Protocol

Official Title of Record: Propylene Glycol-Free Melphalan HCl (EVOMELA®) in Combination with Fludarabine and Total Body Irradiation Based Reduced Intensity Conditioning for Haploidentical Transplantation

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MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER

CLINICAL STUDY PROTOCOL

A Phase II, Open-Label Study of Propylene Glycol-Free Melphalan for Injection (EVOMELA®) in Combination with Fludarabine and Total-Body, Irradiation-Based, Reduced-Intensity Conditioning for Haploidentical Transplantation

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PROTOCOL SUMMARY

Study Title: A Phase II, Open-Label Study of Propylene Glycol-Free Melphalan for Injection (EVOMELA®) in Combination with Fludarabine and Total-Body, Irradiation-Based, Reduced- Intensity Conditioning for Haploidentical Transplantation

Investigators/Study Sites: This is a single-center study that will be conducted through the Froedtert & the Medical College of Wisconsin Clinical Cancer Center.

Study Duration: We plan to accrue a total of 43 haploidentical transplant patients in 2.5 years with two years additional follow-up. The study will be closed to accrual when the last patient is enrolled.

Phase: Phase II

Study Objectives

Primary Objectives:

1. To assess one-year, progression-free survival (PFS) of patients with hematological malignancies undergoing treatment with propylene glycol-free melphalan for injection (EVOMELA®), fludarabine (Flu) and total-body, irradiation (TBI)-based, reduced-intensity conditioning (RIC) for haploidentical hematopoietic cell transplantation (haplo-HCT).

2. To determine the safety of PG-Mel/Flu/TBI-based RIC haplo-HCT.

Secondary Objectives:

1. To assess OS, following RIC haplo HCT at one year.
2. To assess non-relapse mortality (NRM), following RIC haplo-HCT at day +100 and one year.
3. To assess relapse rate, following RIC haplo-HCT at day +100 and one year.
4. To assess time from RIC haplo-HCT to neutrophil and platelet recovery.
5. To assess rates of acute graft-versus-host disease (GVHD) at days +100 and +180.
6. To assess rates of chronic GVHD at one-year post-transplantation.
7. To assess lineage-specific chimerism kinetics of donor cells (or FISH XX/XY per physician discretion) following PG-Mel/Flu/TBI-based RIC haplo-HCT at baseline (approximately day +30) and day +100.
8. To determine kinetics of immune reconstitution, following RIC haplo-HCT at baseline (approximately day +30), day +100, day +180, day +365.
9. To assess rates of primary-graft failure.

10. To assess rates of primary- and secondary-graft rejection.

Number of Patients: Total estimated accrual is 43 patients.

Study Design: This is an open-label, single-arm, phase II study. The primary end point of the study is one-year PFS and safety of EVOMELA®/Flu/TBI-based RIC haplo-HCT.

Study Population

Inclusion criteria:

1. Patients with a diagnosis of hematological malignancy, undergoing a related-donor haploidentical HCT.
2. Patients aged ≥18 are eligible.
3. Bilirubin ≤ 2 x the ULN. For patients with Gilbert's syndrome or suspected mild veno-occlusive disease, bilirubin ≤ 3 x ULN is permitted.
4. Adequate renal function, as defined by a serum creatinine clearance of ≥ 30 mL/min, calculated by Cockcroft-Gault equation.
5. Left ventricular ejection fraction ≥40%. No uncontrolled arrhythmias or New York Heart Association class III-IV heart failure.
6. FEV1 or DLCO (diffusion capacity; corrected for hemoglobin) ≥ 50% of predicted.
7. Karnofsky Performance Status Scale score ≥ 60.
8. Graft source of peripheral blood (the infused CD34+ cell dose will be capped at 5 x 10^6 CD 34+ cells/kg recipients actual body weight) or bone marrow (the ideal infused total nucleated cell dose (TNC) will be targeted at 4 x 10^8/kg recipient actual body weight).
9. A negative pregnancy test will be required for all women of childbearing potential. Females of childbearing potential should agree to practice two effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug. They must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.). Breast-feeding is not permitted.
10. Male patients, even if surgically sterilized (i.e., status postvasectomy), must agree to one of the following: practice an effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation,

symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

11. No evidence of uncontrolled bacterial, viral or fungal infections at the time of enrollment.

12. Transplant recipient able to give informed consent.

Exclusion Criteria:

1. Patient must not have a healthy, eligible and readily available HLA-identical sibling donor or a volunteer adult unrelated donor (matched at allele-level at HLA-A, -B, -C and –DRB1).

2. No serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3. AML/MDS/myeloproliferative neoplasia patients with >5% blasts in bone marrow and/or circulating leukemic blasts in peripheral blood; patients with known active central nervous disease involvement with leukemia/lymphoma or lymphoma patients with progressive disease on clinical and/or radiographic assessment are not eligible for this study.

Study Treatments (prior to haplo-HCT):
For patients who are < 60 years of age:

- Melphalan: 140 mg/m^2/day IV on Day -6.
- Fludarabine: 40 mg/m^2/day IV Days -5 -4, -3, -2 (Adults: creatinine clearance may be estimated by the Cockcroft Formula: CrCl = [(140-age) x weight (kg) x 0.85 (for women only)]/ [72 x creat (mg/dl)].)
- TBI: 200 cGy Day -1.

For patients who are ≥ 60 years and/or HCT-CI score of >3 *(at the discretion of treating physician will have an option to receive):*

- Melphalan: 70 mg/m^2/day IV on Day -6.
- Fludarabine: 40 mg/m^2/day IV Days -5, -4, -3, -2.
- TBI: 200 cGy; Days -1

Propylene glycol-free melphalan for injection (EVOMELA®) will be diluted with 0.9% normal saline to a final concentration equal to 2 mg/mL and infused over 30±5 minutes via a central venous catheter.

EVOMELA® will be dosed according to the adjusted body weight (AjBW), if the patient's actual body weight (ABV) is greater than the ideal body weight (IBW) (using the formula:

AjBW=IBW + [(0.40) x (-IBW)]). If the IBW > actual body weight, then, actual body weight will be used.

For the calculation of BSA, actual body weight should be used for patients who weigh less than their IBW. For patients who weigh more than their IBW, BSA should be calculated, based on adjusted body weight.

The dose of fludarabine is based on actual body weight.

Statistical Procedures:

Sample size estimates:
The primary endpoint of the study is one-year PFS. The historical one-year PFS since transplant, under standard treatment, is 45%; the assumption is that the one-year PFS for haploidentical transplant is 59%. We plan to accrue haploidentical transplant patients in 2.5 years with two years additional follow up. The study will be closed to accrual after the last patient has enrolled. Based on exponential distribution and on a one-sided test with significance level of 5%, we will have 80% power to detect at least a 14% increase in one-year PFS for 41 patients. Allowing 5% subjects to be replaced, we plan to accrue 43 patients in the final study. NRM rate at day +100 and one year will be the key end points to monitor the safety in using this approach.

Independent stopping enrollment for monitoring adverse events

Stopping rule for excess non-relapse mortality:
Based on historical control data, a NRM rate at Day 100 of ≥15% in the current study will be considered unacceptable. We will evaluate and monitor transplant-related mortality (TRM) after the first 15 and 25 patients enrolled in the study. The assumption is that 15% of TRM occurring will stop the enrollment for protocol review. A Pocock-type boundary with the lower limit of 95% confidence interval will be used for monitoring TRM. At planned interim monitoring points, if no more than six or seven TRMs occur, the study will continue to its full enrollment of 43.

Stopping rule for excess primary graft rejection:
Primary graft rejection rate of ≥20% by day +45 would be considered unacceptable.

STUDY CALENDAR

Study Assessment	Baseline[1]	PG-free Mel/Flu/TBI							Days Post-Transplant (~ ±14 days up to day 365 and then ±28 days)[13]					
		-6	-5	-4	-3	-2	-1	0	30	60	100	180	1 year	2 years
Informed consent	X													
H & PE[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky performance status	X								X	X	X	X	X	X
CBC/differential *	X	X	X	X	X	X	X	X*	X	X	X	X		
Serum chemistries panel[4]	X	X	X	X	X	X	X	X	X	X	X	X		
CT/PET	X													
Infectious disease screen ǂ	X													
B-HCG serum pregnancy test [5]	X	X												
CMV/EBV[6]								X	X	X	X			
PFT[7]	X										X	X	X	
Echo or MUGA	X													

Study Assessment	Baseline[1]	PG-free Mel/Flu/TBI							Days Post-Transplant (~ ±14 days up to day 365 and then ±28 days)[13]					
		- 6	- 5	- 4	- 3	- 2	- 1	0	30	60	100	180	1 year	2 years
Sorted chimerisms (or FISH XX/XY as appropriate) [12]	X								X					
Quantitative immunoglobulins[8]									X	X	X	X		
Immune reconstitution panel[9]									X	X	X	X	X	
CD34/CD3 cell dose infused [PB]								X						
Acute GVHD assessment									X	X	X	X	X	X
Chronic GVHD assessment									X	X	X	X	X	X
Toxicity assessment									X	X	X	X		
ANC and platelet recovery[10]									X					
Disease Response[11]											X		X	

Notes:

H & PE= history and physical examination.

***** CBC will be drawn at least weekly until engraftment.

ǂ ID screening will be done per standard institutional practices

[1] Baseline refers to the period prior to enrolling on trial. Assessments should be made within 60 days prior to start of conditioning.

[2] History and height are only required at baseline.

[3] Vital signs: blood pressure, pulse rate, respiratory rate and temperature.

[4] Serum chemistries panel: electrolytes, BUN, ALT, AST, creatinine, bilirubin. Electrolytes to include sodium, potassium. Creatinine clearance to be calculated at baseline, using Cockcroft-Gault calculation. Comprehensive Metabolic Panel/Basic metabolic panel will be performed based on institutional standard.

[5] Females of reproductive potential only. Will be repeated on day of admission for potential childbearing females.

[6] CMV NAAT weekly (duration per BMT SOP), EBV NAAT every two weeks through D +100.
[7] PFTs (DLCO, FEV1, FVC [adjusted for hemoglobin]) recommended at 100, 180 and 365 days but are not mandatory and ordered at the discretion of the treating physician.
[8] IgG, IgM and IgA.
[9] Peripheral blood flow cytometry to assess recipient immune reconstitution, using standard MCW panel (includes CD3, CD4, CD8, CD20, CD56 and Treg assessment).

[10] Record time to neutrophil engraftment, defined as first of three consecutive days with ANC ≥ 500 x 10^9/L, and platelet engraftment, defined as first day of platelet count ≥ 20,000 x 10^9/L, without transfusion for seven consecutive days.

[11] Leukemia and Myelodysplastic Syndrome: Bone marrow aspirate and biopsy to be recorded within three to four months of HCT and at one year postHCT. After one year, it will be up to the discretion of the treating physician, as indicated clinically. Lymphomas: A PET/CT or CT scan to be recorded around day +100 (±30 days) postHCT. Subsequent need for imaging studies will be up to the discretion of the treating physician as indicated clinically. Myelomas: myeloma panel and bone marrow aspirate and biopsy to be recorded around day +100 post HCT. Subsequent need for bone marrow biopsy and/or myeloma panel will be performed, per the discretion of the treating physician, as indicated clinically.

[12] After 30 days, chimerisms can be checked per physician discretion.

