Reduced-Intensity Fludarabine, Melphalan, and Total Body Irradiation Conditioning for Transplantation of HLA-Haploidentical Related Hematopoietic Cells (Haplo-HCT) For Patients With Hematologic Malignancies

Protocol Number: MCC 20131

NCT Identified Number: NCI-2019-08483

Principal Investigator:	**Nelli Bejanyan, MD**
IND number:	**144792 Exempt**
Biostatistician:	**Jongphil Kim, PhD**

Funded by: **Moffitt Cancer Center**

Version Number: v 10

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

Reduced-Intensity Fludarabine, Melphalan, and Total Body Irradiation Conditioning for Transplantation of HLA-Haploidentical Related Hematopoietic Cells (Haplo-HCT) For Patients With Hematologic Malignancies

Study Description:

This is a single arm, phase II trial of HLA-haploidentical related hematopoietic cells transplant (Haplo-HCT) using reduced intensity conditioning (fludarabine and melphalan and total body irradiation). Peripheral blood is the donor graft source. This study is designed to estimate disease-free survival (DFS) at 18 months post-transplant.

Objectives:

Primary Objective: The primary objective is to estimate probability of the 18 months DFS after a HLA-haploidentical related hematopoietic cells transplant (Haplo-HCT) using a reduced intensity conditioning regimen with fludarabine/melphalan/total body irradiation (TBI) conditioning for patients with advanced age or comorbidities.

Secondary Objectives:

- Incidence of day 100 grade II-IV and grade III-IV acute graft versus-host-disease (GVHD)
- Probability of 6 month and 18 months treatment-related mortality (TRM)
- Probability of 18 months relapse incidence
- Probability of 18 months overall survival (OS)

Transplant Related Objectives:

- Incidence of neutrophil recovery by day +56
- Incidence of platelet recovery by day +56
- Donor cell engraftment (chimerism) at day +30, +60, +90, +180 and + 365
- Incidence of 1 year and 18 months chronic GVHD
- Probability of 1 year and 18 months GVHD and relapse-free survival (GRFS)
- Incidence of serious fungal and viral infections at day 100 and 1 year and 18 months post-HCT

Pharmacokinetic Objectives:

- Evaluate pharmacokinetics of mycophenolate mofetil (MMF) measured on day 7 after transplant

- Evaluate single nucleotide polymorphisms (SNPs) in p450, aldehyde dehydrogenase, and glutathione S-transferase that influence Cyclophosphamide metabolism

Endpoints:

Primary Endpoint: The primary endpoint is the probability of disease-free survival (DFS) by 18 months post-transplant. An event will be defined as death or a relapse

Secondary Endpoints:

- Probability of Grade II-IV and Grade III-IV aGVHD at 180 days
- Probability of TRM at 6 months and 18 months
- Probability of relapse at 18 months
- Probability of 18 months year overall survival (OS)

Transplant Related Endpoints

- Probability of neutrophil recovery by day +56
- Probability of platelet recovery by day +56
- Proportion of donor cell engraftment (chimerism) at days +30, +60, +90, +180 and +365
- Probability of 18 months chronic GVHD
- Probability of 18 months GRFS
- Probability of serious fungal and viral infections at day +100, 1 year and 18 months post-HCT

Pharmacokinetic Endpoints:

- Concentrations of MMF metabolites measured on day 6 after transplant
- Prevalence, by ethnicity, of SNPs in p450, aldehyde dehydrogenase, and glutathione S-transferase known to influence Cyclophosphamide metabolism

Study Population:

Estimated Sample Size: 34 patients

- Age $\geq$ 55 years or HCT-CI$\geq$3
- Karnofsky performance status of ≥70% or Lansky play score ≥ 70%
- Acute leukemia in complete remission
  or
- Myelodysplastic syndrome, myeloproliferative neoplasm or chronic myelogenous leukemia with <5% blasts in bone marrow by morphology;
  or
- High risk lymphoma in at least a partial remission (PR)

- The donor and recipient must be HLA identical for at least one haplotype (using high resolution DNA based typing) at the following genetic loci: HLA-A, HLA-B, HLA-C, and HLA-DRB1.

Phase: Phase II

Description of Sites/Facilities Enrolling Participants: H. Lee Moffitt Cancer Center - Single Site

Description of Study Intervention:

Conditioning:

Day -6: Fludarabine IV 30mg/m^2, Melphalan 70 mg/m^2

Day -5: Fludarabine IV 30mg/m^2

Day -4: Fludarabine IV 30mg/m^2

Day -3: Fludarabine IV 30mg/m^2

Day -2: Fludarabine IV 30mg/m^2

Day -1: Total Body Irradiation 2 Gy

Graft:

PBSCT infusion will be administered on day 0 with a minimal dose of $2x10^6$ CD34+ cells and a maximum dose of $5x10^6$ CD34+ cells.

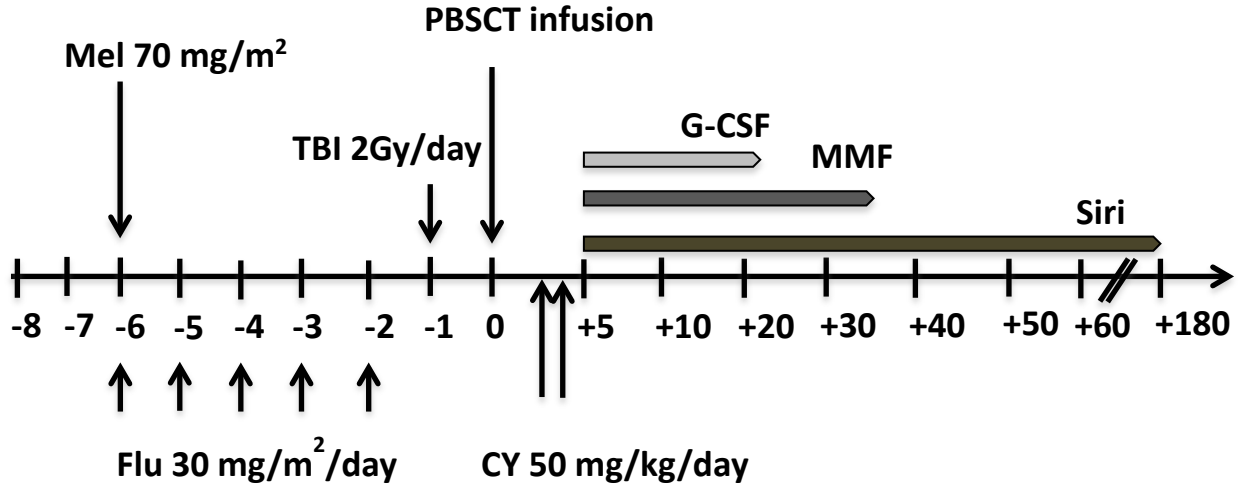
GVHD Prophylaxis:

Cyclophosphamide IV 50 mg/kg will be administered on Day +3 and +4. Mycophenolate mofetil (MMF) and sirolimus will be initiated on day +5. Sirolimus will be dosed to a goal level of 8-14 ng/ml. In absence of GVHD, sirolimus may be tapered after day 90 and should be completed by day 180. MMF will be started at a dose of 15 mg/kg every 8 hours with a maximum daily dose not to exceed 3 gm. MMF will be discontinued on day +35.

Study Duration: 36 Months

Participant Duration: 18 months

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

For explanation of procedures, please see Section 8 (Study Assessments and Procedures).

Pre-BMT work-up evaluations should be completed prior to initiation of conditioning chemotherapy within the screening windows defined in the table below. Evaluations done as a "standard of care" prior to consent on trial may be used for the trial screening if falling within the appropriate window from initiation of conditioning chemotherapy.

Scheduled evaluations after screening and until engraftment may be performed +/-3 days from the targeted date; assessments performed after engraftment and through Day 90 may be done +/-10 days of the targeted date. After Day 90 assessments may be done +/- 30 days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

Activity	Pre-BMT Work-Up	Day 1 To Engraftment[1]	Follow-Up Days 42-90	Follow-Up (>Day 90 through Day 540)
Consent	No Window			
Medical History	Within 30 days	Daily	weekly	X (day 180, 360, 540)
Physical Exam	Within 30 days	Daily	weekly	X (day 180, 360, 540)
RT consultation	No Window			
Karnofsky/Lansky	Within 30 days		day 90	X (day 180, 360, 540)
GVHD Assessment		weekly start day 7	weekly, day 90	X (day 180, 360, 540)
CBC/diff/plt	Within 30 days	Daily	weekly	X (day 180, 360, 540)

Activity	Pre-BMT Work-Up	Day 1 To Engraftment[1]	Follow-Up Days 42-90	Follow-Up (>Day 90 through Day 540)
PT/INR	Within 60 days			
Viral Screen	Within 60 days			
PRA (Donor Specific Antibody)	Within 60 days			
Basic metabolic panel		Daily		
Comprehensive metabolic panel	Within 30 days	2x/wk	weekly	X (day 180, 360, 540)
eGFR for adults with creat > 1.2 or hx or renal dysfunction	Within 30 days			
Pregnancy test (females of childbearing potential)	Within 30 days			
BM Biopsy	Within 60 days	X (day 30)	X (day 90)	X (day 180, 360, 540)
BM chimerism		BM (day 30)	BM (day 90)	BM (day 180, 360, 540)
Blood chimerism		PB (day 30)	PB (day 90)	PB (day 180, 360, 540)
PETCT (lymphoma only)	Within 60 days			X
Minimal Residual Disease	Within 60 days	BM (day30)	BM (day 90)	BM (day 180, 360, 540)
T-Cell Immune Reconstitution Panel	Within 60 days	PB (day 30)	PB (day 90)	PB (day 180, 360, 540)
CMV PCR (blood)		Weekly	Weekly	
HHV6 PCR (blood)		Weekly	Weekly	
PFT/DLCO	Within 60 days			
MUGA or Echo	Within 60 days			
CT Chest/Sinus	Within 60 days			
Disease Evaluation	Within 60 days	X (day 30)	X (day 90)	X (day 180, 360, 540)

Activity	Pre-BMT Work-Up	Day 1 To Engraftment[1]	Follow-Up Days 42-90	Follow-Up (>Day 90 through Day 540)
Research Bone Marrow and Blood[2] Sample	No Window	X (day 30)		X (day 180)
Blood samples for MMF		X (day 7)[3]		

1 Engraftment defined as absolute neutrophil count (ANC) ≥ 5 X 10^8/L for 3 consecutive measurements
2 Research blood samples will be used for cyclophosphamide genomics studies. Research blood samples will be collected in EDTA blood collection tubes and research marrow samples will be collected in sodium heparin tubes. Excess blood and marrow samples from existing samples (including those collected for MCC 14690) may be stored for future correlative studies in lieu of collecting a new sample.
3 Blood for MMF pharmacokinetic studies will be obtained on day 7 at the following time points: pre-dose, post-dose, 1 hour, 2 hour, 4 hour, and 8 hours after dose in EDTA blood collection tubes. Collections may occur +/- 10 minutes from the scheduled interval.

