless patient's actual weight is less than their IBW. If actual weight is less than IBW, then actual weight will be used. Mesna may be used as per institutional guideline.

Additional Standard GVHD Prophylaxis[6,7,14]

Tacrolimus and Mycophenolate Mofetil (MMF)

Tacrolimus will start at 0.015 mg/kg (then adjusted to a level 7-15 ng/mL) as a continuous IV infusion daily (or at an equivalent PO dose) starting Day +5, then continued PO for 6 months post-transplant followed by a taper, unless GVHD present. The dose may be modified as clinically indicated. MMF 15 mg/kg (max 1000 mg per dose, based on actual body weight) PO or IV TID will be given from Day +5 until Day+35 (for 10/10 matched siblings or matched unrelated donors) or until Day +60 (for mismatched, unrelated, and haploidentical donors) unless otherwise indicated. MMF can be discontinued/tapered early if ANC<500 or dropping chimerism. Women of child-bearing potential will require a negative baseline serum/urine beta HCG test, education on the risks associated with MMF.

Supportive Care

- Mesna will be given per SOC guidelines on the days cyclophosphamide is administered.
- Hydration for PTCy: 1.5 to 2 ml/kg/hr (max 150 ml/hr) starting 2 hours prior to each PTCy dose for a total of 10 hours each day of cyclophosphamide.
- All patients will receive infectious disease prophylaxis, growth factors, blood and platelet transfusion and other supportive treatment as per SOC guidelines in patients receiving allogeneic transplant.
- G-CSF (filgrastim-sndz, Zarxio) will be administered at a dose of 5 mcg/kg/day (rounded to the nearest vial size) subcutaneously beginning on D+7 for all patients. G-CSF will continue until the absolute neutrophil count (ANC) is > 500 K/uL for 3 consecutive days.
- All patients will receive ursodiol to prevent VOD at a dose of 12 mg/kg/day in divided doses and rounded to nearest tablet/capsule size. Max dose of 1200 mg/day. Ursodiol should start on the first day of the conditioning regimen.

The first 24 patients in the FM group may receive post-transplant maintenance intrathecal prophylaxis as per our SCT guidelines. If none develops VOD, we will move to the main study and add maintenance therapy in an additional 10 patients. If any develops VOD, study enrollment into this group will terminate.

Patients with Ph+ ALL may receive standard of care maintenance with TKIs after Day 100.

Patients with aggressive lymphoma would be treated on the same arm as ALL (i.e., with FM conditioning).

The safety criteria of treating the first 24 patients with FM maintenance would include patients with ALL as well as those with aggressive lymphomas.

4.5 Post-transplant

4.5.1 Criteria to receive cycle 1 of maintenance of IO Cycle 1 to be started anytime between day 45 and 100 after alloSCT

1. Recovery to grade 1 or baseline non-hematologic related toxicity (including liver function test abnormalities, not including alopecia).
2. Serum bilirubin <1.6, and AST, ALT and alkaline phosphatase <3 x ULN. IO dosing should be permanently discontinued for any patients with possible, probable or confirmed VOD or other severe liver toxicity.
3. Serum creatinine <1.6 mg/dL and Creatinine clearance > 15 ml/min based on Cockcroft-Gault equation using IBW.
4. Platelet count greater than 50,000/uL without transfusion for at least 2 days
5. Absolute neutrophil count > 1,000/uL without growth factor for at least 2 days
6. QTcF </= 470 msec.
7. No steroid refractory GvHD
8. No active uncontrolled GvHD
9. No evidence of life-threatening infection
10. No evidence of overt relapse (MRD positive patients are still eligible)
11. No active bleeding
12. No autologous reconstitution (defined as absence of donor T cells on peripheral blood or donor chimerism)

4.5.2 Criteria to receive cycle 2 of maintenance of IO Cycle 2 to be started 28 to 100 days after start of first cycle.

1. Recovery to grade 1 or baseline non-hematologic related toxicity (including liver function test abnormalities, not including alopecia).
2. Serum bilirubin <1.6, and AST, ALT and alkaline phosphatase <3 x ULN. IO dosing should be permanently discontinued for any patients with possible, probable or confirmed VOD or other severe liver toxicity.
3. Serum creatinine <1.6 mg/dL and Creatinine clearance > 15 ml/min based on Cockcroft-Gault equation using IBW.
4. Platelet count greater than 50,000/uL without transfusion for at least 2 days
5. Absolute neutrophil count > 1,000/uL without growth factor for at least 2 days

6. QTcF </= 470 msec.
7. No steroid refractory GvHD
8. No active uncontrolled GvHD
9. No evidence of life-threatening infection
10. No evidence of overt relapse (MRD positive patients are still eligible)
11. No active bleeding
12. No autologous reconstitution (defined as absence of donor T cells on peripheral blood or donor chimerism)