[13] Or until progression.

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LIST OF ABBREVIATIONS

ABW	Actual Body Weight
AjBW	Adjusted Body Weight
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ASBMT	American Society of Blood and Marrow Transplantation
AST	Aspartate Aminotransferase
ß-HC	Beta Human Chorionic Gonadotropin
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CPK	Creatinine Phosphokinase
CRF	Case Report Form
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in One Second
FLU	Fludarabine
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GVHD	Graft-Versus-Host Disease
HAPLO HCT	Haplo Identical Hematopoietic Cell Transplantation
HCL	Hydrochloride
HCT-CI	Hematopoietic Cell Transplant Co-morbidity Index
HCT	Hematopoietic Cell Transplantation
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IBW	Ideal Body Weight
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IWG	International Working Group
LDH	Lactic Dehydrogenase
LV	Left Ventricular
MEL	Melphalan
MM	Multiple Myeloma
MMF	Mycophenolate Mofetil
MPA	Mycophenolic Acid
MRI	Magnetic Resonance Imaging
MUGA	Multigated Acquisition Scan
NCCN	National Comprehensive Cancer Network

NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMA	Non-Myeloablative
NRM	Non-Relapse PFS Mortality
OS	Overall Survival
PBSC	Peripheral Blood Stem Cell
PFS	Progression-free Survival
PFT	Pulmonary Function Tests
PG	Propylene Glycol-Free
RBC	Red Blood Cell
RIC	Reduced-intensity Conditioning
RPR	Rapid Plasma Regain
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TBI	Total Body Irradiation
TID	Three Times Daily
TRM	Transplant-related Mortality
ULN	Upper Limit of Normal
WBC	White Blood Cell

1 INTRODUCTION

1.1 Background

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative modality for a variety of malignant and benign hematological disorders. However, the vast majority of elderly and infirm patients with advanced hematological malignancies are not candidates for myeloablative allogeneic HCT due to unacceptably high rates of toxicities and nonrelapse mortality (NRM), associated with higher-intensity conditioning allografts. During the last two decades, the observed improved rates of NRM in patients receiving non-myeloablative (NMA) or reduced-intensity conditioning (RIC) transplantation have spurred a dramatic increase in the application of RIC allogeneic transplantation in elderly and unfit patients with hematological malignancies. Clinicians using these regimens seek to reduce early transplant-related mortality (TRM), while maintaining reliable rates of hematopoietic and donor-immune cell engraftment to exert a graft-versus-leukemia (GVL) effect. (1)

The decision to use RIC regimens for patients undergoing transplantation is often empirical, and significant variation exists in the selection criteria used by transplant centers. (2) While poor outcomes for elderly patients, following myeloablative transplantation, are well known, (3) Sorror et al. evaluated the impact of medical comorbidities on transplant outcomes by using the Hematopoietic Cell Transplantation - Comorbidity Index (HCT-CI) and reported significantly higher NRM rates and inferior OS in patients with an HCT-CI score of ≥ 3. (4, 5) Based on these data, it is common practice to offer RIC HCT to patients with advanced age (generally > 50–55 years), HCT-CI > 2 (regardless of age), history of prior autologous transplantation or to patients with recent or active invasive fungal infections.

Owing to the plasma half-life of fludarabine (allowing once-daily administration), RIC regimens often use this agent as the lymphocyte-depleting component to facilitate donor-cell engraftment. In the RIC setting, fludarabine is often combined with either busulfan or melphalan. Fludarabine / busulfan-based conditioning (depending on dose intensity) is, however, often complicated by busulfan-related pulmonary toxicity, neurological toxicity (e.g., seizures) and veno-occlusive disease. An M.D. Anderson Cancer Center group pioneered the use of fludarabine melphalan (Flu/Mel) conditioning, which since has gained wide usage. (6) The use of melphalan for conditioning in allogeneic transplantation is based on its convenience, its broad antitumor activity in hematologic malignancies and its immunosuppressive effects, initially described in animal models, but subsequently confirmed by empirical clinical observations. (7) Fludarabine was added to this conditioning regimen because of its potent immunosuppressive effects and its potential synergism with alkylators. The Flu/Mel conditioning regimen can provide long-term disease control, especially in the subset of patients with chemosensitive disease. (6) Recently, TBI (200 cGy) was used in combination with Flu/Mel for patients with advanced lymphoma (n=22) treated with haploidentical HCT (haplo-HCT). With a median follow-up time close to two years, the survival of these mostly advanced, relapsed/refractory patients was very encouraging with OS of 54% and PFS of 54% for the entire group. (8) TRM was low at day 100 (9.1%) and two years (19%) after transplantation, with stable engraftment achieved in the great majority of patients. Two of four CLL/SLL patients experienced secondary-graft rejection, suggesting that these patients may have a higher risk of engraftment failure and should be closely monitored in the early post-transplantation period. Although the numbers were low, the results were comparable with the NMA Flu/Cy/TBI (Table 1).

TABLE 1: Comparison of Haploidentical Transplantation Outcomes for Lymphoma					
Author	**Regimen**	**Lymphoma Type**	**N**	**2-yr PFS**	**1-yr NRM**
Brammer et al. (8)	Flu/Mel/Tt/TBI	Hodgkin and NHL	22	54%	19%
Burroughs et al. (9)	Flu/Cy/TBI	Hodgkin	28	51%	05%
Raiola et al. (10)	Flu/Cy/TBI	Hodgkin and NHL	26	63%	04%
Castagna et al. (11)	Flu/Cy/TBI	Hodgkin and NHL	49	65%	16%
Kanakry et al. (12)	Flu/Cy/TBI	NHL	69	63%	10%
Kanate et al. (13)	Flu/Cy/TBI	Hodgkin and NHL	185	50%	11%

In theory, intensifying the dose of melphalan in Flu/Mel conditioning could provide better disease control post-HCT, allowing more time for curative GVL effects to emerge. Attempts to escalate the dose intensity of Flu/Mel conditioning (to melphalan doses >140mg/m^2), however, have been complicated by melphalan-related renal, hepatic, pulmonary and gastrointestinal toxicities.(6) Moreover, the current commercial formulation of melphalan (Alkeran®), used off-label as part of autologous and allogeneic HCT, has several limitations when given at these higher doses, based on its marginal solubility that prevents the solution from being administered as a longer infusion. The commercial Alkeran® product must be reconstituted with a sterile diluent that contains propylene glycol, a substance that has been associated with toxic side effects (e.g., hyperosmolality, increased anion gap metabolic acidosis [due to lactic acidosis], acute kidney injury, sepsis-like syndrome, allergic contact dermatitis, hemolysis, central nervous system depression, seizures, arrhythmias and nephrotoxicity).(14–16). After reconstitution of Alkeran®, an impurity (citrate derivative of melphalan) can develop in < 30 minutes and, when further diluted, the potency of melphalan is rapidly lost over time. A single dose of Alkeran®, which is administered at 200 mg/m^2, contains 24 g/m^2 of propylene glycol. Hence, this dose of Alkeran® would include a propylene glycol dose of about 45 g for a 70 kg patient (Alkeran® for injection PI, 2008). If this dose of Alkeran® is infused into the body for myeloablative conditioning in as little time as 15 minutes, due to the limited stability of the product after reconstitution, then, the infusion rate of propylene glycol would be high at 180 g/h, or nearly 60 times faster than the recommended rate. As stated above, such doses of propylene glycol may be associated with renal toxicity and metabolic acidosis.

A number of studies designed to assess the efficacy of high-dose melphalan, followed by autologous HCT have included information regarding dose-limiting toxicities, but not necessarily information about common adverse effects. Despite hematopoietic progenitor cell rescue, myelosuppression with neutropenia and thrombocytopenia occur in all patients. (17, 18) Both the severity and duration of myelosuppression are dose dependent. Gastrointestinal toxicity is the major non-hematological toxicity of high-dose melphalan; it includes mucositis, nausea, vomiting and diarrhea. Although melphalan does not appear to be cardiotoxic like other alkylating agents, atrial fibrillation has been reported after high-dose melphalan administration, particularly in elderly patients. In addition, pulmonary toxicities, such as pulmonary fibrosis, are a rare and late complication of melphalan.

The substitution of Captisol® in propylene glycol-free melphalan for injection (EVOMELA®) for injection (Spectrum Pharmaceuticals, Inc.) for the excipients found in Alkeran® directly overcomes the formulation limitations noted with Alkeran®. Captisol® is a substituted ß-

cyclodextrin that serves as the major functional excipient in (EVOMELA®). When the formulation is administered intravenously, the equilibrium between melphalan and melphalan-Captisol® complex rapidly shifts in favor of melphalan, due to its dilution by blood and the distribution and binding of melphalan to body tissues and blood components. Moreover, melphalan for injection (propylene glycol free) has been shown to be stable for 10 to 24 hours once reconstituted. It may be refrigerated (which extends the use time).

1.2 Nonclinical Experience

1.2.1 Melphalan

Spectrum conducted one nonclinical study to support the use of melphalan for injection (propylene glycol free). The only difference between the Alkeran® for injection formulation and the proposed EVOMELA® is Captisol®. Therefore, the pharmacokinetics (PK) of melphalan were evaluated, following intravenous administration in Sprague-Dawley® rats of a nominal 2 mg/kg melphalan dose, prepared in either a Captisol® or nonCaptisol® (propylene glycol) formulation. (19). There were no significant differences in the mean whole-blood and plasma AUC profiles or in the urinary excretion of melphalan, following intravenous administration, suggesting that the change from a propylene glycol to Captisol® formulation does not affect melphalan PK. Melphalan is an older drug with a history of clinical use since the 1960s. Approved labeling for both the oral and intravenous formulations of melphalan (Alkeran®) support the relatively low clinical doses of melphalan used in multiple cycles of induction chemotherapy for MM. While Alkeran® for injection has not been approved for high-dose (200 mg/m^2 or 100 mg/m^2/day for two days) conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation, it has been successfully used and is the standard of care in the clinic for this indication. The nonclinical data in the paragraphs below are excerpted from the current Alkeran® labeling. Melphalan is a bifunctional (interstrand and intrastrand) alkylating agent that is noncell-cycle specific. It is actively transported into cells by the high-affinity L-amino acid transport system. It exerts an intracellular cytotoxic effect through the formation of interstrand or intrastrand DNA; cross-links or DNA protein cross-links via the two chlorethyl groups of the molecule (alkylation). This leads to impairment of DNA replication and mitotic division and eventually cell death. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells (PACKAGE INSERT DATA: Alkeran® [melphalan hydrochloride] kit. GlaxoSmithKline LLC, Research Triangle Park, North Carolina).

Melphalan acute toxicity, following intravenous administration, was evaluated in the rat and following oral and intraperitoneal administration in mouse and rat. The intravenous median lethal dose (LD_{50}) was determined to be 5.1 and 6.6 mg/kg in male and female rats, respectively. These doses are equivalent to 30.6 and 39.6 mg/m^2 in the male and female rat, respectively, indicating that in animal studies melphalan cannot be administered at doses high enough to support melphalan high-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in humans. Melphalan has been shown to cause chromatid or chromosome damage in humans and was considered to be carcinogenic because chronic administration by intraperitoneal injection produced lymphosarcomas and dose-related increase in lung tumors in mice and peritoneal tumors in rats. Melphalan was embryolethal and teratogenic in rats, following oral and intraperitoneal administration. It has been reported that Alkeran® for injection may cause local tissue damage should extravasation occur, and melphalan was determined to be a mild irritant, following topical application (PACKAGE INSERT DATA: Alkeran® [Melphalan hydrochloride] kit. GlaxoSmithKline LLC, Research Triangle Park, North Carolina).