NOTE: In certain clinical circumstances (e.g. relapsed or terminally ill patients, risk of undue harm to patients, etc.) study tests may be omitted at the physician's discretion. Additionally, tests may be rescheduled as clinically indicated.

2 STUDY RATIONALE AND BACKGROUND

2.1 INTRODUCTION

Allogeneic (allo) hematopoietic cell transplantation (HCT) is widely used as a curative therapy for a number of hematological malignancies. While early conditioning regimens were too toxic for many patients, reduced intensity conditioning (RIC) opened opportunities for older patients and those with comorbid conditions to be eligible for potentially curable transplantation.[1-5]

Historically, implementation of allo HCT required the availability of a human leukocyte antigen (HLA) matched donor to minimize complications including graft-versus-host disease (GVHD) and non-relapse mortality (NRM). An HLA matched sibling donor (MSD) is the preferred donor, but only 30% of patients have an MSD.[6] When no MSD exists, HLA matched unrelated donors (MUDs) may be identified through volunteer donor databases. However, the likelihood of finding a suitable MUD varies dramatically by ethnicity, from <20% for Black populations to ~75% for White Caucasian groups.[6] Overall, the likelihood of finding an HLA matched donor is 60%, and falls below 50% for many ethnic minority groups.[6, 7] In addition, data from the National Marrow Donor Program (NMDP) indicates that the median time from donor search to adult MUD transplant is about 3-4 months. This time delay increases the risk of malignancy relapse in some patients with aggressive diseases.[1, 2]

Given the absence of a matched donor for many patients, alternative donor strategies that use HLA mismatched donors have been developed to expand the donor pool.[8-11] Among the most commonly adopted strategies is the use of HLA haploidentical (HLA "half-matched") related donors. Low cost and easy accessibility of haploidentical transplantation (haplo-HCT) make it an

attractive alternative graft source. As HLA haplotypes follow Mendelian inheritance, the likelihoods of a sibling or offspring being HLA haploidentical to the patient are approximately 50% and 100%, respectively. Per prior reports, inclusion of HLA haploidentical donors in HCT donor search algorithms increases the likelihood of finding a suitable donor to >90%, even in populations for whom unrelated donors are less likely.[7, 12-14] Thus, optimization of haplo HCT protocols allows for transplantation for nearly all patients otherwise eligible for the procedure.

2.2 HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION WITH POST-TRANSPLANT CYCLOPHOSPHAMIDE

Initial experience with haplo HCT using T-cell replete allografts resulted in unacceptably high incidences of severe graft versus host disease (GVHD) and transplant-related mortality (TRM) in about half of the patients.[15-17] A number of strategies have been attempted to reduce the toxicity of haplo HCT by depleting T-cells, which facilitate GVHD. [14, 18-27] *Ex vivo* depletion of T-cells does reduce GVHD, but results in poor engraftment and unacceptably high rates of infection and TRM.[14, 18, 19]

Investigators at the Johns Hopkins University developed a strategy that uses high dose post-transplant cyclophosphamide (PTCy) to deplete T-cells *in vivo*.[28] PTCy after transplant is preferentially toxic to the alloreactive T cells that cause GVHD while also sparing the regulatory T (Treg) cells that help induce immune tolerance. These effects result in a potent anti-GVHD effect that allows for safe transplantation from HLA mismatched donors.[29-31] The original Johns Hopkins PTCy platform uses a RIC regimen consisting of Fludarabine (Flu) 30 mg/m^2/day IV daily from Days -6 to -2, Cy 14.5 mg/kg IV on Day -6 and -5, and 200 cGy total body irradiation (TBI) in a single fraction on Day -1 (Flu150Cy29TBI200), bone marrow graft (BMT), and PTCy 50 mg/kg given on days +3 and +4.[32-35] Multiple studies have demonstrated acceptable toxicity with this platform including rates of TRM ~10-15%, acute GVHD rates ~30%, severe acute GVHD rates of ~10%, and chronic GVHD rates ~10%.[28, 36-39] Immune reconstitution is also favorable given preservation of memory T-cells when PTCy is used in T-cell replete haplo HCT.[23, 25]

Prospective comparative trials comparing the Hopkins haplo BMT with PTCy platform to other donor platforms are lacking. Results of two parallel Blood and Marrow Transplant Clinical trials Network (BMTCTN) multicenter phase 2 trials compared the outcomes of patients with RIC haplo BMT with PTCy (BMTCTN 0603, n=50) to RIC umbilical cord blood transplantation (UCBT; BMTCTN 0604, n=50).[40] Recipients of haplo BMT were conditioned with Flu150Cy29TBI200 and UCBT recipients received Flu 40mg/m^2 Days -6 to -2, Cy 50 mg/kg Day -6 and TBI 200 cGy Day -1 (Flu200/Cy50/TBI200). GVHD prophylaxis for haplo BMTs consisted of Cy 50 mg/kg IV on Days +3 and +4 followed by MMF and tacrolimus beginning on Day +5. UCB recipients received MMF and CSA beginning on Day -3 for GVHD prophylaxis. The 1-year probabilities of OS and DFS were 54% and 46% after double UCB (dUCB) transplantation (n=50) and 62% and 48%, respectively, after haplo BMT (n=50). The cumulative incidence of neutrophil recovery at day 56 was 94% after dUCB and 96% after haplo BMT. The cumulative incidence of grade II-IV acute GVHD at Day 100 was 40% after dUCB and 32% after haplo BMT. The 1-year cumulative incidences of TRM and relapse after dUCB transplantation were 24% and 31%, respectively, and those for haplo BMT were 7% and 45%, respectively. A phase III randomized, prospective trial comparing haplo BMT with PTCy to UCBT is ongoing (NCT01597778). No studies have prospectively compared the Hopkins platform to HLA matched donor transplant, though multiple

retrospective studies have demonstrated favorable safety outcomes and comparable OS with the haplo regimen.[37, 38, 41, 42]

Given its safety, accessibility, and low cost, the haplo HCT with PTCy approach has become widely used in many transplant centers when a matched donor is not available.[24, 26, 43-50]

2.3 RELAPSE IN HAPLO HCT WITH PTCY

Though Flu150Cy29TBI200 haploidentical BMT with PTCy has safely expanded the donor pool with low rates of TRM and GVHD, application has been marred by high rates of disease relapse in high risk diseases such as myeloid malignancies, exceeding 40-50% in some studies.[28, 36, 37, 51] Thus, various modifications have been attempted to optimize haplo BMT with PTCy in these disease groups.

Efforts to reduce relapse by using full intensity conditioning regimens with haplo HCT with PTCy in younger patients with AML lowered the risk of post-transplant relapse to 20-45% without a substantial increase in TRM in some reports.[45, 50] However, since myeloablative conditioning is not an option for older patients and for those with higher comorbidities (HCT-CI >3) due to an unacceptably high risk of TRM, strategies identifying novel RIC regimens can reduce the risk of relapse and improve survival after haplo HCT with PTCy are needed for those >55 years old or with comorbidities.

Recently Flu/Melphalan (Mel) and Flu/Busulfan (Bu) RIC regimens were compared in the matched adult donor allo HCT setting for AML/MDS, with the flu/mel regimen yielding significantly improved relapse rates and DFS.[52] The group from MD Anderson Cancer Center (MDACC) has attempted similarly to implement a melphalan based regimen in the setting of haplo HCT with PTCy. They recently reported their experience with haplo HCT with PTCy following conditioning with Flu 40 mg/m^2 Day -6 to -3, Mel 100 mg/m^2 Day -8 and either Thiotepa 5 mg/kg Day -7 or TBI 200 cGy (FM100) in patients 55 years and older.[49, 50] Despite reported low 1-year relapse rates of 11-19% with the Flu/Mel regimen in these studies, prolonged courses of intensive immune suppression (MMF through Day +90 and Tac through Day +180) were required in order to minimize the risk of excessive acute GVHD.[49, 50] Notably, high doses of Mel exposure per kilogram of body weight (>3.5mg/kg) has been previously shown to increase the risk of oral mucositis and subsequent acute GVHD rates in allo HCT recipients.[53] Intensification of conditioning with the addition Mel, though at a lower dose than used at MDACC, may result in a more favorable balance of efficacy and toxicity.

In addition to conditioning, graft source is a modifiable variable that may be optimized in the setting of high risk for disease relapse. The original Hopkins haplo HCT with PTCy platform used bone marrow (BM) as the graft source. In the setting of MUD HCT, prospective data has shown that transplantation from peripheral blood stem cell grafts (PBSCT) results in higher rates of chronic GVHD than bone marrow transplantation (BMT), without any benefit in disease control.[54] Noting the effectiveness of PTCy in preventing chronic GVHD, the Center for International Blood and Marrow Transplant Research (CIBMTR) pursued a large retrospective study to assess outcomes of haplo PBSCT with PTCy versus BMT with PTCy.[55] Though rates of GVHD remained higher in the PBSCT group, NRM remained comparable in the two groups. Further, patients receiving PBSCT experienced lower relapse rates (RR) and improved disease free survival (DFS). These results are bolstered by similar outcomes in a smaller retrospective analysis.[56] Thus, substitution

of PBSCT for BMT in patients appears acceptably safe and may improve efficacy of the haplo HCT with PTCy platform.