4.5.3 Dosing schema for Inotuzumab Ozogamicin

Dose Level	Day 1 Dose (mg/m2)	Day 8 Dose (mg/m2)	Total dose Per Cycle (mg/m2)
0 (Starting dose)	0.3	0.3	0.6
-1	0.2	0.2	0.4

Heme toxicity: stop current cycle and reduce total dose per cycle dose by 33% for next cycle if the following occurs:

1. Platelet less than 15,000 for more than 4 days, not corrected by transfusion
2. ANC less than 500 for more than 4 days, not responsive to growth factor

5.0 Evaluation During Study

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments completed outside of schedule and occasional missed required research samples.

5.1 Pre-Treatment Evaluations

Studies listed below will be done prior to start treatment only if these were not done before study entry either as part of diagnostic or routine pre-transplant workup.

Disease assessment 30 days prior to start of treatment (baseline):

1. Unilateral bone marrow biopsy and aspiration.
2. Disease specific PCR only if previously detected
3. Cytogenetics and flow cytometry.
4. Disease specific fluorescence in situ hybridization (FISH) only if previously

detected
5. Immunophenotyping.
6. PET for lymphoma patients, only if previously positive.
7. Chest x-ray.
8. Electrocardiogram and echocardiogram.
9. CT neck, chest, abdomen and pelvis for lymphoma patients.
10. Laboratory studies: CBC with differential, platelet count, PT, PTT, creatinine, ALT, bilirubin, LDH, alkaline phosphatase Beta 2 microglobulin level, Hepatitis serology, HIV, HTLV-1, quantitative serum immunoglobulins, baseline peripheral CD4/CD8 counts and immunodeficiency panel. Serum pregnancy test for patients of child bearing potential. This is a female who has not been postmenopausal for at least 12 consecutive months or who has not undergone previous surgical sterilization. Patients of child bearing potential must agree to use birth control while on study.
11. Patients with history of Gilbert's Disease: Right upper quadrant abdominal ultrasound.

5.2 Evaluations During Study

Evaluations during this study follow our standard practice, if clinically indicated these studies may be done at other time points which can replace the nearest planned timepoint. After 12 months, follow-up testing to determine disease status will be done annually around years 2 and 3 as clinically indicated.

1. Assessment and documentation of adverse events present at time of treatment initiation.

2. To be performed around engraftment time:
   a) Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells. After engraftment patients that have 100% donor cells, chimerism studies will be done approximately every 3 months during the first year and then approximately every 6 months while the patient is on study.

3. To be performed as clinically indicated:
   a) Physical examination and adverse event assessment including GvHD assessment.
   b) Laboratory:
      1) Complete blood count with differential
      2) Standard Chemistries including LFT, BUN, Cr, albumin.

4. EKG prior to each cycle of IO. When not feasible to discontinue concomitant drugs known to prolong QTc interval, obtain ECGs and electrolytes prior to the start of IO treatment and periodically as clinically indicated during treatment.

5. Disease assessment to be performed around 1, 3, 6, and 12 months post-transplant:
   a) Unilateral bone marrow aspiration and biopsy. As clinically indicated if this was negative pre-transplant.
   b) PCR (repeat these only if a positive history)
   c) Cytogenetics, flow cytometry.
   d) FISH (disease specific, if previously positive)
   e) CT scans of neck. chest, abdomen and pelvis for patients with lymphoma.
   f) PET if it was positive any time in the past. PET would not be repeated once CR is documented after transplant unless there are suspicious lymph nodes by CT.
   g) Quantitative serum immunoglobulins levels.
   h) Immunodeficiency panel (only repeat in pts with recurrent infections).

5.3 Optional Procedure

Patients will have 10 cc blood sample in EDTA tube drawn pre-transplant and at approximately 3 months, 6 months, and 1 year after transplant to study minimal residual disease by next generation sequencing. De-identified samples from the patient's last bone marrow biopsy or archived lymph node biopsy will also be sent for next generation sequencing. Patients will not be charged for these tests. No clinical data will be shared with Genomic Testing Cooperative or its representatives. De-identified samples will be sent for analyses to:

Maher Albitar, MD
CEO & CMO
Genomic Testing Cooperative
27 Technology Dr. # 100
Irvine, CA 92618
e-mail: malbitar@genomictestingcooperative.com
Phone: (949) 540-9421, Mobile: (949) 275-7564

Leftover samples will be discarded and will not be used for future research.