The acute LD_{50} and chronic administration data indicate that nonclinical species demonstrate toxicity consistent with that seen in humans but at lower doses. Nonclinical studies could not be conducted at dose levels equivalent to the anticipated daily human dose of 100 mg/m2, based on the observed intravenous LD50 values of 5.1 and 6.6 mg/kg (equivalent to 30.6 and 39.6 mg/m2) in male and female rats, respectively. The primary dose-limiting toxicity of therapy relates to the myeloablative pharmacological effect of melphalan — the desired pharmacological activity in the clinical patient population. The high-dose melphalan clinical data (20–22) support the conduct of well-controlled clinical trials with high-dose melphalan for conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with MM.

1.2.2 Captisol®

Captisol® is the major excipient in the propylene glycol-free melphalan for injection (EVOMELA®) formulation. There was no mortality or other evidence of toxicity observed in the single-dose intravenous toxicity studies in which 2,000 mg/kg Captisol® was administered over 10 or 20 seconds in the mouse and rat, respectively. In repeat-dose toxicity studies, vacuolation of renal tubular epithelium cells was observed in rats, dogs and monkeys. This type of vacuolation is commonly seen in animals given substituted ßcyclodextrins. There was no evidence of degeneration, necrosis or pseudocrystal formation in the epithelial cells at doses ≤1,000 mg/kg/day for one month in rats, ≤1,500 mg/kg/day for one month in dogs or ≤5,600 mg/kg/day for 14 days in monkeys. There was no evidence to suggest a deterioration of renal function, and vacuolation was largely reversible. There was no evidence of mutagenicity and no effects on the reproductive function of rats or rabbits were observed in the studies conducted with Captisol®. (23) In conclusion, intravenous toxicity studies with Captisol® doses as high as 1,000 mg/kg/day (equivalent to 6,000 mg/m^2/day) in rats, 1,500 mg/kg/day (equivalent to 30,000 mg/m^2/day) in dogs and 5,600 mg/kg/day (equivalent to 67,200 mg/m^2/day) in monkeys did not produce toxicologically significant findings suggestive of a risk to humans. The recommended dose for EVOMELA® is 200 mg/m^2 which is equivalent to 5,400 mg/m^2/day, based on a 70-kilogram patient with a BSA of 1.8 m^2).

1.3 Previous Clinical Experience

EVOMELA® has been analyzed in humans in two studies to date. The first clinical study of EVOMELA®, Study *CDX-353-001*, established bioequivalence to Alkeran® for Injection. (24) Based on a noncompartmental analysis, the geometric mean ratios for estimated C_{max}, AUC0-∞, and AUC0-t for EVOMELA® to Alkeran® for injection at high dose (100 mg/m2) were 112.00%, 110.90% and 110.77%, respectively; and the associated 90% confidence intervals were contained within the 80% to 125% bioequivalence guidelines established by FDA. Myeloablation and engraftment rates were measured in all patients as a measurement of efficacy in this preliminary efficacy study. All 24 patients exhibited myeloablation and engraftment after administration of the two doses of melphalan at 100 mg/m^2. The median times to myeloablation and engraftment were three days (postgraft) and 11 days (postgraft), respectively.(24) The safety profile was consistent with that already established for high-dose melphalan when given as a conditioning regimen with autologous HCT [Ligand Pharmaceuticals, Inc. Investigational Drug Brochure v3 August 2012]. The phase II, open-label study was the only one where 200 mg/m^2 dose of EVOMELA® was administered to MM patients.(25) This study enrolled 61 MM patients, who received 200 mg/m^2 of CE-melphalan (100 mg/m^2/day x 2), followed by ASCT. The majority of the subjects were male (57%) with a median age of 62 years (range 32–73) and included 56 (92%) subjects receiving upfront auto-HCT and five (8%) after relapse. Median lines

of prior therapy were three (range 2–16). All subjects achieved myeloablation, followed by successful engraftment. Median time to neutrophil engraftment was 12 days post-HCT (range: 10–12); time to platelet engraftment was 13 days (range 10–28). There was no mortality by day100, and as expected, the most common Grade 3 and 4 toxicities were hematologic. Severe mucositis was reported in few patients (Grades 3/4; 10%). At day 100 post-HCT, all patients (100%) had a response with 82% of subjects achieving a >= very good partial response (VGPR) response, including stringent CR in 13%, CR in 8% and VGPR in 61%. (25) Notably, the dosage schema reported did not use the more common approach of a single infusion of melphalan of 200 mg/m2.

The EVOMELA® formulation does not need a second vial of solvent for reconstitution and can be dissolved directly, using saline with relatively small volumes of infusate required to deliver a given high dose. Moreover, it is stable at room temperature for at least four hours upon reconstitution, followed by immediate dilution. This leads to less handling of this cytotoxic agent by pharmacy and nursing staff with a concomitant decrease in exposure risks and an increase in convenience, as well as administration flexibility.

1.4 Rationale for Study

The preliminary data suggest that the substitution of Captisol® in EVOMELA® for the excipients found in Alkeran® directly overcomes the formulation limitations and provides a potentially safer melphalan formulation for administration at higher doses used in HCT conditioning regimens. Based on these observations, we now propose a phase II study of a RIC regimen, consisting of EVOMELA,® in combination with fludarabine and TBI for patients undergoing haplo-HCT. The study will investigate the safety and tolerability of this conditioning approach. While the FDA indication for EVOMELA® is for myeloablative conditioning prior to autologous HCT in patients with multiple myeloma, we anticipate our study will provide critical preliminary data to explore this formulation in allogeneic HCT conditioning.

Given the bioequivalence between Alkeran® and Captisol®, as detailed in section 3.3 (24), 100 mg/m^2 or 140 mg/m^2 of propylene glycol-free melphalan for Injection (EVOMELA®) on day -6 were selected as the dose for the study drug in this study. Fludarabine (40 mg/ m^2/day intravenously on days -5,-4, -3, -2) and TBI (200 cGy; day -1 [or 200 cGy on days -2 and -1]) are administered, based on current clinical practice. Because of observed mucosal toxicity (nausea, vomiting, diarrhea and mucositis) with Flu/Mel-100/400 cGY TBI conditioning option in elderly patients (n=2) enrolled to date (as of 5/22/2018), we decided to amend the protocol to reduce melphalan and TBI does for elderly and frail patients to Flu/Mel-70/200 cGY TBI. This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonization (ICH) guidelines.

2 STUDY OBJECTIVES

2.1 Primary Objective

1. To assess one-year progression-free survival (PFS) of patients with hematological malignancies undergoing propylene glycol-free melphalan for Injection (EVOMELA®), fludarabine, (FLU) and total-body irradiation-based reduced-intensity conditioning (RIC) for haploidentical hematopoietic cell transplantation (haplo-HCT).

2. To determine the safety of EVOMELA®/Flu/TBI-based RIC haplo-HCT.

2.2 Secondary Objectives

1. To assess OS following RIC haplo HCT at one year and two years.
2. To assess NRM following RIC haplo-HCT at day +100 and one year.
3. To assess relapse rate following RIC haplo-HCT at day +100 and one year.
4. To assess time from RIC haplo-HCT to neutrophil and platelet recovery.
5. To assess rates of acute graft-versus-host disease (GVHD) at day +100 and +180.
6. To assess rates of chronic GVHD at 1-year post-transplantation.
7. To assess lineage specific chimerism kinetics of donor cells (or FISH XX/XY per physician discretion) following PG-Mel/Flu/TBI-based RIC haplo-HCT at baseline (approximately day +30), and day +100.
8. To determine kinetics of immune reconstitution following RIC haplo-HCT at baseline (approximately day +30), day +100, day +180, day +365.
9. To assess rates of primary graft failure.
10. To assess rates of primary and secondary graft rejection.

3 SELECTION OF SUBJECTS

3.1 Inclusion criteria

1. Patients with a diagnosis of hematological malignancy undergoing a related-donor haploidentical HCT. (Haplo-identical donor is defined as below:

   Patients must be HLA typed at high resolution, using DNA-based typing at the following HLA loci: HLA-A, -B, -C and DRB1 and have available:
   A related haploidentical donor with two, three or four HLA-mismatches.
   An unidirectional mismatch in either the graft-versus-host or host-versus-graft direction is considered a mismatch. The donor and recipient must be HLA identical for at least one antigen (using high-resolution DNA-based typing) at the following genetic loci: HLA-A, HLA-B, HLA-C, and HLA-DRB1. Fulfillment of this criterion shall be considered sufficient evidence that the donor and recipient share one HLA haplotype and typing of additional family members is not required.

2. Patients ≥18 are eligible.
3. Bilirubin ≤ 2 x the ULN. For patients with Gilbert's syndrome or suspected mild veno-occlusive disease, bilirubin ≤ 3 x ULN is permitted.
4. Adequate renal function, as defined by a serum creatinine clearance of ≥ 30 mL/min, calculated by Cockcroft-Gault equation.

5. Left ventricular ejection fraction ≥40%. No uncontrolled arrhythmias or New York Heart Association class III-IV heart failure.

6. FEV1 or DLCO (diffusion capacity; corrected for hemoglobin) ≥ 50% of predicted.

7. Karnofsky Performance Status Scale Index score ≥ 60.

8. Graft source of either peripheral blood (the infused CD34+ cell dose will be capped at 5 x 10^6 CD 34+ cells/kg recipients actual body weight) or bone marrow (the ideal infused TNC dose will be targeted at 4 x 10^8/kg recipient actual body weight) at the discretion of the transplant physician.

9. A negative pregnancy test will be required for all women of childbearing potential. Females of childbearing potential should agree to practice two effective methods of contraception, from the time of signing the informed consent form through 90 days after the last dose of study drug. They must adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.). Breast-feeding is not permitted.

10. Male patients, even if surgically sterilized (i.e., status postvasectomy), must agree to one of the following: practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, or agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

11. No evidence of uncontrolled bacterial, viral or fungal infections at the time of enrollment.

12. Transplant recipient able to give informed consent.

3.2 Exclusion Criteria

1. Patient must not have a healthy, eligible and readily available HLA-identical sibling donor or a volunteer adult unrelated donor (matched at allele-level at HLA-A, -B, -C and -DRB1).
2. No serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
3. Presence of active disease in AML/MDS: patients with active disease defined as >5% blasts in bone marrow and/or circulating leukemic blasts in peripheral blood, patients with known active central nervous disease involvement with leukemia/lymphoma or lymphoma patients with progressive disease on clinical and/or radiographic assessment are not eligible for this study.

4. STUDY ENTRY AND WITHDRAWAL; STUDY PROCEDURES

4.1 Study Entry Procedures

4.1.1 Required Preregistration Screening Tests and Procedures

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

The following procedures will be performed at specified intervals; please refer to the study calendar . Screening assessments must be performed < 60 days prior to planned initiation of conditioning. Any results falling outside of the reference ranges may be repeated at the investigator's discretion. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

4.1.2 Registration Process

- All patients who are consented will be registered in OnCore®, the MCW Cancer Center clinical trial management system. The system is password protected and meets HIPAA requirements.
- Eligible patients will be identified by the Clinical Trials Office, which will register the patients.
- All source documents that support eligibility include a signed informed consent/HIPAA and signed eligibility checklist. These must be available for review and verification.