2.4 MYCOPHENOLATE MOFETIL PHARMACOKINETICS

The PTCy platform includes mycophenolate mofetil (MMF) through day +35 after transplant as well as either tacrolimus or sirolimus.[28, 31, 57] Tacrolimus/sirolimus levels are monitored and dosing is adjusted to ensure consistent therapeutic exposure. In contrast, MMF in this regimen is dosed at 15 mg/kg three times daily, up to a maximum of 3 grams per day, and most adult patients are treated at the maximum dose of 1000mg three times daily. However, prior studies have demonstrated that there is significant pharmacokinetic variability with this drug. Additionally, in the setting of allogeneic HCT, relative exposure to MMF has been shown to impact outcomes. A study of 85 patients receiving reduced intensity matched unrelated donor (MUD) transplants, higher levels of MMF metabolites in the blood correlated with a higher risk of cytomegalovirus (CMV) activation and lower T-cell chimerism.[58] Investigators from the University of Minnesota found in 87 reduced intensity HCTs including matched related and unrelated donors demonstrated that low unbound blood MMF levels were correlated with higher risks of acute GVHD and graft failure.[59] Recently, the same group showed that weight-based dosing of MMF impacts outcomes, with higher weight-based dosing resulting in lower rates of GVHD but higher rates of relapse.[60] In combination with PTCy, the impact of variable MMF exposure and pharmacokinetics have not been studied.

2.5 CYCLOPOPHOSPHAMIDE METABOLISM

PTCy for GVHD prevention is dosed at 50mg/kg given on day +3 and day +4 based on a reduction in GVHD compared to giving only a single dose on day +3.[28, 31] However, pharmacokinetic data with this platform is lacking. In other HCT settings, Cyclophosphamide metabolism has proven highly variable with high relative exposure correlating with increased toxicity and NRM.[61] Cyclophosphamide is metabolized through the cytochrome p450 system and subsequently detoxified by aldehyde dehydrogenases and glutathione S-transferases. Polymorphisms in these pathways have been shown to correlate with efficacy and specific drug related toxicities in various malignancies, including relapse in the autologous transplant setting.[62, 63] Notably, the patterns of expression of these polymorphisms vary across ethnic groups, translating into different drug responses in these groups.[64, 65] As haplo HCT helps address the challenges of finding a donor for black and hispanic patients, a better understanding of the pharmacokinetics of PTCy in these groups is warranted.

2.6 SUMMARY OF RATIONALE

High risk hematologic malignancies are curable with allo HCT, which offers an overall survival benefit. Haplo HCT with PTCy has improved access to transplant among patients lacking an HLA matched donor. However, this therapy is marred by high rates of relapse. This study seeks to optimize the haplo HCT with PTCy platform with a small increase in conditioning intensity and the use of PBSCT in lieu of BMT.

We hypothesize that intensification of Flu150/Cy29/TBI200 haplo BMT with PTCy to Flu150/Mel 70mg/m^2/TBI200 haplo PBSCT with PTCy can successfully reduce the risk of relapse and improve DFS without substantially increasing the risk of TRM. Additionally, we will substitute sirolimus instead of tacrolimus given recent phase II data from Moffitt that this drug may confer more favorable rates of chronic GVHD when combined with PTCy and peripheral blood stem cell grafts.[66]

If successful, this intervention would further enhance the utility of haplo HCT to expand the donor pool to all eligible patients.

2.7 RISK/BENEFIT ASSESSMENT

2.7.1 KNOWN POTENTIAL RISKS

There are numerous anticipated adverse consequences of transplantation, which include, but are not limited to conditioning regimen related toxicity such as severe mucositis, idiopathic pneumonia syndrome, hepatic veno-occlusive disease and death, early and late infectious complications, potentially severe or fatal acute or chronic graft vs. host disease, and relapse of primary disease and its complications. Specific complications are listed below.

2.7.2 PREPARATIVE REGIMEN

Fludarabine		
Common	**Less Common**	**Rare**
• severe suppression of blood counts • diarrhea • anorexia • mucositis • nausea/vomiting • stomatitis • osteoporosis • dysuria	• chills • fever • GI bleeding • peripheral edema	• neurotoxicity – agitation and confusion – blurred vision – peripheral neuropathy – hearing loss – headache – cerebellar syndrome – blindness – coma – weakness • depression • insomnia

Fludarabine		
Common	**Less Common**	**Rare**
		• hemorrhagic cystitis (except in FA) • abnormal renal function test • autoimmune hemolytic anemia • deep venous thrombosis • aneurysms • pruritic skin rash • abnormal liver function/liver failure • constipation • transient ischemic attack • dysphagia • myalgia • arthralgia • renal failure

Cyclophosphamide		
Common	**Less Common**	**Rare**
• nausea/vomiting • mucositis • sterility • severe suppression of • blood counts • diarrhea • fluid weight gain/edema • alopecia	• hemorrhagic cystitis	• cardiomyopathy • skin rash • SIADH (Syndrome of Inappropriate Anti-diuretic Hormone)

Melphalan		
Common	**Less Common**	**Rare**
• nausea (at higher doses) • vomiting (at higher doses) • low white blood cell count with increased risk of infection • low platelet count with increased risk of bleeding • anemia (low red blood cell count) with symptoms like tiredness, paleness, or trouble catching breath	• short-term or long-term infertility (inability to have children) • weakness	• severe allergic reaction • loss of appetite • scarring (fibrosis) or inflammation of lungs • hair loss, including face and body hair • rash • itching • second type of cancer (may happen years after treatment)

Melphalan		
Common	**Less Common**	**Rare**
• diarrhea		• death from lung damage or other causes

Total Body Irradiation		
Common	**Less Common**	**Rare**
• nausea and vomiting • diarrhea • cataracts • sterility (inability to have children) • endocrinopathies (hormone imbalance due to damage to the endocrine gland) • stunted growth in children • intestinal cramps • mucositis (mouth sores)	• parotitis (swelling and inflammation of the parotid gland) • interstitial pneumonitis (explained below in the damage to vital organs section) • generalized mild reddening of the skin • veno-occlusive disease (VOD - explained below in the damage to vital organs section)	• dysphagia (difficulty swallowing) • deformities of the backbone (vertebrae) • nephropathy (numbness or tingling in hands and/or feet) • risk of 2nd malignancy years later (when given along with chemotherapy)

2.7.3 HAPLOIDENTICAL DONOR STEM CELL INFUSION

With the cell infusion

- Nausea and vomiting
- Possible allergic reaction (including itching, hives, flushing [red face], shortness of breath, wheezing, chest tightness, skin rash, fever, chills, stiff muscles, or trouble breathing)

General transplant related risks

- Slow recovery of blood counts
- graft failure
- Cytokine release syndrome (CRS, see appendix I for grading and management)
- Graft-Versus-Host Disease (GVHD)
- Other complications including:
  - damage to the vital organs
  - serious infections
  - relapse of disease or a new blood cancer
  - risk to the unborn

2.7.4 GVHD PROPHYLAXIS

Sirolimus		
Common	**Less Common**	**Rare, but may be serious**
▪ Pain or body aches ▪ Fever ▪ High blood pressure ▪ kidney problems ▪ Swelling of the hands, feet, ankles, or lower legs ▪ Low red blood cell count (anemia) ▪ Low platelets ▪ Unusual bleeding/bruising ▪ Headaches ▪ Ulcers of the lips/mouth ▪ Shortness of breath ▪	▪ Blood clots ▪ High cholesterol ▪ Reduced number of platelets, red, and white blood cells ▪ Hoarse voice ▪	▪ Severe liver damage ▪ Increased risk of lymphoma or other cancers

Mycophenolate mofetil (MMF)		
Common	**Less Common**	**Rare, but may be serious**
• miscarriage • birth defects • diarrhea • damage to unborn baby • limited effectiveness of birth control • stomach pain • upset stomach • vomiting • headache • tremors • low white blood cell count with increased risk of infection • increased blood cholesterols • swelling of the hands, feet, ankles or lower legs	• anemia • rash • difficulty falling asleep or staying asleep • dizziness • uncontrollable hand shakes	• difficulty breathing • unusual bruising • fast heartbeat • excessive tiredness • weakness • blood in stool • bloody vomit • change in vision • secondary cancers, such as lymphoproliferative disease or lymphoma • Progressive Multifocal Leukoencephalopathy

2.7.5 G-CSF

Common	**Less Common**	**Rare, but may be serious**
none	• local irritation at injection site • ache or pain inside the bones • increased levels of liver enzymes • uric acid in the blood • low number of platelets in the blood	• allergic reaction, low fever • enlargement of the spleen and even splenic rupture • worsening of pre-existing skin rashes, • hair loss • inflammation of a blood vessel in the skin

2.7.6 KNOWN POTENTIAL BENEFITS

High risk hematologic malignancies are curable with allo HCT, which offers an overall survival benefit. Unfortunately, some patients lack an HLA matched donor. Haplo BMT with PTCy has improved access to transplant among these patients. However, this therapy is marred by high rates of relapse. This study seeks to optimize the haplo HCT with PTCy platform with a small increase in conditioning intensity and the use of PBSCT in lieu of BMT. If successful, this intervention will improve efficacy without a significant concomitant increase in toxicity. This would further enhance the utility of haplo HCT to expand the donor pool to all eligible patients. In particular, this would significantly improve outcomes in patients lacking an HLA matched donor and are, thus, at high risk of relapse using existing haplo transplant protocols.