6.0 Statistical Considerations

6.1 Overview

This will be a Phase II trial of IO in patients with who are undergoing stem cell transplant for CD22+ hematologic disease. The primary objective is to assess the safety of this regimen. Secondary objectives include assessing TRM, relapse, OS, PFS, and acute and chronic GvHD. A maximum of 44 patients will be enrolled into two cohorts: 1) Lymphoma patients receiving Bendamustine,

Fludarabine, and Rituximab (BFR) in their conditioning regimen and 2) ALL patients receiving Fludarabine and Melphalan (FM) in their conditioning regimen. The first 24 patients in the FM cohort will be enrolled in a safety lead-in period, after which an additional 10 patients will be enrolled. We will enroll 10 patients in the Lymphoma/BFR cohort, yielding a total of 44 patients.

6.2 FM Cohort Safety

The first 24 patients in the FM cohort may receive post-transplant maintenance intrathecal prophylaxis as per our SCT guidelines. If none develops VOD, we will move to the main study and add maintenance therapy in an additional 10 patients. If any develops VOD, study enrollment into this cohort will terminate.

Patients with Ph+ ALL may receive standard of care maintenance with TKIs after Day 100.

6.3 Safety Monitoring

The PI will work with the study statistician to monitor safety. Safety will be monitored in three ways: first, by monitoring the rate of VOD separately by cohort (BFR or FM); second, by monitoring the rate of targeted toxicity separately by cohort, and third, by monitoring the rate of treatment-related mortality (TRM) separately by cohort.

VOD

VOD will be monitored in two ways in this trial, separately by cohorts defined by the conditioning regimen (BFR or FM). As noted above, in the FM cohort, if any of the first 24 patients develop VOD, enrollment into this cohort will stop. Second, if at least 3 of the first 10 patients develop VOD with IO as part of their conditioning regimen at a dose of 0.6 mg/m^2 for either BFR or FM, the conditioning dose for subsequent patients will drop to 0.3 mg/m^2. After the first 10 patients in either cohort are treated with IO at the starting dose, accrual will stop temporarily until all patients have been evaluated at 45 days. If the true rate in a cohort of VOD is 15%, the chance that at least 3 patients out of 10 in the lymphoma cohort develop this condition is approximately 18%.

Targeted Toxicity

In addition, patients will be monitored separately by cohort defined by conditioning regimen (BFR or FM) for the development of grade 3 or higher renal, bladder cystitis, hepatic, cardiac, pulmonary, or neurologic toxicity through day 30 after cycle 1 of maintenance using the Bayesian method of Thall, Simon, and Estey.[12] We will cease enrollment in either cohort if it is likely that this rate is higher than 30% and will monitor patients in groups of size 3.

Lymphoma/BFR Arm
Enrollment into the lymphoma/BFR conditioning cohort will cease

if: Pr [prob(toxicity) > 0.30 | data] > 0.80

That is, if we determine that there is a greater than 80% chance that the toxicity rate (as defined above) is greater than 30% in the BFR cohort, enrollment in that cohort will be stopped. We assume a beta (0.6, 1.4) prior distribution for the toxicity rate in this cohort, which has a mean of 0.3 corresponding to the 30% target toxicity rate. Stopping boundaries corresponding to this probability criterion are to terminate accrual if

Stopping Boundaries for BFR Cohort

Number of Patients Evaluated in Cohort	Stop Enrollment in Cohort if this Many Patients have Toxicity
3	2-3
6	3-6
9	5-9
10	Always stop

All patients who receive study treatment will be included in the monitoring rule.

This stopping rule was chosen to satisfy concerns from the FDA about excess toxicity. The operating characteristics of this rule are shown below.

Operating Characteristics for Toxicity Stopping Rule for BFR Cohort

If the true toxicity rate is…	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th percentiles		
0.1	0.036	10	10	10
0.2	0.150	10	10	10
0.3	0.328	6	10	10
0.4	0.534	3	6	10
0.5	0.727	3	3	10
0.6	0.873	3	3	6

FM Cohort
Enrollment into the FM conditioning cohort will cease if:

Pr [prob(toxicity) > 0.30 | data] > 0.80

That is, if we determine that there is a greater than 80% chance that the toxicity rate (as defined above) is greater than 30% in the FM conditioning cohort, enrollment in that cohort will be stopped. Only the 10 patients in the treatment phase will be included in this monitoring rule. We assume a beta (0.6, 1.4) prior distribution for the toxicity rate in this cohort, which has a mean of 0.3 corresponding to the 30% target toxicity rate. Stopping boundaries corresponding to this probability criterion are to terminate accrual if:

Number of Patients Evaluated in Cohort	Stop enrollment in Cohort if this Many Patients have Toxicity
3	2-3
6	3-6
9	5-9
10	Always stop

All patients who receive study treatment will be included in the monitoring rule.

This stopping rule was chosen to satisfy concerns from the FDA about excess toxicity. The operating characteristics of this rule are shown below.