4.1.3 Pretreatment Period

Baseline Assessments
After a patient signs the consent form, the baseline procedures and assessments must be completed within ≤60 days from the planned initiation of conditioning, unless otherwise indicated.

- Complete medical history (only required at baseline), physical examination, height and weight.
- Vital signs: blood pressure, pulse rate, respiratory rate and temperature.
- Karnofsky Performance Status Scale score.
- Complete blood count (CBC) with differential.
- Serum Chemistries
- CT/PET.
- Infectious disease markers: HIV, EBV, CMV, hepatitis B surface antigen and HCV. If the

HCV antibody is positive, a screening HCV RNA by any RT-PCR or bDNA assay must be performed. Patients with HIV or Hep B positivity will be excluded from the study.

- B-HCG serum pregnancy test for females of childbearing potential.
- Additional viral testing (EBV/Adeno/CMV) will be performed at the discretion of the treating physicians.
- Pulmonary function tests (PFT), including DLCO (adjusted for hemoglobin) and FEV1.
- Echo or MUGA.
- Sorted chimerisms (or FISH XX/XY per physician discretion).

4.2 Study Procedures during Treatment

4.2.1 Day -6 through Day -1

- Physical examination.
- Vital signs: blood pressure, pulse rate, respiratory rate and temperature.
- Complete blood count (CBC) with differential.
- Serum Chemistries

For patients <60 years old:

- Melphalan**:** 140 mg/m^2/day IV on Day -6.
- Fludarabine: 40 mg/ m^2/day IV Days -5, -4, -3, -2.
- Total-body irradiation: 200 cGy on Day -1.

For patients with age ≥60 years and/or HCT-CI score of >3 will have the option of receiving the following regimen:

- Melphalan: 70 mg/m2/day IV on Day -6.
- Fludarabine: 40 mg/m2/day IV Days -5, -4, -3, -2.
- Total-body irradiation: 200 cGy on Day -1.

4.2.2 Day 0

- Physical exam.
- Vital signs: blood pressure, pulse rate, respiratory rate and temperature.

- Complete blood count (CBC) with differential.
- Serum Chemistry
- CD34/CD3 cell dose infused (peripheral blood or bone marrow graft).
- CMV and EBV.

4.2.3 Follow-Up Visits Post-transplant Evaluations

Patients will be followed for two years post-transplant or until disease progression. The following procedures will be performed at specified intervals; please refer to the study calendar.

- Physical examination, including weight and review of adverse events.
- Vital signs: blood pressure, temperature, respiratory rate, pulse.
- CBC with differential.
- Serum Chemistry
- Bone marrow transplant markers.
- Quantitative immunoglobulins (IgG, IgM, and IgA).
- Bone marrow biopsy and aspirate (to be performed as determined by treating physician to meet standard-of-care clinical needs).
- Chimerisms.
- CMV/EBV/Adeno.
- Acute and chronic GVHD.
- PFTs (DLCO and FEV1, adjusted for hemoglobin).
- Karnofsky Performance Status.
- Assessment of ANC and platelet recovery.

4.3 Duration of Therapy

We plan to accrue a total of 43 haploidentical transplant patients in two and a half years with two years additional follow-up. The study will be closed to accrual after the last patient is enrolled.

4.4 Withdrawal Criteria

The subject has the right to withdraw from the study at any time.

The subject will be withdrawn from the study if:

- There is deterioration in the subject's signs/symptoms and/or the subject develops a disease or condition that, in the opinion of the Investigator, would compromise the subject's safety by continuing in the study.

- In the investigator's judgment, it is in the subject's best interest.

If a subject withdraws prematurely from the trial due to the above criteria or any other reason, study staff should make every effort (at withdrawal) to complete the full set of evaluations scheduled for the end-of-study evaluation. The reason for subject withdrawal must be documented in the CRF.

If a subject withdraws from the study due to an AE (e.g., clinical signs, symptoms or clinically significant laboratory abnormality), the subject will be asked to return to the clinic for the evaluations scheduled for the post-treatment follow-up period, at a minimum. If the AE has still not resolved, additional follow-up will be performed, as appropriate and documented in the subject's medical records. As a minimum requirement, AEs should be followed for seven days after the date of engraftment or until any treatment-emergent AE or laboratory abnormality has resolved or is otherwise explained.

In the case of a subject lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

Withdrawn subjects will not be replaced.

4.5 End Point Analysis

Response assessments for leukemia will be based on the International Working Group (IWG) response criteria (26) (see Appendix 1). Lymphoma response assessments will be performed based on the revised response criteria (27) (see Appendix 2). Treatment responses in multiple myeloma will be assessed based on International Myeloma Working Group (IMWG) response criteria (28) (see Appendix 3).

5 TREATMENT PLAN

All patients may undergo conditioning and post-transplant treatments either as an inpatient or outpatient, as medically appropriate. See the below table for more information.

HLA-Haploidentical, RIC HCT Treatment Plan						
	Days					
	−6	−5	−4	−3	−2	−1
Conditioning						
Evomela 140mg/m^2	●					

FLU 40 mg/m^2/day		●	●	●	●							
TBI 200 cGy						●						
HCT							0					
Post-Transplantation							+3	+4	+5	+35	+100	+180
CY 50 mg/kg							●	●				
MESNA (dosed 100% CY dose)							●	●				
MMF									Start	Stop*		
Tacrolimus									Start	→	Taper*	Stop*
G-CSF 5µg/kg/day									Start^			

Conditioning consists of Evomela 140 mg/m2, FLU 40 mg/m^2, and 200 cGy TBI.
Stem cell infused on Day 0.
^G-CSF begins day +5 after stem cell infusion and continues until engraftment is seen.
Post-transplantation immunosuppression consists of CY (day +3 and +4), MMF and tacrolimus that must begin at least 24 hours after the CY infusion in order to prevent blunting of the alloreactive response needed for effective CY targeting of proliferating lymphocytes.
*If there is no evidence of GVHD.
Please note that patients who are ≥60 years and/or with an HCT-CI >3 can have the option to receive PG-free MEL 70 mg/m2 IV on day -6, FLU 40 mg/m^2 IV days -5 to -2 and TBI dose of 200cGy on day -1.

5.1 Administration Schedule to Transplant Recipients

For patients who are <60 years of age.
EVOMELA®: 140 mg/ m^2/day IV on day -6.
Fludarabine: 40 mg/ m^2/day IV days -5, -4, -3, -2.
TBI: 200 cGy; day -1.
Stem Cell infusion on day 0.
Cyclophosphamide: 50 mg/ kg IV on days +3, +4.
Mesna: 50 mg/kg IV, divided into three doses IV on cyclophosphamide days +3, +4.
Tacrolimus: Dosed per institutional standards starting day +5 to +90, target level 5-**10 ng/ml. Mycophenolate mofetil:** 15 mg/kg PO three times daily (max dose 1gram TID) starting day +5. **MMF** will be stopped on day +35, if there is no evidence of GVHD.
G-CSF: 5 µg/kg subcutaneously daily, starting day +5 until neutrophil recovery.

For patients with age ≥60 years and/or HCT-CI score of >3 will have the option of receiving the following regimen:
EVOMELA®: 70 mg/ m2/day IV on day -6.
Fludarabine: 40 mg/ m2/day IV days -5, -4, -3, -2.
TBI: 200 cGy; days -1
Stem Cell infusion on day 0.
Cyclophosphamide: 50 mg/ kg IV on days +3, +4.
Mesna: 50 mg/kg IV, divided into three doses IV on cyclophosphamide days +3, +4.
Tacrolimus: Dosed per institutional standards starting Day +5 to +90, target level 5-10

ng/mL Mycophenolate mofetil: 15 mg/kg PO three times daily (max dose 1gram TID) starting day +5. **MMF** will be stopped on day +35, if there is no evidence of GVHD.
G-CSF: 5 µg/kg subcutaneously daily, starting day +5 until neutrophil recovery.

5.2 Conditioning Regimen

5.2.1 Propylene Glycol-Free Melphalan for Injection (EVOMELA®)

EVOMELA® will be administered at 140 mg/m^2/day IV on day -6. In patients who are 60 years and older or have an HCT-CI score of >3, EVOMELA® may be administered at 70 mg/m^2 on day -6 (optional).

It will be dosed according to the adjusted body weight, if the patient's actual body weight is greater than the ideal body weight.
If the ideal body weight (IBW) > actual body weight, then, actual body weight will be used.

For the calculation of BSA, actual body weight should be used for patients who weigh less than their IBW. For patients who weigh more than their IBW, BSA should be calculated, based on adjusted body weight.

BSA (m^2) = SQR RT ([Height (cm) x Weight (kg)]/ 3600).

Adjusted body weight= IBW + 0.4(actual weight - IBW).

Institutional standard of care rounding policies may be followed for calculating the final dose of melphalan.

5.2.2 Fludarabine

- Fludarabine dose is based on estimated creatinine clearance.
- Adults: creatinine clearance may be estimated by the Cockcroft-Gault Formula, using actual body weight: CrCl = [(140-age) x weight (kg) x 0.85 (for women only)]/ [72 x creat (mg/dl)].
- Fludarabine will be administered by IV infusion over 30 minutes in a dose of 40 mg/m^2/day on days -5 to -2.
- The dose of fludarabine will be based on actual body weight.

Fludarabine dose, based on creatinine clearance	
Creatinine Clearance ml/min	**Daily Fludarabine Dose (mg/m^2)**
> 60	40
46–60	32 (80% of full dose)

31–45	30 (75% of full dose)
21–30	26 (65% of full dose)

5.2.3 Total Body Irradiation

200 cGy TBI will be given on day -1 at a rate of 6–15 cGy/minutes per radiation oncology standard guidelines.

5.3 Transplantation Procedure

Both peripheral blood and bone marrow graft sources are acceptable for transplantation and will be decided in advance by the transplant physician. Infused peripheral blood product dose will be capped at 5 x 10^6 CD34+ cell/kg recipient actual body weight. (30) Unmanipulated stem cells will be infused on day 0, per Foundation for the Accreditation of Cellular Therapy (FACT) guidelines. Donor bone marrow will be harvested with a target yield of 4 x 10^8 nucleated cells/kg recipient actual body weight. In addition to calculating the total nucleated cell dose, CD34+ cell content in the graft will be calculated by flow cytometry. Unprocessed marrow will be infused on day 0 unless there is a major and/or minor ABO incompatibility, in which case red blood cells and/or plasma will be depleted from the donor marrow in accordance with the institutional practices.

5.4 Post-transplantation Immunosuppression

Immunosuppression to permit engraftment and provide GVHD prophylaxis will be performed with cyclophosphamide (CY), mycophenolate mofetil (MMF) and tacrolimus.

5.4.1 Cyclophosphamide

- On Days +3 and Day +4, CY will be given as a single dose of 50 mg/kg IV.
- Use adjusted body weight.
- Adjusted body weight = IBW + 0.4 (actual weight — IBW).
- If actual body weight is less than ideal body weight, use actual body weight. Post-transplant --
- CY will be given within 48–72 hours of peripheral blood or bone marrow stem cell infusion as a one-hour infusion with MESNA prophylaxis and IV hydration.
- Refer to standard practice guidelines.
- Urine output and signs of hematuria will be monitored closely.
- *To maximize the effectiveness of post-transplant CY, it is critical that immunosuppressive agents are avoided FROM THE MORNING OF STEM CELL INFUSION until 24 hours AFTER the completion of the post-transplant CY, unless there is medical necessity. This includes corticosteroids as anti-emetics.* Standard of care fluids should be used for Cytoxan.