Immediate Benefits:

- Decreased toxicity (GVHD, TRM) in the immediate post-transplant period as compared to many standard melphalan based conditioning regimens

Long-range Potential Benefits:

- Improved disease control and survival as compared to currently standard conditioning regimens used prior to haplo HCT with PTCy

2.7.7 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Allogeneic HCT is the only curative therapy for a number of hematologic malignancies. The long term outcomes for patients after HCT can be generally categorized as disease free survival (i.e., cure), survival with disease relapse, and death due to transplant. Generally, increasing the intensity of pre-transplant conditioning results in lower relapse rates, but at the cost of higher rates of transplant related mortality (TRM). Conversely, reduced intensity regimens decrease TRM but at cost of higher rates of relapse. Thus, a large proportion of transplant patients succumb to either the transplant or disease relapse. The goal of this study is to use a novel conditioning regimen to optimize the balance of toxicity and efficacy in patients undergoing haploidentical donor HCT with PTCy based GVHD prophylaxis.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective is to estimate probability of the 18 month disease free survival (DFS) after a HLA-haploidentical related hematopoietic cell transplant (Haplo-HCT)	The primary endpoint is the probability of disease-free survival (DFS) by 18 months post-transplant. An event will be defined as death or a relapse.	As HCT is intended as a curative therapy, DFS is an optimal endpoint as it encompasses both elimination of the

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
using a reduced intensity fludarabine/melphalan/total body irradiation (TBI) conditioning in older patients in patients with a myeloid hematologic malignancy.		disease and overall survival.
Secondary		
• Incidence of day 90 grade II-IV and grade III-IV acute graft versus-host-disease (GVHD) • Probability of 6 month and 18 month TRM • Probability of 18 month relapse incidence • Probability of 18 month OS	• Probability of Grade II-IV and Grade III-IV aGVHD at 100 days • Probability of treatment-related mortality (TRM) at 6 months and 18 months • Probability of relapse at 18 months • Probability of OS at 18 months	These are standard outcomes of interest following transplant. These outcomes will further elucidate causes of treatment failure contributing to the primary outcome (DFS).
Tertiary/Exploratory		
• Incidence of neutrophil recovery by day +30 • Incidence of platelet recovery by day +60 • Donor cell engraftment (chimerism) at day +30, +60, +90, +180 and + 365 • Incidence of 18 month chronic GVHD • Probability of 18 month year GVHD and relapse-free survival (GRFS) • Incidence of 100 day, 1 year, and 18 month serious fungal and viral infection	• Probability of neutrophil recovery by day +30 • Probability of platelet recovery by day +60 • Proportion of donor cell engraftment (chimerism) at days +30, +60, +90, +180 and +365 • Probability of 18 month chronic GVHD • Probability of 18 month GVHD and relapse-free survival (GFRS) • Probability of 100 day, 1 year, and 18 month serious fungal and viral infection	These are standard outcomes of interest following transplant. These outcomes will further elucidate causes of treatment failure contributing to the primary outcome (DFS).
Pharmacologic		
• Evaluate pharmacokinetics of mycophenolate mofetil (MMF) measured on day 6 after transplant • Evaluate single nucleotide polymorphisms (SNPs) in p450, aldehyde	• Concentrations of MMF metabolites measured on day 6 after transplant • Prevalence, by ethnicity, of SNPs in p450, aldehyde dehydrogenase, and glutathione S-transferase known to influence Cyclophosphamide metabolism	• Metabolism of relevant drugs may impact clinical outcomes.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
dehydrogenase, and glutathione S-transferase that influence Cyclophosphamide metabolism		

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single institution phase II study of a reduced intensity conditioning (RIC) followed by a haploidentical hematopoietic cell transplant (haplo-HCT) in persons with diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

Conditioning will consist of a reduced intensity fludarabine, melphalan and total body irradiation (TBI) preparative regimen for patients ≥55 years old or those with HCT Comorbidity Index (CI) ≥3. The graft source will be peripheral blood stem cells.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study will be a single arm, phase II study to evaluate the feasibility, efficacy, and safety of a modified reduced intensity conditioning regimen of fludarabine, melphalan, and TBI followed by haploidentical PBSCT with PTCy based GVHD prophylaxis.[67-69] These regimens are standard of care in allogeneic transplant at higher doses, so a phase I portion is not required in this study that will use a lower dose to decrease toxicity. This trial will determine the estimated efficacy of this regimen based on DFS at 18 months. This will allow a basis for future, larger comparative studies.

4.3 JUSTIFICATION FOR DOSE

Recently Flu/Mel and Flu/Bu RIC regimens were compared in the matched adult donor allo HCT setting for AML/MDS, with the Flu/Mel regimen yielding significantly improved relapse rates and DFS.[52] The group from MD Anderson Cancer Center (MDACC) has attempted similarly to implement a melphalan based regimen in the setting of haplo HCT with PTCy. They recently reported their experience with haplo HCT with PTCy following conditioning with Flu 40 mg/m^2 Day -6 to -3, Mel 100 mg/m^2 Day -8 and either Thiotepa 5 mg/kg Day -7 or TBI 200 cGy (FM100) in patients 55 years and older.[49, 50] Despite reported low 1-year relapse rates of 11-19% with the Flu/Mel regimen in these studies, prolonged courses of intensive immune suppression (MMF through Day +90 and Tac through Day +180) were required in order to minimize the risk of excessive acute GVHD.[49, 50] Notably, high dose of Mel exposure per kilogram of body weight (>3.5mg/kg) has been previously shown to increase the risk of oral mucositis and subsequent acute GVHD rates in allo HCT recipients.[53] Thus, a reduction in melphalan dosing may result in a more favorable balance of efficacy and toxicity.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

5.1.1 Age, Performance Status, and Graft Criteria

- Age ≥ 55 years or HCT Co-Morbidity score (HCT-CI) ≥ 3 (*http://www.qxmd.com/calculate-online/hematology/hct-ci*)
- Lack of a suitable 8/8 HLA-matched sibling donor
- Adequate performance status is defined as Karnofsky score ≥ 70% (> 16 years of age) or Lansky score ≥ 70 (pediatrics) (Appendix II)
- Patients and selected donor must be HLA typed at high resolution using DNA based typing at the following HLA-loci: HLA-A, -B, -C and DRB1. Donors must be HLA-haploidentical relatives including, but not limited to, children, siblings, or parents, defined as having a shared HLA haplotype between donor and patient at HLA-A, -B, -C, and -DRB1.Refer to donor selection in section 5.3.

5.1.2 Eligible Diseases

Acute Myeloid Leukemia (AML): Must be in remission by morphology (<5% blasts). Note cytogenetic relapse or persistent disease without morphologic relapse is acceptable. Also a small percentage of blasts that is equivocal between marrow regeneration vs. early relapse are acceptable provided there are no associated cytogenetic markers consistent with relapse. (Refer to exclusion criteria section 3.5 for more detailed definition).

- Second or greater complete remission (CR)
- First CR (CR1) in patients ≥60 years old
- CR1 in <60 years old that is NOT considered as favorable risk (see exclusion criteria).
    - Acute prolymphocytic leukemia (APL) in first molecular remission at the end of consolidation

Acute lymphoblastic leukemia (ALL)/lymphoma: second or greater CR; CR1 unable to tolerate consolidation chemotherapy due to chemotherapy-related toxicities; CR1 high-risk ALL.

High risk ALL is defined as having one of the following:

- Evidence of high risk cytogenetics, e.g. t(9;22), t(1;19), t(4;11), other *MLL* rearrangements, *IKZF1*
- Recipient age 30 years and older at diagnosis
- White blood cell counts of greater than 30,000/mcL (B-ALL) or greater than 100,000/mcL (T-ALL) at diagnosis
- CNS leukemia involvement during the course of disease

- Slow cytologic response (>10% lymphoblasts in bone marrow on Day 14 of induction therapy)
- Evidence of persistent immonophenotypic or molecular MRD at the end of induction and consolidation therapy

Biphenotypic/Undifferentiated/Prolymphocytic Leukemias in first or subsequent CR.

Myelodysplastic syndrome: any subtype including refractory anemia (RA) if severe pancytopenia or complex cytogenetics. Blasts must be less than 10%. If 10% or more, then requires chemotherapy for cytoreduction to ≤10% prior to transplantation.

Chronic myelogenous leukemia in chronic or accelerated phase. Chronic phase patients must failed at least two different TKIs, been intolerant to all available TKIs or have *T315I* mutation. Accelerated phase requires remission as defined in "AML" section above.

Myeloproliferative neoplasms/myelofibrosis. Blasts must be less than 5%. If 5% or more requires chemotherapy for cytoreduction to ≤5% prior to transplantation.

Relapsed large-cell lymphoma, mantle-cell lymphoma and Hodgkin lymphoma that is chemotherapy sensitive and has failed or ineligible for an autologous transplant.

Burkitt's lymphoma in CR2 or subsequent CR.

Relapsed T-cell lymphoma that is chemotherapy sensitive in CR/PR that has failed or ineligible for an autologous transplant.

Natural Killer cell malignancies.

Relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma, follicular lymphoma with any of the following:

- Progressed within 12 months of achieving a partial or complete remission.
- Patients who had remissions lasting > 12 months are eligible after at least two prior therapies.
- Patients with primary refractory disease.

  Note: Bulky disease and an estimated tumor doubling time of less than one month require debulking therapy prior to transplant.

Lymphoplasmacytic lymphoma is eligible after initial therapy if chemotherapy sensitive.

5.1.3 Organ Function Criteria

Adequate organ function is defined as:

Cardiac: Absence of decompensated congestive heart failure, or uncontrolled arrhythmia and left ventricular ejection fraction ≥ 40%. For children that are not able to cooperate with MUGA and echocardiography, such should be clearly stated in the physician's note

Pulmonary: DLCO, FEV_1, FVC > 40% predicted, and absence of O_2 requirements. For children that are not able to cooperate with PFTs, a pulse oximetry with exercise should be attempted. If nether test can be obtained it should be clearly stated in the provider's note.

Liver: Transaminases < 5 x upper limit of normal (ULN) and total bilirubin ≤ 2.5 mg/dL except for patients with Gilbert's syndrome or hemolysis.

Renal: Creatinine ≤ 2.0 mg/dL (adults) and creatinine clearance > 40 mL/min (pediatrics). Adults with a creatinine > 1.2 or a history of renal dysfunction must have estimated creatinine clearance > 40 ml/min/1.73m^2.

5.1.4 Sexually active females of childbearing potential and males with partners of child-bearing potential must agree to use adequate birth control during study treatment.

5.1.5 Voluntary written consent (adult or parent/guardian with presentation of the minor information sheet, if appropriate)

5.2 EXCLUSION CRITERIA

5.2.1 Pregnant or breast feeding. The agents used in this study include Pregnancy Category D: known to cause harm to a fetus. Females of childbearing potential must have a negative pregnancy test prior to starting therapy.