Operating Characteristics for Toxicity Stopping Rule for FM Cohort

If the true toxicity rate is…	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th percentiles		
0.1	0.036	10	10	10
0.2	0.150	10	10	10
0.3	0.328	6	10	10
0.4	0.534	3	6	10
0.5	0.727	3	6	10
0.6	0.872	3	3	6

Treatment-Related Mortality

Finally, patients will be monitored separately by cohort defined by conditioning regimen (BFR or FM) for treatment-related mortality at 1 year. Similar to the targeted toxicity rules above, the Bayesian method of Thall, Simon, and Estey[15] will be used in monitoring. We will cease enrollment in either cohort if it is likely that this rate is higher than 20%. We will monitor patients in groups of size 3.

Indolent Lymphoma/BFR Cohort

Enrollment into the lymphoma/BFR conditioning cohort will cease if: Pr [

$$\text{prob(1-year TRM)} > 0.20 \mid \text{data}] > 0.9$$

That is, if we determine that there is a greater than 90% chance that the 1-year TRM rate is greater than 20% in the BFR cohort, enrollment in that cohort will be stopped. We assume a beta (0.4, 1.6) prior distribution for the 1-year TRM rate in the BFR cohort, which has a mean of 0.20 corresponding to the 20% targeted maximum TRM Rate in this cohort. Stopping boundaries corresponding to this probability criterion are to terminate accrual if:

Stopping Boundaries for TRM Rule for BFR Cohort

Number of Patients Evaluated in Cohort	Stop Enrollment in Cohort if this Many Patients Experience TRM
3	2-3
6	4-6
9	5-9
10	Always stop

All patients who receive study treatment will be included in the TRM monitoring rule.

This stopping rule was chosen to assure that if 15 patients are enrolled into this cohort, the probability of early stopping will be less than 20% if the true 1-year TRM rate is no more than 20%. The operating characteristics of this rule are shown below.

Operating Characteristics for TRM Stopping Rule for BFR Cohort

If the true 1-year TRM rate is...	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th percentiles		
0.10	0.038	10	10	10
0.20	0.172	10	10	10
0.30	0.385	6	10	10
0.40	0.617	3	6	10
0.50	0.809	3	3	9

<u>FM Cohort</u>

Enrollment into the FM conditioning cohort will cease if:

$$\Pr [\text{prob(1-year TRM)} > 0.20 \mid \text{data}] > 0.95$$

That is, if we determine that there is a greater than 95% chance that the 1-year TRM rate is greater than 20% in the FM conditioning cohort, enrollment in that cohort will be stopped. We assume a beta (0.4, 1.6) prior distribution for the 1-year rate in this cohort, which has a mean of 0.20 corresponding to the 20%

maximum 1-year TRM rate. Stopping boundaries corresponding to this probability criterion are to terminate accrual if:

Number of Patients Evaluated in Cohort	Stop Enrollment in Cohort if this Many Patients Experience TRM
3	3
6	4-6
9	5-9
12	6-12
15	7-15
18	7-18
21	8-21
24	9-24
27	10-27
30	11-30
33	11-33
34	Always stop

All patients who receive study treatment will be included in the monitoring rule.

This stopping rule was chosen to assure that if 34 patients are enrolled into this cohort, the probability of early stopping will be approximately 10% if the true 1-year TRM rate in the FM cohort is no more than 20%. The operating characteristics of this rule are shown below.

Operating Characteristics for TRM Stopping Rule for FM Cohort

If the true 1-year TRM rate is...	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th percentiles		
0.1	0.004	34	34	34
0.2	0.103	34	34	34
0.3	0.490	18	34	34
0.4	0.868	9	18	24
0.5	0.987	6	9	15

Each of the monitoring rules will be implemented by the clinic with assistance from the study statistician as necessary.

6.4 Analysis Plan

All analyses will be performed separately by cohorts and by GvHD prophylaxis

groups. We understand that with small numbers of patients in some groups, conclusions will be limited. Analyses of the FM cohort will be performed separately by phase (24 lead-in phase/10 full treatment phase) and by GvHD prophylaxis group, but some analyses may be performed on the full cohort of 34.

At the end of the trial, the rates of severe toxicity will be summarized separately for each cohort and group, and analyses will be performed to assess the relationship between each toxicity endpoint and covariates of interest using logistic regression. The cumulative incidence of TRM will be assessed in a competing risks framework with the competing risk of disease relapse. Regression models will be fit to assess the relationship between each and covariates of interest using the method of Fine and Gray.[16] The distribution of OS and PFS will be assessed using the Kaplan-Meier method, and distributions will be compared using the log-rank test. Cox proportional hazards regression models will be fit to assess the relationship between OS and PFS and covariates of interest. The cumulative incidence of acute GvHD and chronic GvHD will be assessed in a competing risks framework with competing risks of death without relapse and disease relapse. The method of Fine and Gray will be used to assess the association between GvHD and covariates of interest.