5.4.2 Mesna

Mesna dose will be administered IV at 50 mg/kg based on adjusted body weight, divided into 3 doses (first dose 30 min prior, second dose 4 hours after completion, and 3rd dose 8 hours after completion of Cy) on cyclophosphamide days +3, +4.

5.4.3 Mycophenolate Mofetil

Starting on Day +5 (24–36 hours after last dose of CY), MMF will be given orally at a dose of 15 mg/kg based on adjusted body weight every eight hours.

MMF will be stopped on day +35 if there is no evidence of GVHD.

5.4.3.1 Guidelines for MMF Dose Adjustment and Monitoring

- Initiating MMF therapy: Oral administration of MMF will be at 15 mg/kg orally every eight hours (45 mg/kg/day), starting on Day +5.
- Maximum dose will be capped at 1 gm TID.
- If there is nausea and vomiting at any time preventing the oral administration of MMF, MMF should be administered intravenously at the appropriate dose.

5.4.3.2 Maintaining MMF

- Markedly low (<40%) donor T-cell chimerism after HCT may indicate impending graft rejection.
- MMF should be continued at full dose or if the MMF taper has been initiated, reinstitution of full dose MMF should occur.
- If MMF has been discontinued, MMF should be reinitiated at full dose.

5.4.3.3 Guidelines for MMF Dose Adjustment, Based on Toxicity

If, in the clinical judgment of the attending physician, the observed toxicity is related to MMF administration, a dose adjustment may occur. The discontinuation of MMF at any point should be discussed with the Study PI and should be documented in the permanent medical record and all Case Report Forms (CRF).

5.4.3.4 Gastrointestinal Toxicity

- Severe gastrointestinal toxicities, such as gastrointestinal hemorrhage, have been very rare after non-myeloablative HCT.
- In the event of gastrointestinal toxicity that requires medical intervention, including medication for control of persistent vomiting or diarrhea that is considered to be due to MMF after day 28, a 20% dose reduction will be made or the drug may be given IV.
- If severe refractory diarrhea or overt gastrointestinal bleeding occurs, MMF may be temporarily stopped.
- The MMF should be restarted at 20% reduced dose when the underlying toxicity subsides.

5.4.3.5 Neutropenia

Based on previous experience in patients after non-myeloablative HCT, dose adjustments are likely to occur because of hematopoietic adverse effects, in particular neutropenia.
- A thorough evaluation of neutropenia should occur, including peripheral blood chimerism studies, marrow aspiration and review of marrow-suppressive medications.

- If all other potential causes of marrow toxicity are ruled out, dose adjustments will only

be made for severe, prolonged neutropenia (ANC <500/ul for 5 days or more) that persists after day +21 post-transplant. Dose reductions should be conservative (20%).
- After day +21, the use of G-CSF will be permitted for severe neutropenia. For severe hematological toxicity related to MMF (neutropenia > 5 days refractory to G-CSF), MMF may be temporarily stopped. The MMF should be restarted at 20% reduced dose, when the underlying toxicity subsides. The discontinuation of MMF at any point should be discussed with the study principal investigator and should be documented in the permanent medical record and all CRFs.

5.4.4 Tacrolimus

- Starting on Day +5 (24-36 hours after last dose of CY), tacrolimus will be dosed per institutional standards starting Day +5 to +90, target level 5-10 ng/ml
- Serum levels of tacrolimus should be measured on Day +8 and then at least weekly until Day +30 and the dose adjusted to maintain a level of 5-10 ng/ml.
- Dose reduction should be made if toxicity is present, or if whole blood levels are above the therapeutic range, in the absence of toxicity.
- Tacrolimus will be tapered after Day +100 (adapted dose-reduction to be discontinued by day +180) if there is no evidence of GVHD.

5.4.4.1 Guidelines for Tacrolimus Dose Adjustment and Monitoring

- If there are nausea and vomiting, which prevent oral intake at any time during tacrolimus treatment, the drug should be given intravenously at the appropriate dose that was used to obtain a therapeutic level. (IV: PO ratio = 1: 4).
- Whole-blood trough levels of tacrolimus (i.e., just prior to the next dose) should be obtained on Day +8, and then, twice weekly until the taper is initiated, unless high levels (>20 ng/ml) are detected or toxicity is suspected, in which case more frequent monitoring will be performed, as clinically indicated. The dose should be adjusted accordingly to maintain a level of 5–15 ng/ml.
- Dose reductions should only be made if tacrolimus toxicity is present or levels exceed 20ng/ml, in the absence of toxicity.
- Dose reductions of tacrolimus for high levels without toxicity should be conservative, e.g. 25%, to avoid inadequate immunosuppression.
- If creatinine is greater or equal to two times the baseline level, then the tacrolimus dose will be reduced by 25%.

Medications that Affect Tacrolimus Levels (use with caution)

Decrease Tacrolimus Levels	Increase Tacrolimus Levels
Dilantin	Steroids
Phenobarbital	Fluconazole
Carbamazepine	Ketoconazole
Rifampin	Itraconazole
Caspofungin	Voriconazole*

	Cimetidine
	Macrolide antibiotics
	Calcium channel blockers
	Danazol
	Metoclopramide
* When initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose, (a 67% reduction) and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored, and the dose increased as necessary.	

- Blood pressure, renal function tests (creatinine, BUN), electrolytes and magnesium need to be followed at least two to three times per week, while receiving tacrolimus to full dose, and then, twice weekly or per attending, until tacrolimus is discontinued.
- Tacrolimus levels should be performed more frequently when
    - drug is converted from oral to IV or IV to oral.
    - dose adjustments are made due to levels outside the therapeutic range.
    - voriconazole (see table below) is initiated or withdrawn, if toxicity is suspected.
    - steady-state levels will not be achieved for at least 72 hours after any change in dosing, i.e., levels determined earlier may not reflect an accurate steady state concentration.
- Patients requiring hemodialysis should have tacrolimus levels maintained in the therapeutic range (5 to15 ng/ml).
- Grapefruit and grapefruit juice affect the metabolism of tacrolimus and should be avoided. Oral tacrolimus should be taken consistently with or without food.

5.5 Growth Factor Support

Patients will receive G-CSF at 5ug/kg/day SC starting **at day +5** and continuing until the ANC >500/uL for three days.

6 DISEASE ASSESSMENT

The team will follow standard institutional guidelines for post HCT disease assessment. The following time periods are suggestions, and disease assessments may be performed earlier or later at the discretion of the treating physician.

6.1 Leukemias and Myelodysplastic Syndrome

Bone marrow aspirate and biopsy to be recorded within three to four months of HCT and at one year post HCT. After one year, it will be up to the discretion of the treating physician, as indicated clinically.

6.2 Lymphomas

A PET/CT or CT scan to be recorded around day +100 (±30 days) post HCT. Subsequent need for imaging studies will be up to the discretion of the treating physician as indicated

clinically.

6.3 Myelomas

- Myeloma panel and bone marrow aspirate and biopsy to be recorded approximately day +100 post HCT.
- Subsequent need for bone marrow biopsy and/or myeloma panel will be performed, per the discretion of the treating physician, as indicated clinically.

6.4 Graft Failure and Rejection

6.4.1 Graft Failure

Primary graft failure is defined as the absence of absolute neutrophil count (ANC) recovery after HCT nadir to ≥500/μL by day +35 post HCT.

6.4.2 Graft Rejection

Primary graft rejection is defined as the failure to demonstrate donor-derived hematopoiesis after haplo-HCT (i.e., no evidence of donor-cell chimerisms of ≥5% on unsorted or lineage-specific chimerism analysis [LSCA] at any time point post HCT), while complete loss of donor- cell chimerism (i.e., <5% donor-cells on chimerism analysis) after demonstrating evidence of donor-derived hematopoiesis is termed secondary graft rejection.

6.5 Acute and Chronic GVHD

6.5.1 Acute GVHD

Diagnosis of acute GVHD will ideally require biopsy confirmation in at least one involved organ. When more than one organ is involved, biopsy confirmation of all involved organs is recommended, but not necessary. Liver-only GVHD must be confirmed by biopsy. Acute GVHD will be assessed by consensus criteria (Appendix 4) and graded on Blood Marrow Transplant Clinical Trials Network Manual of Procedures-suggested grading sheets (Appendix 5). Acute GVHD assessment and grading will be performed by treating physicians.

6.5.2 Chronic GVHD

Chronic GVHD diagnosis and grading will be according to NIH Criteria. Please see the appendix.

6.5.3 Clinical Grading of Chronic GVHD (According to Appendix 6)

- None
- Mild chronic GVHD involves only one or two organs or sites (except the lung: see below ‡), with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites).
- Moderate chronic GVHD involves: (1) at least one organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) three or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites).

‡A lung score of 1 will also be considered moderate chronic GVHD. Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site).
‡A lung score of 2 or greater will also be considered severe chronic GVHD.

Presence of limited or extensive chronic GVHD will be also recorded.

7 PHARMACEUTICAL INFORMATION

For the calculation of body surface area, the most recent height and weight available on day -6 will be used. Institutional standard-of-care rounding policies may be followed for calculating the final dose of administered medications.

7.1 Investigational Product (EVOMELA®)

7.1.1 Description

EVOMELA® is a white lyophilized powder containing 56 mg of melphalan for Injection (equivalent to 50 mg of melphalan free base) and 2,700 mg sulfobutylether-beta-cyclodextrin Captisol®. There is also sodium hydroxide and hydrochloric acid, if necessary, present in the product that is used to adjust the pH of the solution prior to lyophilization to a physiologically well-tolerated range of
pH 5.0 ± 1.0. Evomela® will be supplied by the sponsor.

7.1.2 Storage and Administration

Normal saline solution (0.9% sodium chloride injection, USP) is used to reconstitute (8.6 mL) and dilute (for infusion) the product prior to clinical use. After reconstitution with 0.9% normal saline, the concentration of the diluted vial is 5 mg/mL. Immediately, further dilute with 0.9% normal saline to a final concentration equal to 2 mg/mL. EVOMELA® is stable at room temperature for at least four hours after reconstitution, if followed by immediate dilution. EVOMELA® will be supplied by Spectrum in a 20-mL glass vial, Type I, with a 20-mm finish, a 20-mm lyophilization type rubber stopper and a crimp seal. EVOMELA® vials should be stored protected from light and at a controlled room temperature of 20–25 °C (68–77 °F) with excursions permitted between 15 and 30 °C (59 and 86 °F).
Below is an example of the information that may appear on the label of the study medication:

- Spectrum
- EVOMELA® lyophilized powder containing 56 mg melphalan for Injection (equivalent to 50 mg melphalan free base)
- Each vial contains melphalan for Injection, Captisol® and sodium hydroxide
- Reconstitute with normal saline prior to infusion
- Protocol Number IIT-MEL-MCW-001
- Lot number
- Manufacture date
- Manufactured by DSM Pharmaceuticals, Inc., Greenville, North Carolina,
- U.S.A; for Spectrum Pharmaceuticals, Inc., USA
- Storage conditions

7.1.3 Assigning Subjects to Treatment Group

All patients will receive 140 mg/m^2 of EVOMELA® on day -6 administered over 30±5 minutes as a 2-mg/ml solution, followed by fludarabine (40 mg/m^2 IV days -5 to -2) and TBI (200 cGy on day -1). In patients who are 60 years and older, and/or have an HCT-CI score of >3, EVOMELA® may be administered at 70 mg/m^2 on day -6 (optional).