5.2.2 Untreated active infection

5.2.3 Active HIV infection

5.2.4 Prior allogeneic HCT at any time point or less than 6 months since prior autologous transplant (if applicable)

5.2.5 Evidence of progressive disease by imaging modalities or biopsy - persistent PET activity thought unrelated to lymphoma is not an exclusion criterion in the absence of CT changes indicating progression.

5.2.6 Active central nervous system malignancy

5.2.7 Favorable risk AML defined as having one of the following:

- t(8,21) without *cKIT* mutation or evidence of immunophenotypic, cytogenetic or molecular minimal residual disease (MRD)
- inv(16) or t(16;16) without *cKIT* mutation or evidence of MRD
- Normal karyotype with mutated *NPM1* but *FLT3-ITD* wild type without evidence of MRD
- Normal karyotype with double mutated *CEBPA* without evidence of MRD

5.3 DONOR SELECTION

Donor selection will be in compliance with 21 CFR 1271. Donors will be evaluated, consented and enrolled via standard operating procedures of the Moffitt Cancer Center Department of Blood and Marrow Transplantation. However information in this protocol (including match criteria, donor selection priority if more than 1 available donor, cell collection target) overrules those procedures.

In addition, the following criteria must be met:

5.3.1 Must be HLA-haploidentical relatives of the patient (biological parents, siblings, half-siblings, offspring, or other non-first degree relatives), defined as having a shared HLA haplotype between donor and patient at HLA-A, -B, -C, and -DRB1

5.3.2 14 to 70 years of age

5.3.4 Negative for HIV and active hepatitis B

5.3.5 Not pregnant - females of childbearing potential must have a negative pregnancy test within 7 days of marrow collection

Donor Prioritization Schema

In the event that two or more eligible donors are identified, the following order of priority is suggested:

- Medically fit to donate
- Absence of recipient donor-specific anti-HLA antibodies (DSA). Positive DSA is defined as a positive crossmatch test of any titer (by complement-dependent cytotoxicity or flow cytometric testing) or the presence of DSA to the high expression loci HLA-A, - B, -C, or -DRB1 with mean fluorescence intensity >1000 by solid phase immunoassay.
- Donor age 18-40 is prioritized over donor age < 18, then >40-60 years. If multiple 18-40 year old donors are available, the donor should be selected based on the following criteria.
- Lack of major ABO incompatibility
- For cytomegalovirus (CMV) seronegative recipients, a CMV seronegative donor. For CMV seropositive recipients, a CMV seropositive donor.
- Lack of minor ABO incompatibility
- Male donor or non-parous female are preferable.

5.4 LIFESTYLE CONSIDERATIONS

Patients on trial will be required to follow standard post-transplant care per Moffitt Cancer Center BMT/CI standard operating procedures.

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Screen failure individuals who do not meet the criteria for participation in this trial because of a correctable comorbidity (e.g., active infection, elevated blast percentage, etc.) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

All the patients evaluated at Moffitt Cancer Center BMTCI department will be considered for this trial if they are otherwise eligible. Women and minorities will be enrolled if they are considered for haploidentical related hematopoietic Cells (Haplo-HCT) and meet eligibility criteria. All efforts will be made to conform to NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. This trial is expected to enroll a high proportion of ethnic minorities as these patients are less likely to have matched donor options. Demographic information regarding ethnicity/race will be collected for future reporting. This information may be collected at any time after consent through the end of the trial. Patients will be followed for 1.5 years from the date of HCT.

To facilitate collection of demographic data, patients will be asked to answer the following survey:

“In this trial we want to accurately collect the race and ethnicity of all our patients. Please check the race/ethnicity category that you belong to:

1.White

2.Black or African American

3.Hispanic

4.American Indian or Alaska native

5.Asian, Hawaiian or pacific islander

6.Other, not included, please explain:”

5.7 PATIENT REGISTRATION IN ONCORE

Registration will occur after the patient/guardian has signed the subject consent and eligibility is confirmed. To be eligible for registration to this study, the patient must meet each criteria listed on the eligibility checklist based on the eligibility assessment documented in the patient's medical record. A copy of the eligibility checklist is under attachments within the study in OnCore.

Patients will be registered in OnCore by the Moffitt Cancer Center's Clinical Trial Coordinator(s).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

TREATMENT PLAN

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (e.g., acetaminophen, diphenhydramine, antimicrobials, etc.).

The administration of the preparative regimen will follow institutional drug and supportive care guidelines. Timing of infusions below may be modified per institutional practice or as clinically indicated.

Dose and/or schedule adjustments to the dosing or administration of the treatment plan may be made on an individual patient basis as needed for safety (e.g., for drug-drug interactions or toxicity).

All drugs used in this study are commercially available by prescription.

6.1.2 DOSING AND ADMINISTRATION

Treatment Day	Treatment	Protocol Section
Day –6	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then Melphalan 70 mg/ m^2 IV over 45 minutes	6.1.2.1
Days -5	Fludarabine 30 mg/m^2 IV over 30-60 minutes, then	6.1.2.1
Day -4	Fludarabine 30 mg/m^2 IV over 30-60 minutes	6.1.2.1
Day -3	Fludarabine 30 mg/m^2 IV over 30-60 minutes	6.1.2.1

Day -2	Fludarabine 30 mg/m^2 IV over 30-60 minutes	6.1.2.1
Day -1	TBI 200 cGy	6.1.2.1 Appendix III
Day 0	Peripheral Blood Stem Cell Transplant	6.1.2.2
Day 3	Cyclophosphamide 50 mg/kg IV Mesna IV	6.1.2.3
Day 4	Cyclophosphamide 50 mg/kg IV Mesna IV	6.1.2.3
Day 5	Begin sirolimus, mycophenolate mofetil, and G-CSF	6.1.3

6.1.2.1 CONDITIONING REGIMEN

Fludarabine 30 mg/m^2/day will be administered over 30-60 minutes intravenous infusion on Days –6 through –2 for a total dose of 150 mg/m^2. Fludarabine will be dosed according to the recipient's actual body weight. For patients who have an estimated or measured creatinine clearance < 70 ml/min/1.73 m^2, or either prior CNS disease, prior brain radiation, or prior intrathecal chemotherapy, the fludarabine dose should be reduced by 20%. Fludarabine dosing is based on the last creatinine clearance prior to the start of conditioning. The fludarabine dose should be the same on Days -6 to -2, even if the patient's creatinine changes.

Melphalan 70 mg/m^2 over 45 minutes will be administered on Day –6. Melphalan dose will be calculated based on Actual Body Weight. High-dose melphalan will be administered following oral cryotherapy per standard institutional practice. High-dose Melphalan is administered via a central venous catheter following reconstitution with the provided sterile diluent. High-dose melphalan should be administered diluted with sodium chloride and infused over 45 minutes. Vigorous maintenance hydration will be administered with high dose melphalan per institutional practice (day –6).

TBI 200 cGy will be administered on Day -1. Refer to appendix II.

6.1.2.2 HAPLOIDENTICAL PERIPHERAL BLOOD STEM CELL COLLECTION AND INFUSION (DAY 0)

On day 0, patients will receive a peripheral blood hematopoietic cell graft. Donor peripheral blood hematopoietic cells will be collected for a target yield of 5 x 10^6 CD34+ cells/kg, minimal accepted number is 2 x 10^6 CD34+ cells/kg recipient IBW. The maximum infused cell dose will be 7 x 10^6 CD34+ cells/kg. Sample of the infused graft will be sent for flow cytometry to determine the content of CD34+, CD3+ cells and for correlative studies.

6.1.2.3 POST-TRANSPLANT CYCLOPHOSPHAMIDE (DAY 3 AND DAY 4)

Hydration will be given according to our institutional standards.

Cyclophosphamide 50 mg/kg will be given as an IV infusion over 1 hour on Days +3 post-transplant (between 62 and 72 hours after start of stem cell infusion) and on Day +4 post-transplant (approximately 24 hours after Day +3 cyclophosphamide).

Mesna 20 mg/kg will be given as an IV infusion over 15 minutes for four doses on Days +3 post-transplant and for four doses on Day +4 post-transplant. Mesna doses will be given starting 30 minutes prior to the first dose of cyclophosphamide, then 3, 6, and 9 hours following the start of cyclophosphamide infusion each day.

Both cyclophosphamide and mesna dosing is calculated based on ideal body weight (IBW) unless actual body weight (ABW) is < IBW (then ABW should be used).

Ideal body weight is calculated using 50kg + [2.3kg x (height in inches – 60)] for men; 45.5kg + [2.3kg x (height in inches – 60)] for women.

6.1.3 GVHD PROPHYLAXIS AND GROWTH FACTOR SUPPORT (BEGIN DAY 5)

All patients will receive prophylaxis for GVHD with two drugs both beginning at Day 5 as follows:

6.1.3.1 SIROLIMUS

Sirolimus (SIR) will be administered as a 9 mg oral loading dose on day +5, followed by 4 mg oral daily as maintenance to target blood level 5-14 ng/ml. SIR levels will be monitored according to BMT program standard operating procedures (BMT-G-103). Serum levels of sirolimus will be measured around Day +7 and then should be checked twice weekly thereafter and the dose adjusted accordingly to maintain a goal trough level of 8-14 ng/mL. Frequency of sirolimus levels may be decreased once the goal target has been achieved. Sirolimus should be continued for at least 90 days if tolerated. In absence of GVHD, sirolimus should be discontinued by day 180.

The goal sirolimus trough may be adjusted as clinically indicated (e.g., for GVHD, infection, graft failure, relapse). Tacrolimus (trough level of 5-15 ng/ml) may be substituted for sirolimus if the patient is intolerant of sirolimus.

6.1.3.2 MYCOPHENOLATE MOFETIL (MMF)

MMF will be initiated at a dose of 15 mg/kg PO TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1 g PO TID). Dosing may be adjusted for toxicity or as clinically indicated. MMF prophylaxis will begin on Day +5 post-transplant and will be discontinued after the last dose on Day +35 as tolerated or may be continued if active GVHD is present.