6.5 Safety Monitoring Plan

The investigator will submit toxicity/TRM summaries to Clinical Trials Safety team. These will be submitted to INDSummariesReview@mdanderson.org as follows:

Targeted Toxicity Monitoring

- BFR cohort and FM with maintenance cohort: A toxicity summary must be submitted after every 3 subjects per cohort complete the first cycle (30 days) of maintenance therapy or discontinue maintenance therapy due to toxicity, whichever occurs first.

Treatment Related Mortality (TRM) Monitoring:

- BFR cohort and FM (with or without maintenance IO) cohort: A TRM summary should be submitted after every 3 subjects per cohort complete 1 year post-transplant or experience treatment related mortality, whichever occurs first.

VOD Monitoring:

- FM cohort (with and without maintenance IO): If any of the first 24 patients develop VOD within 45 days of initial conditioning dose of IO on Day -13, enrollment to that cohort must be stopped and Clinical Trial Safety must be notified immediately via email at INDSummariesReview@mdanderson.org.
- BFR cohort: If 3 patients develop VOD, enrollment to that cohort must be stopped and Clinical Trial Safety must be notified immediately via email at INDSummariesReview@mdanderson.org.

7.0 Criteria for Removal from the Study

1. Patient withdrawal of the informed consent.
2. Patient not being compliant or fails to return for follow-up.
3. An increasing or unexpected pattern of toxicity observed deemed unacceptable by the Study Chairman.
4. Investigator judgment when the well being and best interest of the patient is compromised.
5. Three years after the last dose of inotuzumab ozogamicin.

8.0 Adverse Events and Reporting Requirements

Adverse event definition:
An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

8.1 Adverse Events and Data Collection

8.1.1 For the purpose of this study, the investigational component of the treatment plan is the addition of Inotuzumab Ozogamicin pre- and post- allogeneic transplantation in patients with CD22-positive hematological malignancies. Therefore, serious and unexpected adverse events occurring up to 30 days of the intervention, as defined below, will be reported according to MDACC policy and procedures below. The end of active treatment is the completion of two cycles of maintenance therapy post-transplant. Serious adverse events must be followed until clinical recovery and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

8.1.2 Common Terminology Criteria Adverse Events (CTCAE) – a descriptive terminology developed by the National Cancer Institute (NCI) for use in reporting adverse events. The CTCAE includes a grading (severity) scale for each adverse event term. A copy of the current CTCAE guidelines (Version 5.0) is located at http://ctep.cancer.gov/reporting/.

Grade – Severity of the adverse event. Grades were developed using the following guidelines:

Grade 0 – No adverse event or within normal limits
1 – Mild adverse event

2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

8.1.3 Time for AE Collection

Adverse events will be collected for 45 post first dose of IO infused, and for 30 days post last cycle of IO maintenance post-transplant

8.1.4 Adverse Event Reporting

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events, and assigning attribution for each event on all subjects enrolled on this study.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.1.5 Data collection

Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period.

Adverse events will be documented in the patient's electronic medical record.

Events not to be considered adverse events in this study are those related to original disease or expected in the post-allogeneic transplant period.

Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of GPT, GOT, LDH and

alkaline phosphatase will not be collected.

Adverse events and protocol specific data will be entered into BMTWeb. BMTWeb will be used as the electronic case report form for this protocol.

8.1.6 Concomitant medications

Patients treated on this protocol will require supportive care treatment (concomitant medications). These medications are considered standard of care and have no scientific contribution to the protocol; therefore no data will be captured on various medications needed or their side effects. All antiviral therapy will be captured in the medical record.

8.2 Serious Adverse Event Reporting (SAE) Reporting

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

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

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the

definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5working days of knowledge of the event).

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

8.2.1 Reporting to FDA

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

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor’s guidelines, and Institutional Review Board policy.

8.2.2 Reporting to Pfizer

Reporting of Serious Adverse Events. Within twenty four (24) hours of first awareness of the event (immediately if the event is fatal or life-threatening), Principal Investigator will report to Pfizer by facsimile certain Serious Adverse Events (“SAEs,” as defined below) for which reporting is required under this provision (as described below).

SAE Definition. An SAE is any adverse event at any time, without regard to causality, that is life-threatening (i.e., causes an immediate risk of death) or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life

functions); or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

Subset of SAEs Reportable for this Study. Because the Pfizer Product used in this Study is a mature marketed product with a well-established safety profile, only SAEs that fit into any of the following categories need to be reported to Pfizer: (1) a death, regardless of whether it is considered related to treatment with the Pfizer Product, (2) a non-fatal SAE that occurs during the reporting period and that is assessed by the Principal Investigator as both related to treatment with the Pfizer Product and unexpected for that Product, (3) an SAE assessed by the Principal Investigator as related to the Pfizer Product that occurs after the SAE reporting period, or (4) an otherwise reportable event. An event should be considered "related" to the Pfizer Product if a relationship is at least a reasonable possibility, and "unexpectedness" should be based upon a single safety reference document identified by the Principal Investigator and documented in association with the study.

Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure, and Lack Of Effect. Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy, exposure to the Pfizer Product during lactation, and occupational exposure to the Pfizer Product are reportable, and lack of effect of the Pfizer Product may also be reportable. These requirements are further explained in the training material provided by Pfizer (see Pfizer-Provided Training, below). As used in this Agreement, the term SAE will be understood to include exposure during pregnancy, exposure during lactation, occupational exposure, and reportable instances of lack of effect.

9.0 Background Drug Information

9.1 Bendamustine

Description: Bendamustine is a bifunctional alkylating agent containing a purine-like benzimidazole ring. Bendamustine forms covalent bonds with DNA causing both single and double-strand DNA breaks leading to cell death.

Preparation and stability: BENDEKA™ (Bendamustine) is supplied as 100mg/4mL (25 mg/mL) as a clear and colorless to yellow ready-to-dilute solution in a multiple-dose vial. Bendamustine hydrochloride injection contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration. If diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or

36-46°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. **Administration of diluted bendamustine hydrochloride (BENDEKATM) injection must be completed within this period of time.**

In the event that 5% Dextrose Injection, USP is utilized, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for only 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. **Administration of diluted BENDEKA™ must be completed within this period of time.** Retain the partially used vial in original package to protect from light and store refrigerated (2-8°C or 36-46°F) if additional dose withdraw from the same vial is intended.

Stability of Partially Used Vials (Needle Punched Vials):
Bendamustine hydrochloride (BENDEKA™) is supplied in a multiple-dose vial. Although it does not contain any antimicrobial preservative, it is bacteriostatic. The partially used vials are stable for up to 28 days when stored in its original carton under refrigeration (2-8°C or 36-46°F). Each vial is not recommended for more than a total of six (6) dose withdrawals. After first use, the partially used vial should be stored in the refrigerator in the original carton at 2°C to 8°C or 36-46°F and then discarded after 28 days.

Aseptically withdraw the volume needed for the required dose from the 25 mg/mL solution as per Table (available in the package insert) and immediately transfer the solution to a 50 mL infusion bag of one of the following diluents:
- 0.9% Sodium Chloride Injection, USP; or
- 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or
- 5% Dextrose Injection, USP

The resulting final concentration of bendamustine hydrochloride in the infusion bag should be within 1.85 mg/mL – 5.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag.

Administration: Administer each bendamustine dose intravenously over 30 to 60 minutes.

Adverse reactions: myelosuppression, infection, infusion reactions (rarely anaphylaxis), extravasation, skin reactions such as mild rash/itching or rarely toxic epidermal necrolysis, tumor lysis syndrome, diarrhea, nausea/vomiting, fatigue, and rarely secondary malignancies such as myelodysplastic syndrome or acute leukemia.

See package insert for additional information.

9.2 Melphalan

Description: Melphalan is an alkylating agent with cell cycle nonspecific cytotoxic effects on tumor cells. It inhibits DNA replication and transcription of RNA ultimately disrupting nucleic acid function.

Dosing Information: The usual dose for conditioning in stem cell transplantation is 100-200 mg/m2/day intravenously.

Administration: Administer according to institutional standards.

Adverse Reactions: Hematologic: The most common adverse effect is bone marrow suppression. Leukopenia and thrombocytopenia are the major dose limiting side effects. GI toxicity is frequent with higher doses and includes nausea and vomiting, stomatitis, abdominal cramping and diarrhea. Other adverse effects: Pulmonary fibrosis and infiltrates, amenorrhea, alopecia, sterility, and inappropriate ADH secretion. Hypersensitivity reactions: Acute hypersensitivity reactions have been reported including urticaria, pruritus, edema, tachycardia, bronchospasm and anaphylaxis (reported in 2.4% of patients receiving melphalan for myeloma). These patients respond to antihistamine and corticosteroid therapy.

Special Precautions: None

9.3 Fludarabine

Therapeutic classification: Fluorinated nucleoside analog

Pharmaceutical data: Each vial contains 50 mg lyophilized drug, to be reconstituted prior to its use.
Reconstitute each vial with 2 ml sterile water, each ml of solution will contain 25 mg of fludarabine phosphate. Vials should be stored refrigerated at 2-8 degrees C.

Solution Preparation: mix each vial with 100mL NS and infuse over 30 minutes. Reconstituted solution should be used within 8 hours.