7.1.4 Study Medication Accountability

The investigator/pharmacist must maintain accurate records of study drug disposition, patient administration (including date and time), in addition to noting any accidentally destroyed drugs. At the end of the study, information describing study drug supplies (e.g., lot numbers) and disposition of supplies for each patient must be provided, signed by the investigator. If any errors or irregularities in any shipment of study medication to the site are discovered at any time, Spectrum must be contacted immediately.

At the end of the study, all medication not dispensed or administered, and packaging materials will be collected with supervision of the monitor and returned to Spectrum or destroyed on site, as dictated by the appropriate SOP at this institution.

7.1.5 Blinding/Masking of Treatments

This is an open-label study. All patients enrolled in the study will receive EVOMELA® on day -6 prior to haplo-HCT. No blinding or masking of the study drug will occur.

7.1.6 Treatment Administration

EVOMELA® will be infused over 30±5 minutes in a 2-mg/mL solution via a central venous catheter by a trained health care professional. Records of study medication administered (date, time and dose administered relative to reconstitution time) will be recorded in the patient's CRF.

EVOMELA® will be administered at 140 mg/m^2/day IV on day -6. In patients who are 60 years and older, and/or have an HCT-CI score of >3, EVOMELA® may be administered at 70 mg/m^2 on day -6 (optional). It will be dosed according to the adjusted body weight, if the patient's actual body weight is >100% of the ideal body weight.

If the ideal body weight (IBW) > actual body weight, then, actual body weight will be used. For the calculation of BSA, actual body weight should be used for patients who weigh less than their IBW. For patients who weigh more than their IBW, BSA should be calculated, based on adjusted body weight.

BSA (m^2) = SQR RT ([Height (cm) x Weight (kg)]/ 3600).
Adjusted body weight= IBW + 0.4(actual weight IBW).

7.2 Fludarabine

7.2.1 Description

Fludarabine's active metabolite 2-fluoro-ara-A is an antimetabolite that inhibits DNA primase, DNA polymerase alpha and ribonucleotide nuclease. This is commercially available.

7.2.2 Dosage and Administration

Fludarabine monophosphate is commercially available as a 50-mg vial, which is reconstituted with 2 ml of sterile water, resulting in a 25-mg/ml solution. The desired dose is further diluted to concentrations of 0.04–1 mg/ml in normal saline or 5% dextrose (50–100ml) for injection and will be administered by IV infusion over 30 minutes or longer.

Fludarabine will be administered by IV infusion over 30 minutes in a dose of 40 mg/m^2/day on days -5 to -2. The dose of fludarabine is based on actual body weight.

7.2.3 Side Effects and Toxicities

- The dose of fludarabine used in this protocol is nonmyeloablative; however, it can cause severe immunosuppression, particularly in the CD4+ T-cell compartment. Immunosuppression increases the risk of infection, which can be life threatening. Immunosuppression observed with the use of fludarabine increases the risk of infection, which can be life threatening.

- In addition, clinical toxicities of fludarabine monophosphate include myelosuppression, primarily lymphopenia and granulocytopenia, alopecia, rash, dermatitis, nausea, vomiting, anorexia, stomatitis, diarrhea, somnolence, fatigue, peripheral neuropathy, mental status changes, cortical blindness, hepatocellular toxicity with elevation in serum transaminases, neurotoxicity and interstitial pneumonitis. These effects are reversible when the drug is discontinued.

7.3 Total Body Irradiation

- TBI, given at high doses in conventional transplants, may cause nausea, vomiting, diarrhea, temporary hair loss and painful swelling of the salivary glands for a few days.
- TBI may destroy normal marrow cells, in addition to the cancer cells. The dose of TBI (200 cGy,) used in this protocol is about one-sixth of that used in conventional transplant protocols and severe acute side effects have so far not been observed. TBI has been associated with causing sterility and there is a risk of major genetic damage to any children conceived after transplantation. There is a risk that a small percentage of patients may develop a secondary cancer resulting from this treatment.

7.4 Cyclophosphamide

7.4.1 Description

Cyclophosphamide is an alkylating agent, which prevents cell division primarily by cross-linking DNA strands. Cyclophosphamide is cell-cycle nonspecific. Cyclophosphamide is not stem cell toxic.

7.4.2 Storage and Administration

Cyclophosphamide for injection is commercially available in 2000-mg vials, which are

reconstituted with 100-ml sterile water for injection. The concentration of the reconstituted product is 20 mg/ml. The calculated dose will be diluted further in 250–500 ml of dextrose 5% in water. Each dose will be infused over one to two hours (depending on the total volume).

Cyclophosphamide 50 mg/ kg IV will be administered on days +3 and +4.

7.4.3 Side Effects and Toxicity

Clinical toxicities of cyclophosphamide include alopecia, nausea and vomiting, headache and dizziness, hemorrhagic cystitis, cardiotoxicity, immunosuppression, myelosuppression, pulmonary fibrosis, increased hepatic enzymes and syndrome of appropriate antidiuretic hormone (SIADH).

7.4.4 Precautions

Avoid steroids (>10 mg prednisone/equivalent) from day 0 until 24 hours after completion of cyclophosphamide.

7.5 Mesna

7.5.1 Description

Mesna is a prophylactic agent used to prevent hemorrhagic cystitis induced by the oxazaphosphorine (cyclophosphamide and iphosphamide). It has no intrinsic cytotoxicity and no antagonistic effects on chemotherapy. Mesna binds with acrolein, the urotoxic metabolite produced by oxazaphosphorine, to produce a nontoxic thioether and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxazaphosphorine.

7.5.2 Storage and Administration

Mesna is commercially available in 200-mg, 400-mg and 1000-mg vials containing a 100-mg/ml solution. Each dose of mesna will be diluted further in 50 ml of normal saline to be infused over 15 minutes. Mesna dose will be administered IV at 50 mg/kg, divided into three doses on cyclophosphamide days +3 and +4.

7.5.3 Side Effects and Toxicity

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.

7.6 Tacrolimus

7.6.1 Description

Tacrolimus, also known as FK-506, is a macrolide immunosuppressive agent and is commercially available. Tacrolimus inhibits lymphocytes by forming a complex with FKBP-12, calcium and calmodulin, leading to the decrease in the phosphatase activity of calcineurin. Calcineurin mediates the first intracellular signal required for T-cell activation after antigen

recognition by the T-cell receptor. This drug is used with corticosteroids for prophylaxis of organ rejection in patients receiving allogeneic liver transplants and for prophylaxis of GVHD in the setting of HCT. It also is used for immunosuppression after kidney, cardiac, pancreas, pancreatic islet cell and small bowel transplantation. This drug is well absorbed orally. It is metabolized in the liver by unknown mechanisms, but demethylation and hydroxylation have been proposed based on *in vitro* studies. The metabolized products are excreted in the urine.

7.6.2 Dosage and Administration

Oral
Tacrolimus 0.06 mg/kg, PO every 12 hours starting day +5 to +90. Target level 5 to 15 ng/ml. For better absorption, it is recommended that tacrolimus capsules be taken on an empty stomach.

Tacrolimus should not be taken with grapefruit juice as it may increase blood levels. If a patient vomits within one hour of oral administration, repeat the dose. If vomiting persists, switch to IV administration.

Conversion from IV to PO dosing of tacrolimus.
Patients should be converted to an oral dose at four times the IV dose to be given in divided (Q 12 hour) doses.

7.6.3 Side Effects and Toxicities

- **Renal** – Rise in serum creatinine, hemolytic uremic syndrome.
- **Neurological** – Peripheral: paresthesia, tremor. Central: seizures, headache, insomnia, dizziness, depression, confusion, hallucinations, psychosis, myoclonus, neuropathy, agitation.
- **Gastrointestinal** – Nausea, vomiting, anorexia, constipation, diarrhea.
- **Cardiovascular** – Hypertension, myocardial hypertrophy.
- **Endocrine** – Hyperglycemia, hyper/hypokalemia, hypophosphatemia, hypomagnesemia.
- **Integument** – Itching, rash.
- **Hematologic** – Leukocytosis, thrombocytopenia, leukopenia, anemia, PTLD, thrombotic microangiopathy.
- **Liver** – Abnormal liver function tests.
- **Ocular** – Blurred vision, photophobia.
- **Respiratory** – Pleural effusion, atelectasis, cough, dyspnea.
- **Musculoskeletal** – Arthralgia.

7.7 Mycophenolate Mofetil (MMF)

7.7.1 Description

MMF is the morpholinylethylester of mycophenolic acid (MPA) and reversibly inhibits inosine monophosphate dehydrogenase, particularly the type II isoform that is more prominent in activated lymphocytes. As a result of the inhibition of *de novo* purine synthesis, proliferation of B and T lymphocytes is blocked, and antibody production is inhibited. MMF is commercially available.

7.7.2 Storage and Administration

MMF is available in an oral and an intravenous formulation. The oral formulation is supplied in 250-mg hard gelatin capsules and can be stored at room temperature. MMF for IV administration is supplied as a lyophilized powder in a glass vial containing the equivalent of 500 mg. Mycophenolate mofetil will be administered at 15 mg/kg PO three times daily (max dose 1 gram three times a day) starting day +5 and stopped on day +35, if there is no evidence of GVHD.

7.7.3 Side Effects and Toxicity

MMF has been studied extensively among patients after non-myeloablative HCT. Previous clinical studies in patients after allografting suggest that the principal adverse reactions associated with the administration of MMF include nausea, vomiting, neutropenia, diarrhea and on one occasion bloody diarrhea. In the setting of marrow transplantation, several etiologic factors may contribute to alterations in gastrointestinal and hematologic parameters. MMF has an increased incidence of digestive system adverse events, including GI tract ulceration, and hemorrhage (3% of patients receiving MMF). GI tract perforations have rarely been observed. Most patients in these studies were also on other drugs known to be associated with these complications. Up to 2% of patients receiving MMF for prevention of rejection developed severe neutropenia (ANC <500). The development of neutropenia may be related to MMF itself, concomitant medications, viral infections or some combination of these causes. MMF dose adjustments will be made if clinically indicated if in the opinion of the attending physician, no other cause is thought to be responsible for the abnormality. These adjustments should be discussed with the principal investigator and documented in the medical records and the clinical reporting form (CRF).

7.8 Prophylaxis and Other Therapy

7.8.1 Hematopoietic Growth Factors

Filgrastim is required. Administer filgrastim 5 micrograms/kg/day subcutaneous (SC) (may be rounded to the nearest vial), based on actual body weight, beginning on Day +5. In the absence of toxicity, continue filgrastim until the postnadir ANC is ≥ 500 / µL on three consecutive measurements over different days.

7.8.2 Prophylactic Treatment for Opportunistic Infections

All patients will receive prophylaxis against bacterial, fungal and viral infections during the peri-transplant period, according to institutional guidelines.