6.1.3.3 GROWTH FACTOR SUPPORT

G-CSF will be given beginning on Day +5 at a dose of 300 mcg if patient weight is ≤ 70 kg or 480 mcg if the patient weight is >70 kg.(rounding to the nearest vial dose is allowed), until absolute neutrophil count (ANC) is ≥ 1,500/mm^3 for three consecutive measurements on 3 different days. G-CSF may be restarted to maintain ANC > 1,000/mm^3. G-CSF may be given by IV or subcutaneously.

6.1.4 SUPPORTIVE CARE

Supportive care will be provided per Moffitt Cancer Center's institutional guidelines for transplant patients including any supportive care research protocols.

All patients will receive standard supportive transfusion care according to transfusion committee guidelines or as modified based on clinical parameters.

Acute and chronic GVHD will be staged and treated using current Moffitt Cancer Center BMT-CI program GVHD protocols

Antimicrobial prophylaxis directed towards bacteria, fungi and viruses will be per Moffitt Cancer Center's current institutional guidelines for transplant patients.

6.1.5 FOLLOW-UP

Patients will be followed for 1.5 years post-transplant per institutional standard and the schedule in section 8.

Follow-up after 1.5 years will be per the Moffitt Cancer Center standard hematopoietic stem cell transplantation protocol for long-term follow-up.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not Applicable

6.3 STUDY INTERVENTION COMPLIANCE

Patients will admitted for conditioning and treatment in the inpatient BMT unit at the Moffitt Cancer Center from the initiation of conditioning through neutrophil engraftment. Patients will subsequently follow-up as outpatient per institutional protocol and the clinical trial calendar. Compliance with sirolimus (or tacrolimus) will be assessed via serum levels. Compliance with other medications will be confirmed at follow-up visits.

6.4 CONCOMITANT THERAPY

Patients on this trial may not be concomitantly treated on an alternate interventional clinical trial.

6.4.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The PMC and/or IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to subjects. The PMC/IRB will notify the PI in wiring of such suspensions or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies, including OHRP, FDA as applicable.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded within the patient's medical record and OnCore and/or the Clinical Trial Management System (CTMS). Subjects who sign the informed consent form but do not receive the study

intervention may be replaced. Subjects may be replaced if they signed the informed consent form and received the study intervention, and then were withdrawn or discontinued from the study.

All efforts will be made to continue to follow-up of withdrawn or terminated participants or participants who discontinue therapy but remain in the study for follow-up, especially for safety and efficacy study endpoints (if applicable). Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs).

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and if study site staff are unable to contact the participant.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, by making 3 telephone calls and, if necessary, by sending a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- A minimum of 2 years should be spent attempting to locate the patient. If after that period of time the coordinator has sufficiently documented all failed attempts to locate the patient, including sending a certified letter with no response, then he or she will be considered to have withdrawn from the study for the primary reason of being lost to follow-up.]

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Prior to engraftment, patients will remain in the hospital and study related assessments will be performed on an inpatient basis. Post-transplantation study visits occur on day 30, 90, 180, 1 year, and 18 months (with acceptable windows as outlined in the study calendar).

All clinic assessments and laboratory studies needed to inform study endpoints captured at these time points are part of Moffitt standard practices (with exception of underlined research samples).

1. Day 30 study visit
    - Capture ANC/PLT engraftment data, day 30 disease response assessment and donor chimerism, and any occurrence of acute GVHD
    - Monitor AE/SAE throughout observation period
    - Collect day 30 immune deficiency panel IMDFP Tregs.
    - Collect day 30 research blood sample and bone marrow sample

3. Day 90 study visit
    - Capture acute GVHD data, day 90 disease response assessment and donor chimerism, and death events.
    - Capture initiation of sirolimus (or tacrolimus) taper.
    - Monitor AE/SAE throughout observation period
    - Collect day 90 immune deficiency panel IMDFP Tregs

4. Day 180 study visit
    - Capture acute and chronic GVHD data, day 180 disease response assessment and donor chimerism, mortality events
    - Capture time of sirolimus discontinuation
    - monitor AE/SAE throughout observation period
    - Collect day 180 immune deficiency panel IMDFP Tregs
    - collect day 180 research blood sample and bone marrow sample

5. 1 year and 18 months study visits
    - capture chronic GVHD data, response assessment and donor chimerism, mortality

Pre-BMT work-up evaluations should be completed prior to initiation of conditioning chemotherapy within the screening windows defined in the table below. Evaluations done as a “standard of care” prior to consent on trial may be used for the trial screening if falling within the appropriate window from initiation of conditioning chemotherapy.

Scheduled evaluations after screening and until engraftment may be performed +/-3 days from the targeted date; assessments performed after engraftment and through Day 90 may be done +/-10 days of the targeted date. After Day 90 assessments may be done +/- 30 days of the targeted date. In addition, targeted days may be altered as clinically appropriate.

Activity	Pre-BMT Work-Up	Day 1 To Engraftment[1]	Follow-Up Days 42-90	Follow-Up (>Day 90 through Day 540)
Consent	No Window			
Medical History	Within 30 days	Daily	weekly	X (day 180, 360, 540)
Physical Exam	Within 30 days	Daily	weekly	X (day 180, 360, 540)
RT consultation	No Window			
Karnofsky/Lansky	Within 30 days		day 90	X (day 180, 360, 540)
GVHD Assessment		weekly start day 7	weekly, day 90	X (day 180, 360, 540)
CBC/diff/plt	Within 30 days	Daily	weekly	X (day 180, 360, 540)
PT/INR	Within 60 days			
Viral Screen	Within 60 days			
PRA (Donor Specific Antibody)	Within 60 days			
Basic metabolic panel		Daily		
Comprehensive metabolic panel	Within 30 days	2x/wk	weekly	X (day 180, 360, 540)
eGFR for adults with creat > 1.2 or hx or renal dysfunction	Within 30 days			
Pregnancy test (females of childbearing potential)	Within 30 days			
BM Biopsy	Within 60 days	X (day 30)	X (day 90)	X (day 180, 360, 540)
BM chimerism		BM (day 30)	BM (day 90)	BM (day 180, 360, 540)
Blood chimerism		PB (day 30)	PB (day 90)	PB (day 180, 360, 540)
PETCT (lymphoma only)	Within 60 days			X
Minimal Residual Disease	Within 60 days	BM (day 30)	BM (day 90)	BM (day 180, 360, 540)
T-Cell Immune Reconstitution Panel	Within 60 days	PB (day 30)	PB (day 90)	PB (day 180, 360, 540)

Activity	Pre-BMT Work-Up	Day 1 To Engraftment[1]	Follow-Up Days 42-90	Follow-Up (>Day 90 through Day 540)
CMV PCR (blood)		Weekly	Weekly	
HHV6 PCR (blood)		Weekly	Weekly	
PFT/DLCO	Within 60 days			
MUGA or Echo	Within 60 days			
CT Chest/Sinus	Within 60 days			
Disease Evaluation	Within 60 days	X (day 30)	X (day 90)	X (day 180, 360, 540)
Research Bone Marrow and Blood Sample[2]	No Window	X (day 30)		X (day 180)
Blood samples for MMF		X (day 7)[3]		

1 Engraftment defined as absolute neutrophil count (ANC) ≥ 5 X 10^8/L for 3 consecutive measurements
2 Research blood samples will be used for cyclophosphamide genomics studies. Research blood samples will be collected in EDTA blood collection tubes and research marrow samples will be collected in sodium heparin tubes. Excess blood and marrow samples from existing samples (including those collected for MCC 14690) may be stored for future correlative studies in lieu of collecting a new sample.
3 Blood for MMF pharmacokinetic studies will be obtained on day 7 at the following time points: pre-dose, post-dose, 1 hour, 2 hour, 4 hour, and 8 hours after dose in EDTA blood collection tubes. Collections may occur +/- 10 minutes from the scheduled interval.

NOTE: Patients with a history of MDS or a history of 2 or more consecutive inductions/re-inductions to treat acute leukemia or CML blast crisis or prolonged neutropenia of at least 2 months immediately preceding transplant should have a chest CT without contrast to exclude occult fungal infection prior to transplant.

NOTE: In certain clinical circumstances (e.g.relapsed or terminally ill patients, risk of undue harm to patients, etc.) study tests may be omitted at the physician's discretion. Additionally, tests may be rescheduled as clinically indicated.

8.2 SAFETY AND OTHER ASSESSMENTS

Study participants will be monitored closely by study investigators based on clinical, laboratory and imaging studies as outlined in study calendar and per Moffitt institutional standard procedures. Adverse events, vital signs, clinical and laboratory tests will be assessed according to Schedule of Events until protocol termination. Treatment emergent adverse experiences will be summarized based on CTCAE severity grade.

8.3 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES OR OTHER ENDPOINTS

Specimen Type	**Baseline (Pre-treatment)**	***Day 7***	***Day 30***	***Day 180***
Cyclophosphamide Genomics (EDTA blood samples)	*X*			
Mycophophenolate pharmacokinetics (EDTA blood samples)		X		
*Blood and marrow for future studies (EDTA tubes for blood, heparin tubes for marrow)**	*X*		X	X
*Blood and marrow samples for future studies may be added on to previously collected (off-trial) samples and/or research samples from other protocols (including MCC 14690) if excess sample is available.				

8.3.1 MYCOPHENOLATE PHARMACOKINETICS

Blood samples for the determination of Mycophenolate mofetil (MMF) and Mycophenolic Acid (MPA) concentrations will be collected in the study. Free and total drug will be determined for both. The actual PK sampling times should be recorded accurately in the PK requisition forms. Measurements will be taken on post-transplant day 7 at pre-dose and then at the end of the infusion, followed by 1, 2, 4, 8 hours after the end of infusion. Collections may occur +/- 10 minutes from the scheduled interval. If samples are not collected on day 7 (e.g., due to day 7 falling on a holiday or weekend), then samples may be collected within 3 days of day 7 (days 8, 9, or 10). MMF PK samples should NOT be collected prior to day 7.

a. Pharmacokinetic Blood Sample Collection and Handling

At each specified time point, a single 10 mL EDTA tube will be used to collect blood. Vacutainers will be kept on crushed ice after blood collection. Within 30 minutes, the tubes will be centrifuged for 5 minutes at 1100 x g at 4°C to separate the plasma. After centrifugation, plasma will be transferred into polypropylene screw-cap tubes labeled appropriately for total drug assays of MMF and MPA. Remaining plasma will be added to specialty centrifuge devices to create free-fractionate of drug. These aliquots will be assayed for free concentrations of each drug. All samples will be stored at of -80ºC until analysis.