Side effects: Pancytopenia, immunosuppression, autoimmune hemolytic anemia has (rarely) been reported, and recurred when patients were retreated with the drug.

Nausea, vomiting, anorexia, weakness.

From the CNS: Agitation, visual disturbances, confusion, coma, peripheral neuropathies have been reported. With high dose use confusion, blindness, coma and death have been reported.

Special Precautions: As for other antineoplastic agents Fludarabine should be handled by trained personnel using procedures for proper handling. The use of gloves and protective glasses is recommended to avoid exposure upon accidental spillage.

Mechanism of action: After phosphorylation to fluoro-ara-ATP the drug appears to incorporate into DNA and inhibit DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis.

Human safety and pharmacology: The half-life of the activated compound is approximately 10 hours, but the pharmacology is incompletely understood. Excretion is impaired in patients with impaired renal function.

See package insert for additional information.

9.4 Inotuzumab Ozogamicin

Description: Inotuzumab Ozogamicin is a humanized monoclonal antibody target to CD22 and conjugated to calicheamicin. It is supplied as amber vials with white, unpreserved, lyophilized cake. Each vial contains 0.9 mg.

Preparation and stability: Allow vials to reach room temperature prior to reconstitution. Reconstitute each vial with 4mL sterile water for injection for a concentration of 1mg/mL. Gently swirl each vial to dissolve. Do not shake vigorously. Dilute reconstituted solution (entire dose) with 0.9% sodium chloride to a final volume of 50mL. Infusion must be completed within 8 hours of reconstitution. Bags made of PVC or polyolefin are recommended. Unused or expired drug will be destroyed per institutional policy.

Administration: Each dose should be administered at 50mL/hr. Flush line with 22mL 0.9% sodium chloride after infusion is complete. Protect from light during preparation and administration.

Adverse events: common and expected are thrombocytopenia and neutropenia, low grade liver function tests, increased risk of infections due to neutropenia and depletion of B-cells, nausea, vomiting, abdominal pain, constipation, diarrhea, and decreased appetite.

Less common but serious and sometimes fatal are venoocclusive liver disease/sinusoidal obstructive syndrome (VOD/SOS), nodular regenerative hyperplasia, hepatic fibrosis / biliary cirrhosis, hepatic failure, ascites, hyperbilirubinemia, cytolytic hepatitis, hepatitis/hepatitis acute, and abnormal hepatic function.

Fatigue and asthenia are common and sometimes severe. Chills, headache, pyrexia, and epistaxis have also been reported.

Intracranial bleed resulting in death was reported in one patient with COVID-19 as possibly related to inotuzumab ozogamicin in September, 2020.

No serious prolongation of QTc although no well characterized have been observed.

Storage: Vials should be refrigerated (2-8°C) and protected from light.
For additional information, please see the investigator's brochure (Appendix G).

9.5 Rituximab

Description: Rituximab is a monoclonal antibody targeted against CD20 primarily found on B lymphocytes. Rituximab causes cell lysis through complement mediated cytotoxicity and antibody-dependent cytotoxicity. A biosimilar of rituximab may be used.

Preparation and stability: Dilute with NS or D5W to a final concentration of 1-4mg/mL. Solution is stable at 2-8 degrees C for 24 hours and additional 24 hours at room temperature. Rituximab is supplied as 100mg and 500mg vials.

Administration: Administer according to institutional standards.

Adverse reactions: infusion reactions (fever, chills, hypotension), rarely anaphylaxis, acute respiratory distress syndrome, arrhythmias, lymphopenia, infection, hepatitis B reactivation, rarely progressive multifocal leukoencephalopathy, skin rash, tumor lysis syndrome, nausea/vomiting, arthralgias, myalgias, and severe mucocutaneous reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis).

Storage: Diluted solutions of Rituximab should be stored refrigerated at 2-8 degrees C. Rituximab vials should be stored at 2-8 degrees C. and protected from direct sunlight. Do not freeze or shake.

See package insert for additional information.

9.6 Cyclophosphamide

Cyclophosphamide is an alkylating agent.

Mechanism of Action: Cyclophosphamide prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is cell cycle phase non-specific. Cyclophosphamide also possesses potent

immunosuppressive properties. It is a pro-drug metabolized by the liver to active metabolites.

Known Side Effects: Hematologic: Leukopenia, anemia, alopecia. GI: Nausea, vomiting, increased AST, ALT, mucositis, and diarrhea. Neurologic: Headache, dizziness. Cardiovascular: Cardiomyopathy, non-specific ST changes on EKG. Please refer to the package insert for a complete listing of all toxicities.

9.7 MESNA

Mesna is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxazophosphorines (cyclophosphamide and ifosfamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy.

Mechanism of Action: Mesna binds with acrolein, the urotoxic metabolite produced by the oxazophosphorines, to produce a non-toxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxazophosphorines.