7.8.3 Antiemetics

Patients will receive antiemetics with conditioning regimen in accordance with institutional guidelines.

7.8.4 Blood Products

Transfusion thresholds for blood-product support will be in accordance with institutional

guidelines.

8. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term “descriptive statistics” refers to number of subjects (*n*), mean, median, standard deviation, minimum and maximum for continuous data and frequencies and percentages for categorical data. The progression-free survival (PFS) and overall survival (OS) postHCT will be calculated, using the Kaplan-Meier estimator and the probabilities of NRM, relapse, neutrophil and platelet recovery, acute and chronic GVHD will be calculated, using cumulative incidence curves to accommodate competing risks, and treating withdrawn subjects as censored subjects. Approximately 95% confidence interval of estimated probability will be reported.

All statistical analyses will be conducted with the SAS® System, Version 9.1.3 or higher.

8.1 Study Design

This is an open-label, single-arm, phase II study. The primary end point of the study is one-year PFS and safety of EVOMELA®/Flu/TBI-based RIC haplo-HCT.

8.2 Safety/Stopping Rules

8.2.1 Stopping Rule for Excess NRM

NRM rate will be the key end point to monitor safety of this approach. Based on historical control data, an NRM rate at day 100 of ≥15% in the current study will be considered unacceptable. We will evaluate and monitor TRM after the first 15 and 25 patients enrolled the study. Assuming 15% of TRM occurring will stop the enrollment for protocol review. A Pocock- type boundary with the lower limit of 95% confidence interval will be used for monitoring TRM. At planned interim monitoring points, if no more than six or seven TRMs occur, the study will continue to its full enrollment of 43.

8.2.2 Stopping rule for excess primary graft rejection

Primary graft rejection rate of ≥20% by day +45 would be considered unacceptable.

8.3 Accrual Estimate

We plan to accrue 43 haploidentical transplant patients in two and a half years.

8.4 Accrual and Follow-up Period

The expected accrual period is two and a half years with two years additional follow-up. The study will be closed to accrual after the last patient is enrolled.

8.5 Sample Size Estimates

The primary end point of the study is one-year PFS. The historical one-year PFS since transplant under standard treatment is 45%. Assuming one-year PFS for haploidentical transplant is 59%. We plan to accrue haploidentical transplant patients in two and a half years with two years additional follow-up. The study will be closed to accrual after the last patient has been enrolled.

Based on exponential distribution and on a one-sided test with significance level of 5%, we will have 80% power to detect at least a 14% increase in one-year PFS for 41 patients. Allowing 5% subjects to be lost to follow-up or withdrawn, we plan to accrue 43 patients in the final study.

8.6 Data Collection Methods

The data will be recorded on the OnCore® CRF. The clinical research coordinator must submit a completed CRF for each subject who signs an informed consent form (ICF), regardless of duration. All documentation supporting the CRF data, such as laboratory or hospital records, must be readily available to verify entries in the CRF.

9 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse Event (AE) and Serious Adverse Events (SAE)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to adverse event reporting. This information may be found on the Human Research Protection Program website. (http://www.mcw.edu/hrpp/InvestigatorsandStudyStaff.htm).

Serious AE (SAE) means any untoward occurrence that at any dose:

Definitions

An SAE is defined as any untoward medical occurrence at any dose that:

• **Death**. Results in death.

• **Life threatening**. Is life threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

• **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

• **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

• **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an

infectious agent. 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; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations. Planned hospitalizations will not be considered an adverse event.

9.2 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website. (http://www.mcw.edu/hrpp/InvestigatorsandStudyStaff.htm)

9.3 AE Attribution and Grading

Adverse Event Grading

Grade	Description
0	No AE (or within normal limits).
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention (e.g., packing cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

9.4 Adverse Event Attribution

Attribution is an assessment of the relationship between the AE and the medical intervention.

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

9.5 Relationship Assessment: In-depth Definitions

For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality, based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related**: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure, if necessary.

- **Probably Related**: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related**: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

- **Unrelated**: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.6 Time Period and Grade of AE Capture

AEs will be captured from signing the informed consent through 30 days after last dose of Evomela. CTCAE v4.0 will be used to grade and report AEs.

9.7 Monitoring and Recording an Adverse Event

Definition. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.
Reporting source. AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.
Prior to the trial. Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).
Pretreatment events following signed informed consent. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.
Treatment events. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.
Not serious AEs. For non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

9.8 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management 30 days following the last dose of the Evomela or until they are resolved, if they are related to the study treatment.

9.9 Procedure for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant, or suspects that she is pregnant, while participating in this study, she must inform the investigator immediately and permanently discontinue the study drug. The sponsor-investigator must notify the DSMC by email. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately notify the DSMC by email. Every effort

should be made to follow the pregnancy for the final pregnancy outcome.

Routine Reporting Procedures for AEs

Signs or symptoms reported as adverse events will be graded and recorded by the investigator, according to the CTCAE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

The investigator will assess all adverse events and determine reporting requirements to the MCWCC Data and Safety Monitoring Committee (DSMC) and MCW's Institutional Review Board.

The DSMC will review unexpected grade 3, as well as all grade 4 and 5 adverse events. Nonhematological grade 4 and all grade 5 events must be reported to the DSMC via email within five calendar days of study staff's knowledge. Hematological grade 4 events may be routine reported.

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®.

9.10 Reporting of SAEs

Since this is an investigator-initiated study, the principal investigator, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency, the sponsor- investigator's IRB, and Spectrum Pharmaceuticals, Inc.

9.11 Reporting to the Data and Safety Monitoring Committee

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to the DSMC as soon as possible, but no later than **five** calendar days of the sponsor-investigator's observation or awareness of the event.

As noted, the DSMC will review unexpected grade 3, as well as all grade 4 and 5 adverse events. Nonhematological grade 4 and all grade 5 events must be reported to the DSMC via email within five calendar days of study staff's knowledge. Hematological grade 4 events may be routine reported.

Report Method: The investigator will use email to report SAEs to the DSMC. The SAE report must include event term(s), serious criteria and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE as a guideline whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

9.12 Reporting to MCW Committee Institutional Review Board

The principal investigator must report events to the MCW IRB within **five** business days of his/her awareness of the event. [Guidance on Adverse Event Reporting to the IRB is available online at MCW IRB Policies and Procedures.]

9.13 Reporting to Spectrum Pharmaceuticals, Inc.

When study staff becomes aware of a SAE, they will report to Spectrum Pharmaceuticals, Inc. within **24 hours** of his/her awareness of the event. [Guidance on Adverse Event Reporting to Spectrum Pharmaceuticals, Inc. is available in the contract]

10. REGULATORY COMPLIANCE, ETHICS, AND STUDY MANAGEMENT

10.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

10.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners) and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.3 Prestudy Documentation

Prior to implementing this protocol at Froedtert & the Medical College of Wisconsin, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB.

10.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.5 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families.

Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Potential subjects will be told and a statement will be included that this study is designed to determine both safety and effectiveness. The consent forms will include the approved MCW IRB template language.

Consent forms will be IRB approved and the subject (and legally authorized representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., “Although not required, the subject’s spouse was present during the consenting process and signed as the witness.” Or “Although not required, hospital staff was present for consenting process and signed as a witness.”)

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients that require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB’s policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject’s visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject’s satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject’s study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

10.6 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff, [and the sponsor(s) and their agents]. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized

third party without prior written approval of the principal investigator.

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked clinical research office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the case report forms contain the study identifiers, subject initials, date of birth and date of service.

Personal identifiers, such as name and medical record number, will be removed from accompanying lab reports and test results. Any data/PHI that are not stored for the purposes of the study are shredded in the Clinical Trials Office.

After all study queries and analyses are completed, the data/PHI will not be destroyed but will be archived in a secure long-term storage site in order to keep an accurate record of screened and enrolled subjects for the sponsor and potential audit purposes only specific for this study. Data/PHI would not be destroyed until permission is granted by the sponsor to destroy the records.

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor or other authorized representatives of the principal investigator 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 subjects in this study. The clinical study site will permit access to such records.

10.7 Protection of Human Subjects

10.7.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.7.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information

generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

10.7.3 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment.

The IRB 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. The investigator will submit all protocol modifications to the sponsor and the regulatory authority (ies) in accordance with the governing regulations.

Changes to the protocol may require approval from Spectrum Pharmaceuticals, Inc.

Any deviations from the protocol must be fully documented in the source documents.

10.7.4 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority (ies).

Onsite Audits

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor 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.

High-risk trials are reviewed every six months. Approximately 30% of subject files will be selected randomly for review (a maximum of 10 subjects at each monitoring timepoint). Consent/eligibility and objective-based data will be reviewed for those files selected. One file will be selected randomly for a comprehensive review at each monitoring time point. Regulatory documents (IRB submissions, reportable events, etc.) will be reviewed at each monitoring timepoint.

10.7.5 Data and Safety Monitoring Committee

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). Information on the DSMC is available online (https://www.mcw.edu/Cancer-Center/Clinical-Trials-/Starting-a-Cancer-Clinical-Trial.htm). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety.
- Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others

requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within five calendar days of study staff's knowledge.)

- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for patients.

The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record, as required.

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APPENDICES

Appendix 1 Response Assessment in Leukemia, Lymphoma & Multiple Myeloma

Category	Definition
Complete remission (CR)[1]	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1000/µL); platelet count >100 x 10^9/L (100,000/µL); independence of red cell transfusions.
CR with incomplete recovery (CRi)[2]	All CR criteria except for residual neutropenia (<1.0 x 10^9/L (1000/µL)) or thrombocytopenia (<100 x 10^9/L (100,000/µL).
Morphologic leukemia-free state [3]	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required.
Partial remission (PR)	Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent and decrease of pretreatment bone marrow blast percentage by at least 50 percent.
Cytogenetic CR (CRc)	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow.
Molecular CR (CRm)[4]	No standard definition; depends on molecular target.
Treatment Failure	
Resistant disease (RD)	Patient survives ≥ seven days post-CT; persistent AML in blood or bone marrow.
Death in aplasia	Patient survives ≥ seven days post-CT; death while cytopenic, with aplastic bone marrow.

Death from indeterminate cause	Patients who die < seven days posttherapy; Patients who die > seven days posttherapy with no PB blasts, but no bone marrow examination; Patients who do not complete the first course of therapy.
Relapse[5]	Bone marrow blasts ≥5 percent; or reappearance of blasts in the blood; or development of extramedullary disease.

1. All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after five to seven days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

2. The criterion of CRi is of value in protocols using intensified induction or double-induction strategies in which hematologic recovery is not awaited and intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.

3. This category may be useful in the clinical development of novel agents within phase I clinical trials in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.

4. As an example, in CBF AML, low-level PCR-positivity can be detected in patients, even in long-term remission. Normalizing to 104 copies of ABL1, in accordance with standardized criteria, transcript levels below 10 to 12 copies appear to be predictive for long-term remission.

5. In cases with low-blast percentages (5 to 10 percent), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Appendix 2 Revised Criteria for Lymphoma Response Assessment

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease.	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted, if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared.	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative.
PR	Regression of measurable disease and no new sites.	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes. (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site. (b) Variably FDG-avid or PET negative; regression on CT.	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen.	Irrelevant if positive prior to therapy; cell type should be specified.
SD	Failure to attain CR/PR or PD.	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET. (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT.		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir.	Appearance of a new lesion(s) 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy.	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
Abbreviations: CR, complete remission; FDG, [18F] fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.				