Day	MMF/MPA PK 1
Day 7	Pre-dose

Day 7	EOI
Day 7	1 hr post +/-10 min
Day 7	2 hr post +/-10 min
Day 7	4 hr post +/-10 min
Day 7	8 hr post +/-10 min

1. All collection time points after administration are relative to the end of infusion, regardless of length of administration and dosage.

b. Analytical Methods

Concentrations of MMF and MPA will be determined by the Translational Research Core at the Moffitt Cancer Center using LC/MS/MS methods that have been validated according to ICH/FDA guidelines for bio-analytical analysis.

8.3.2 CYCLOPHOSPHAMIDE PHARMACOGENOMICS

In order to assess the presence of single nucleotide polymorphisms (SNPs) in 6 genes of interest that influence drug metabolism (CYP2B6, CYP2C19, CYP2C9, CYP3A5, GSTP1, ALDH1A1), targeted sequencing will be performed using a Qiagen QiaSeq Pharmacogenomics Panel. Qiagen QiaSeq panels incorporate unique molecular indices (UMIs) which facilitate accurate variant allele frequency reporting while also reducing the number of artefactual variants. Briefly, the sample DNA will be enzymatically fragmented, followed by followed by end-repair, A-addition, and adaptor ligation. Target enrichment with locus-specific primers and library amplification will be performed, and the final libraries will be screened on an Agilent TapeStation (Agilent Technologies, Inc., Santa Clara, CA) and quantitated by qPCR with the Kapa Library Quantification Kit (Roche Diagnostics, U.S., Indianapolis, IN). The indexed samples will be sequenced on the NextSeq 500 sequencer (Illumina, Inc. San Diego, CA) with150-base paired-end reads. Data analysis including alignment and variant calling will be performed using the QiaSeq data analysis pipeline.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any unexpected medical occurrence associated with the use of a drug or therapy in humans, whether or not considered drug related. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a drug. Infection, acute and chronic GVHD will not be considered adverse events.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

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

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 5.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page *http://evs.nci.nih.gov/ftp1/CTCAE/About.html*

8.4.3.2 EVENT DOCUMENTATION

Transplant related outcomes and events will be recorded in the Blood and Marrow Transplantation (BMT) database.

Events requiring prompt reporting to the Moffitt Cancer Center Protocol Monitoring Committee, the Institutional Review Board (IRB), early stopping rule events, and protocol deviations will be documented in OnCore.

8.4.3.3 RELATIONSHIP TO STUDY INTERVENTION

Anticipated toxicity following allogeneic transplantation:

There are numerous anticipated adverse consequences of transplantation, which include, but are not limited to conditioning regimen related toxicity such as severe mucositis, cytokine release syndrome, idiopathic pneumonia syndrome, hepatic veno-occlusive disease and death, early and late infectious complications, potentially severe or fatal acute or chronic graft vs. host disease,

and relapse of primary disease and its complications. Thus, expected complications of transplantation will not be collected as adverse events on this trial.

Suspected Adverse Events

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the event.

Unexpected

An adverse event is considered unexpected if it is not listed in the investigator brochure, occurs in severity greater than previously described, or - for the purpose of this protocol - if it is not in keeping with expected post-transplantation toxicity.

Adverse event recording:

Non-serious AE: Only unexpected, grade 3-5 AE will be recorded.

Serious AE: All SAE will be recorded.

Adverse event reporting:

Non-serious AE: Unexpected, grade 3-5 AE will be reported to the IRB in summary form on an annual basis.

8.4.3.4 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate case report form (CRF). Information to be collected will include event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All events beginning with start of study intervention until 30 days after the last day of study intervention will be reported. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4.5 ADVERSE EVENT REPORTING

Grade 3 or higher unexpected AEDs will be recorded from initiation of conditioning chemotherapy through day +90 after transplant infusion at each examination on the Adverse Event case report forms/worksheets.

8.4.6 SERIOUS ADVERSE EVENT REPORTING

The principal investigator will report each serious adverse event, regardless attribution, within 24 hours of learning of the occurrence. In the event that the principal investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the principal investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. The SAE report must include event term(s), serious criteria, and the investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration.

8.4.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.4.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.4.9 REPORTING OF PREGNANCY

Pregnancy, although not itself a serious adverse event, should also be reported and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.5.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Moffitt Cancer Center Protocol Monitoring Committee. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 7 days of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL ENDPOINTS

Primary Endpoint: The primary endpoint is the probability of disease-free survival (DFS) by 1.5 years post-transplant. An event will be defined as death or a relapse.

Secondary Endpoints:

- Probability of Grade II-IV and Grade III-IV aGVHD at 180 days
- Probability of TRM at 6 months and 18 months
- Probability of relapse at 18 months
- Probability of OS at 18 months

Transplant Related Endpoints

- Probability of neutrophil recovery by day +30
- Probability of platelet recovery by day +60
- Proportion of donor cell engraftment (chimerism) at days +30, +60, +90, +180 and +365
- Probability of 18 months chronic GVHD
- Probability of 18 months overall GVHD
- Probability of 18 months GRFS
- Probability of serious fungal and viral infections at day +100 and 18 months post-HCT

9.2 SAMPLE SIZE DETERMINATION

The primary endpoint of this study is disease-free survival (DFS). The historic DFS at 18 months is 40%.[67-69] We assume that the DFS at 18 months in patients treated with Flu/TBI and low dose Mel will be 60%, corresponding to a hazard ratio (HR) of 0.557. A total of 18 events will be required to have 90.2% power to detect a HR of 0.557 using a log-rank test at a one-sided significance level of 0.1. Assuming uniform accrual over an 18-month accrual period and total study duration of 36 months, the estimated sample size is 34 subjects.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

The final analysis for the primary endpoint will be conducted when 18 events are observed. The time-to-event endpoint will be analyzed by using the Kaplan-Meier (KM) method as the primary analytic tool. The association with time-to-event endpoint will be explored by using Cox proportional hazard regression model. If the competing risk exists, the competing risk approach and Fine-Gray regression model will be used.

Cumulative incidence will be used to estimate the probabilities of GVHD, relapse, infection, and neutrophil and platelet recovery treating deaths as a competing risk. For GVHD endpoint, relapse and death will serve as the competing risks. The Gray test will be used accordingly. The probability of TRM will be estimated in a similar manner but treating relapse as a competing risk.

Ninety-five percent confidence intervals will be estimated from respective standard errors and the complementary log-log transformation. The proportion of donor chimerism (classified as ≥70% donor cells at various time-points will be estimated among patients who have survived to the evaluated time-point). Descriptive plots and measures will also be used to evaluate chimerism as a continuous measure. Medians, ranges and inter-quartile ranges will be given for actual chimerism values. Analyses will be performed and plots generated using SAS 9.3 (SAS Institute, Cary, NC) and/or R 3.0.2.

9.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The disease-free survival (DFS) is defined as the time from the date of PBSCT to first documentation of relapse or death due to any cause, whichever comes first. Patients who do not relapse and are still on the study at the time of an analysis, will be censored at the date of the last disease assessment documenting absence of relapse. The final statistical analysis will be conducted when 18 events (deaths or relapses) are observed. The Kaplan-Meier (KM) method and complementary log-log transformation will be used to estimate the DFS and the associated confidence interval. If the lower limit of one-sided 90% confidence interval at 18 months is greater than 40%, then the null hypothesis will be rejected. As a secondary approach, the Cox proportional hazard regression model will be used to explore the association with covariates.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Overall survival (OS) is defined as the time from the date of PBSCT to the date of death due to any cause. OS will be censored at the last date the patient is known to be alive. The GVHD-free/relapse-free survival (GRFS) is defined as the time from the date of PBSCT to date of events which include grade 3-4 acute GVHD, systemic therapy-requiring chronic GVHD, relapse, or death, whichever comes first. OS, GRFS, and 95% confidence interval will be computed by the KM method and complementary log-log transformation. The cumulative incidence of acute GVHD, relapse, and treatment-related mortality will be estimated by the competing risk approach

as described in section 9.3.1. As these are secondary endpoints, no multiplicity adjustment is considered.

9.3.4 MYCOPHENOLATE PHARMACOKINETIC ANALYSES

Non-compartmental methods will be used to calculate the pharmacokinetic parameters. The parameters will be determined separately for each subject using the concentration at each sampling time. Phoenix™ WinNonlin® ver 8.1 (www.Pharsight.com) will be used for the pharmacokinetic calculations. The maximum measured concentration, C_{max}, and its associated time will be used as the C_{max}, and T_{max} values for each subject. The area under the plasma concentration curve from time zero to the time of the last measurable concentration (AUC_{0-t}) and from time zero to infinity ($AUC_{0-\infty}$) will be calculated where applicable. The elimination rate constant (k_e) clearance (CL), and volume of distribution (V_z) calculated from the terminal elimination phase will also be calculated where applicable. The elimination rate constant will be converted to the terminal half-life, $t_{1/2}$, ($t_{1/2} = \ln 2/k_e$). The reliability of the pharmacokinetic parameters will be determined using the correlation coefficient, r^2, for the fit of the elimination constant to the terminal data points. Data with good fits are characterized by $r^2 > 0.9$. Subjects will be dichotomized by using the median value (i.e., ≤ median vs. > median). The incidence of acute GVHD by PK parameters will be estimated by the competing risk approach. The association with the incidence of acute GVHD will be explored by the Fine-Gray regression model. No multiplicity adjustment is considered. Correlations with clinical endpoints may be pursued.