Known Side Effects: At the doses used for uroprotection, mesna is virtually non-toxic. However, adverse effects which may be attributable to mesna include nausea and vomiting, diarrhea, abdominal pain, altered taste, rash, urticaria, headache, joint or limb pain, hypotension and fatigue. Please refer to the package insert for a complete listing of all toxicities.

10.0 Data Security/Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency, as applicable.

All research activities will be conducted in as private a setting as possible.

10.1 Access to Study Records

Study records may be accessed by IRB approved study personnel, or authorized inspectors. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will

permit access to such records.

10.2 Methods of Storage of Study Records

All data collected from MD Anderson Cancer Center (MDACC) sources will be maintained on a password protected server compliant with HIPAA. Study staff will have role based restricted access to directories and files on the server, according to project responsibilities. Only those with data entry permissions can add records. The PI or a delegate will review the conditions under which data will be released to recipient- investigators. Each application for use will need IRB approval and consents, if appropriate. The level of identifiability will determine the process for review and approval as well as the way information is shared.

Any study data or records maintained in paper documents will be stored in the offices of the PI or other delegated study staff, in a locked cabinet or other comparable controlled environment, and will be accessible only to authorized study team members or authorized inspectors.

10.3 Duration of Study Record Storage

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

10.4 Sharing of Study Records

There are no plans to share study data with entities external to MD Anderson Cancer Center, aside from authorized inspectors as applicable (i.e. authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product). If data will be shared, IRB approval will be sought, and applicable inter-institutional agreements executed, prior to data sharing.

10.5 Consent Process and Documentation

Please select one of the following:

☒ This protocol will follow the SOP 04_Informed Consent Process. SOP 04 has been read by the research staff and investigators.

☐ This protocol will follow SOP 04_Informed Consent Process with the following changes: SOP 04 has been read by the research staff and investigators.

Informed consent may be obtained using the following methods: (check all that apply):

☒ Remote consent

☒ In-person consent

11.0 References

1. Shor B, Gerber HP, Sapra P. Preclinical and clinical development of inotuzumab-ozogamicin in hematological malignancies. Mol Immunol. 2015; 67: 107–16.

2. Kantarjian HM, DeAngelo DJ, Advani AS, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol 2017; 4: e387-398.

3. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol 2012; **13**(4): 403-411.

4. O'Brien MM, Ji L, Shah NN, et al. A phase 2 trial of Inotuzumab Ozogamicin (InO) in children and young adults with relapsed or refractory (R/R) CD22+ B-acute lymphoblastic leukemia (B-ALL): Results from Children's Oncology Group Protocol AALL1621. Blood 2019; 134 (Suppl1): 741.

5. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia 2019;33(4):884-892.

6. Khouri IF, Gulbis AM, Milton DR, et al. Safety of addition of inotuzumab ozogamicin (CMC 544) to bendamustine, fludarabine, and rituximab (BFR) allogeneic conditioning for lymphoid malignancies. Blood/ASH Annual Meeting 2017; Abstract #3240.

7. Khouri IF, Wei W, Korbling M, et al. BFR (bendamustine, fludarabine, and rituximab) allogeneic conditioning for chronic lymphocytic leukemia/lymphoma: reduced myelosuppression and GVHD. Blood. 2014;124:2306-2312.

8. Stein AS, Palmer JM, O'Donnell MR, et al. Reduced-intensity conditioning followed by peripheral blood stem cell transplantation for adult patients with high-risk acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2009;15: 1407-1414.

9. Kawamura K, Kako S, Mizuta S, et al. Comparison of conditioning with fludarabine/busulfan and fludarabine/melphalan in allogeneic transplantation recipients 50 years or older. Biol Blood Marrow Transplant. 2017;23:2079-2087.

10. Bachanova V, Marks DI, Zhang M-J, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. Leukemia. 2014;28:658-665.

11. Jabbour E, Pui C-H, Kantarjian H. Progress and innovations in the management of adult lymphoblastic leukemia. JAMA Oncol {E-Pub, 6-21-2018].

12. Thall PF, Simon RM, and Estey EH. New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. J Clin Oncol. 1996. 14(1): p. 296-303.

13. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496-509.

14. Brammer JE, Khouri K, and Ciurea SO. Outcomes of Haploidentical Stem Cell Transplantation for Lymphoma with Melphalan-Based Conditioning, Biology of Blood and Marrow Transplantation. 2016 Mar;22(3):493-8.

15. Giralt S, Thall PF, and Champlin R. Melphalan and purine analog–containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. Blood. 2001 Feb 1;97(3):631-7.

16. Bolanos-Meade J, Hamadani M, and Holton GD. Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis. N Engl J Med 2023;388:2338-48.