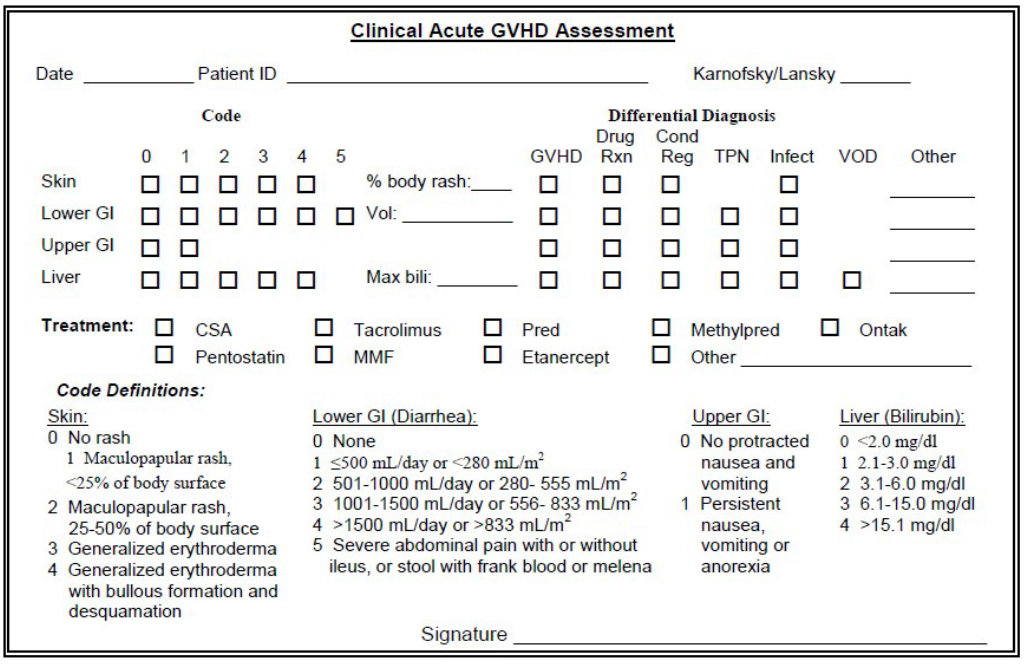
Appendix 3 International Myeloma Working Group Uniform Response Criteria

Response subcategory	Response criteria[1]
CR	Negative immunofixation on the serum and urine and
	Disappearance of any soft tissue plasmacytomas and
	≤5% plasma cells in bone marrow [2]
sCR	CR as defined above plus
	Normal FLC ratio and
	Absence of clonal cells in bone marrow [b] by immunohistochemistry or immunofluorescence [3]
VGPR	Serum and urine M-component detectable by immunofixation but not on electrophoresis or
	90 or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to <200 mg per 24 h
	If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
	If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%
	In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

1. All response categories require two consecutive assessments made at any time before the institution of any new therapy; complete and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
2. Confirmation with repeat bone marrow biopsy not needed.
3. Presence/absence of clonal cells is based upon the k/ ratio. An abnormal k/ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/ of >4:1 or <1;2. Alternatively, the absence of clonal plasma cells can be defined based on the investigation of phenotypically aberrant PC. The sensitivity level is 10-3 (less than one phenotypically aberrant PC within a total of 1000 Pc). Examples of aberrant phenotypes include (1) CD38 +dim and CD56+ strong and CD19- and CD45-; (2) CD38+dim and CD138+ and CD56++ and CD28+; (3) CD138+, CD19- CD56++, CD117+.

Appendix 4 Assessment of Acute GVHD



Clinical Acute GVHD Assessment

Date _____ Patient ID _____ Karnofsky/Lansky _____

	Code							Differential Diagnosis						
	0	1	2	3	4	5		GVHD	Drug Rxn	Cond Reg	TPN	Infect	VOD	Other
Skin	☐	☐	☐	☐	☐		% body rash:____	☐	☐	☐		☐		_____
Lower GI	☐	☐	☐	☐	☐	☐	Vol: _____	☐	☐	☐	☐	☐		_____
Upper GI	☐	☐						☐	☐	☐	☐	☐		_____
Liver	☐	☐	☐	☐	☐		Max bili: _____	☐	☐	☐	☐	☐	☐	_____

Treatment: ☐ CSA ☐ Tacrolimus ☐ Pred ☐ Methylpred ☐ Ontak
☐ Pentostatin ☐ MMF ☐ Etanercept ☐ Other _____

Code Definitions:

Skin:
0 No rash
1 Maculopapular rash, <25% of body surface
2 Maculopapular rash, 25-50% of body surface
3 Generalized erythroderma
4 Generalized erythroderma with bullous formation and desquamation

Lower GI (Diarrhea):
0 None
1 ≤500 mL/day or <280 mL/m^2
2 501-1000 mL/day or 280- 555 mL/m^2
3 1001-1500 mL/day or 556- 833 mL/m^2
4 >1500 mL/day or >833 mL/m^2
5 Severe abdominal pain with or without ileus, or stool with frank blood or melena

Upper GI:
0 No protracted nausea and vomiting
1 Persistent nausea, vomiting or anorexia

Liver (Bilirubin):
0 <2.0 mg/dl
1 2.1-3.0 mg/dl
2 3.1-6.0 mg/dl
3 6.1-15.0 mg/dl
4 >15.1 mg/dl

Signature _____

Appendix 5 Staging/Grading of Acute GVHD

GVHD STAGING

Stage	Skin	GI	Liver
1	< 25% rash	Diarrhea > 500ml/d or persistent nausea	Bilirubin 2-3mg/dl
2	25-50%	> 1000 ml/d	Bilirubin 3-6 mg/dl
3	> 50%	> 1500 ml/d	Bilirubin 6-15 mg/dl
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain ± ileus	Bilirubin > 15 mg/dl

Consensus GVHD Grading (PRZEPIORKA, ET AL.,

Grade	Skin	GI	Liver
I	Stage 1-2	0	0
II	Stage 3 or	Stage 1 or	Stage 1
III	---	Stage 2-4	Stage 2-3
IV	Stage 4	---	Stage 4

Appendix 6 Grading of Chronic GVHD (NIH Criteria)

Check all that apply	Score 0 - None	Score 1 - Mild	Score 2 - Moderate	Score 3 - Severe
Skin: *Clinical features:* ❑Maculopapular rash ❑Lichen planus-like features ❑Papulosquamous lesions or ichthyosis ❑Hyperpigmentation ❑Hypopigmentation ❑Keratosis pilaris ❑Erythema ❑Erythroderma ❑Sclerotic features ❑Poikiloderma ❑Pruritus ❑Hair Involvement ❑Nail Involvement % BSA involved __%	❑No symptoms	❑< 18% BSA with disease signs but NO sclerotic features	❑19-50% BSA, ❑Involvement with superficial sclerotic features "not hidebound" (able to pinch)	❑> 50% BSA ❑Deep sclerotic features "hidebound" (unable to pinch) ❑Impaired mobility, ulceration or severe pruritis
Mouth:	❑No symptoms	❑Mild symptoms with disease signs but not limiting oral intake significantly	❑Moderate symptoms with disease signs WITH partial limitation of oral intake	❑Severe symptoms with disease signs WITH major limitation of oral intake
Eyes: Mean tear test (mm): ❑ > 10 ❑ 6-10 ❑ ≤ 5 ❑ Not done	❑	❑Mild dry eyes symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) ❑Asymptomatic signs of keratoconjunctivitis sicca	❑Moderate dry eyes symptoms partially affecting ADL (requiring eyedrops > 3 x per day or punctual plugs) WITHOUT vision impairment	❑Severe dry eyes symptoms significantly affecting ADL (special eyewear to relieve pain) ❑Unable to work because of ocular symptoms ❑Loss of vision caused by keratoconjuctivitis sicca
Pulmonary **FEV1** ❑Not done **Pulmonary Fibrosis** **Bronchiolitis Obliterans** **Supplemental O2 required?** ❑Yes ❑No	❑No symptoms ❑FEV1> 80% ❑None ❑Not assessed ❑None ❑Yes, clinical ❑Yes, histologic ❑Not assessed	❑Mild symptoms (shortness of breath after climbing one flight of steps) ❑FEV1 60-78% ❑ Minimal radiographic findings	❑Moderate symptoms (shortness of breath after walking on flat ground) ❑FEV1 40-51% ❑Patchy or bi-basilar radiographic findings	❑Severe symptoms (shortness of breath at rest; requiring O_2) ❑FEV1 ≤ 39% ❑Extensive radiographic findings
GI Tract:	❑No symptoms	❑Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (< 5%)	❑Symptoms associated with mild to moderate weight loss (5 – 15%)	❑Symptoms associated with significant weight loss > 15% ❑ Requires nutritional supplement for most caloric needs ❑Esophageal dilation
Liver:	❑Normal LFT	❑Elevated Bilirubin, AP, AST or ALT < 2 x ULN	❑Bilirubin 3 – 10 mg/dl; liver enzymes 2-5 x ULN	❑Bilirubin > 10 mg/dL; liver enzymes > 5 x ULN
Genital Tract:	❑No symptoms	❑Symptomatic with mild signs on exam AND no effect on coitus and minimal discomfort with gynecological exam	❑Symptomatic with moderate signs on exam AND with mild dyspareunia or discomfort with gynecological exam	❑Symptomatic WITH advanced signs (stricture, labial agglutination or severe ulceration) AND severe pain with coitus or inability to insert vaginal speculum

Check all that apply	**Score 0** - None	**Score 1** - Mild	**Score 2** - Moderate	**Score 3** - Severe
Joints and Fascia:	❑ No symptoms	❑ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	❑ Tightness of arms or legs ❑ Joint contractures, erythema thought due to fascitis, moderate decreased ROM AND mild to moderate limitation of ADL	❑ Contractures WITH significant decrease of ROM AND significant limitation of ADLs (unable to tie shoes, button shirts, dress self etc.)

Other indicators, clinical manifestations or complications related to Chronic GvHD (check all that apply).
Assign a score to it's severity based on functional impact, where applicable (0= none, 1=mild, 2 = moderate, 3= severe)

❑ Ascites (serositis) ___	❑ Esophageal stricture or web___	❑ Nephrotic syndrome ___	❑ Pleural effusions ___
❑ Cardiac conduction defects ___	❑ Eosinophilia > 500 µl ___	❑ Pericardial effusion ___	❑ Polymyositis ___
❑ Cardiomyopathy ___	❑ Myasthenia Gravis ___	❑ Peripheral neuropathy ___	❑ Progressive onset___
❑ Coronary artery involvement ___		❑ Platelets < 100,000/µl ___	
❑ Other(s): Specify & score___			

Based on observations checked in the above table, select the severity of chronic GvHD for this assessment (Check only one)

☐ **None**

☐ **Mild chronic GVHD** involves only 1 or 2 organs or sites (except the lung: see below ‡), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites)

☐ **Moderate chronic GVHD** involves: (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). ‡*A lung score of 1 will also be considered moderate chronic GVHD.*

☐ **Severe chronic GVHD** indicates major disability caused by chronic GVHD (score of 3 in any organ or site). ‡*A lung score of 2 or greater will also be considered severe chronic GVHD.*