9.3.5 CYCLOPHOSPHAMIDE PHARMACOGENETIC ANALYSES

The single nucleotide polymorphisms (SNPs) in the 6 genes (CYP2B6, CYP2C19, CYP2C9, CYP3A5, GSTP1, ALDH1A1) known to impact cyclophosphamide metabolism will be analyzed by QiaSeq pharmacogenomics panel. The incidence of acute GVHD by SNPs will be estimated by the competing risk approach. The association with the incidence of acute GVHD will be explored by the Fine-Gray regression model. No multiplicity adjustment is considered. Correlations with clinical endpoints may be pursued.

9.3.6 EXPLORATORY ANALYSES

Not applicable

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 SCIENTIFIC REVIEW COMMITTEE (SRC)

The Cancer Center's internal SRC provides the review for scientific merit and prioritization and monitors scientific progress for all protocols at the Cancer Center. The SRC has a defined membership representing all of the major research divisions of the cancer center, including biostatisticians. The SRC reviews newly proposed clinical research studies based on the following categories:

a. study significance to evaluate its potential for contribution to medical science.

b. the adequacy of study objectives, design, specific aims and hypotheses.

c. the methods to be employed to conduct the study. Ensuring that the study is adequately described, including inclusion/exclusion criteria, sample size, procedures and instruments to be used.

d. Feasibility of the study. Ensuring the investigator has adequate staffing and facilities to conduct the study. Ensuring that the timeframe for the study and projected annual accrual are adequately addressed.

e. Review of all data and safety monitoring plans.

The SRC will also evaluate the risk/benefit assessment and corresponding Data & Safety Monitoring Plan (DSMP), evaluate and may recommend frequency of monitoring. The SRC will identify any potential conflicts of interest related to the proposed research. The SRC may also evaluate and recommend the monitoring frequency of clinical trials they approve.

10.1.2 THE PROTOCOL MONITORING COMMITTEE (PMC)

The Protocol Monitoring Committee (PMC) is a multidisciplinary, peer review, standing committee established to oversee clinical research conducted at Moffitt Cancer Center to monitor scientific progress and data quality. It also serves as a component of the Data Safety Monitoring Plan (DSMP) for oncology trials at MCC. The membership of the PMC includes physicians and scientists from various program areas.

The PMC provides ongoing monitoring of all clinical research studies for safety, validity and integrity of data, adverse events, conflicts of interest, and overall compliance with GCP or other applicable clinical research guidelines or regulations. In addition to the protocol stopping rules, the PMC is authorized to suspend a trial for non-compliance with a DSMP or as a result of audit findings deemed unacceptable.

10.1.3 CORPORATE COMPLIANCE

The Corporate Compliance Office is the coordinating center for internal audits of clinical trials conducted at the Cancer Center and its affiliates. These audits will provide for a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data was recorded, analyzed and accurately reported, according to the Institutional Review Board (IRB) approved protocol, Center's policies, Good Clinical Practices (GCP): Consolidated Guidance, and applicable regulatory requirements.

Audits are conducted by Corporate Compliance in accordance with applicable regulatory standards. Corporate Compliance will conduct and report the findings of audits to the PMC.

The PMC will determine the findings to be: *acceptable, acceptable with corrective action, or unacceptable.* Corporate Compliance will follow up to ascertain whether corrective actions, which have been agreed to, are achieving the desired results. The PMC will be informed of all significant open follow-up items. For those observations where no action has been taken, Corporate Compliance will inform the PMC who may take action as appropriate.

10.1.4 INTERNAL MONITORING

Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice(GCP) guidelines, and applicable regulatory requirements.

10.1.5 INSTITUTIONAL REVIEW BOARD (IRB)

The trial will not be initiated without approval of the appropriate Institutional Review Board (IRB). All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments will be approved by the IRB in compliance with current regulations of the Food and Drug Administration prior to initiation unless necessary to protect the safety and welfare of subjects; in which case, the IRB will be notified within 24 hours of implementing the change.

The IRB will be kept informed by the investigator as to the progress of the study as well as to any serious or unusual adverse events.

10.1.6 INFORMED CONSENT PROCESS

10.1.7 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

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

10.1.8 CONSENT PROCEDURES AND DOCUMENTATION

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. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document.

The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants 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.

10.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.2.1 TOXICITY MONITORING AND STOPPING RULES

Sequential boundaries will be used to monitor for TRM, graft failure, and relapse rate. The tables below show the stopping boundaries for TRM (T_n), graft failure (G_n), and Relapse (R_n), for a given number of patients up to that point. The trial will be halted if at least one of the stopping boundaries is reached, and the data will be reviewed by the Moffitt Cancer Center Protocol Monitoring Committee. This is a Pocock-type stopping boundary proposed by Ivanova et al. that yields the probability of crossing the boundary at most 10% if

- TRM rate at day 100 is ≤30%,
- graft failure rate at day 100 is ≤20%,
- relapse rate at day 100 is ≤30%.

For example, if 2 TRMs are observed in 3 patients, the trial will be halted due to the excessive TRM. Table 2 contains the probability of early stopping for given true TRM, graft failure, and relapse rates. If the true TRM rate, for example, is unacceptably high (30%), the stopping rule has greater than 92% probability of early stopping.

Table 1: Early Stopping Boundaries for the TRM (T_n), graft failure (G_n), and Relapse (R_n)

Number of Patients, n	Stopping Boundaries			Number of Patients, n	Stopping Boundaries		
	T_n	G_n	R_n		T_n	G_n	R_n
1	NA	NA	NA	18	10	8	10
2	NA	NA	NA	19	11	8	11
3	3	3	3	20	11	8	11
4	4	3	4	21	11	9	11
5	5	4	5	22	12	9	12
6	5	4	5	23	12	9	12
7	5	5	5	24	13	10	13
8	6	5	6	25	13	10	13
9	6	5	6	26	13	10	13
10	7	5	7	27	14	10	14
11	7	6	7	28	14	11	14
12	8	6	8	29	14	11	14
13	8	6	8	30	15	11	15
14	9	7	9	31	15	11	15
15	9	7	9	32	16	12	16
16	9	7	9	33	16	12	16
17	10	8	10	34	16	12	16

Table 2: Probability of early stopping for given true TRM, graft failure, and relapse rates

Ture TRM rate	Probability of Early Stopping	Ture Graft Failure rate	Probability of Early Stopping	Ture Relapse rate	Probability of Early Stopping
0.3	0.0984	0.2	0.0986	0.3	0.0984
0.4	0.392	0.3	0.454	0.4	0.392
0.5	0.7867	0.4	0.8437	0.5	0.7867
0.6	0.9721	0.5	0.9825	0.6	0.9721
0.7	0.9991	0.6	0.9995	0.7	0.9991
0.8	1	0.7	1	0.8	1
0.9	1	0.8	1	0.9	1
1	1	0.9	1	1	1

10.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Moffitt Cancer Center. With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Moffitt Cancer Center. These samples could be used to research the causes of hematologic malignancies and/or post-transplant outcomes. The Moffitt Cancer Center will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

10.3.1 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Nelli Bejanyan, MD
Moffitt Cancer Center
12902 Magnolia Drive *Tampa, FL 33612*
813-745-6008
Nelli.Bejanyan@moffitt.org

10.3.2 SAFETY OVERSIGHT

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB and the study sponsor. The Protocol Monitoring Committee (PMC) will review these SAEs in accordance with the protocol-specific DSMP. The data and safety plan will define dose limiting toxicities, rules for escalation of dose, and criteria for stopping the trial and defining the Maximum Tolerated Dose (MTD) according to rules set forth by this protocol. This trial will be continuously monitored by the PI and the research team and reviewed at monthly BMT Research Group meetings. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

10.3.3 CLINICAL MONITORING

MCC's Internal Monitors will periodically monitor regulatory documents and case report forms according to the protocol specific clinical monitoring plan. Monitoring will include review of data for accuracy, completeness, and source verification, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

10.3.4 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.]

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.3.5 DATA HANDLING AND RECORD KEEPING

10.3.6 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The Principal Investigator and the Clinical Trial Coordinator(s) assigned to the case will be primarily responsible for maintaining all study related documents including clinical research forms, as

applicable. ONCORE is the database of record for all CRF entries and will be verified with source documentation. The review of medical records within PowerChart will be done in a manner to assure that patient confidentiality is maintained.

Data collected will be stored in Moffitt Cancer Center's database system, ONCORE. Identifying patient information will be kept confidential. Representatives of the IRB and the FDA will have access to patient information as it pertains to the study. Privacy and confidentiality of the information will be protected to the extent provided by law.

10.3.7 STUDY RECORDS RETENTION

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

10.3.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

10.3.9 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information

from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.3.10 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.4 ADDITIONAL CONSIDERATIONS

Not applicable

10.5 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
CTMS	Clinical Trial Management System
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies

HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICH E6	International Conference on Harmonization Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
MCC	Moffitt Cancer Center
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PMC	Protocol Monitoring Committee
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem

10.6 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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Appendix

APPENDIX I CYTOKINE RELEASE SYNDROME GRADING

Grading of Cytokine Release Syndrome
(Assess daily and any time there is a change in patient status)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor (with or without vasopressin)	Requiring multiple vasopressors (excluding vasopressin)
❖ And/or				
Hypoxia	None	Requiring low-flow nasal cannula	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

Adapted from Lee DW, et al. Biol Blood Marrow Transplant. 2018 Dec 25. [Epub ahead of print]

- ❖ CRS grade is determined by the most severe event: hypotension or hypoxia not attributable to any other cause
- Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but do not influence CRS grading

Terms	Definitions
Fever	• Temperature ≥ 38°C not attributable to any other cause. • In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab/steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
Low-flow nasal cannula	• Oxygen delivered at ≤ 6 liters/minute. • Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics.
High-flow nasal cannula	• Oxygen delivered at >6 liters/minute.

Management of Cytokine Release Syndrome

CRS Grade	Sign or Symptom	Management
Grade 1	**Fever**	• Symptomatic management of constitutional symptoms and organ toxicities • Acetaminophen and hypothermia blanket as needed for fever • Assess for infection, empiric broad spectrum antibiotics • IV fluids as needed • Consider tocilizumab for persistent fever lasting >3 days in patients with significant comorbidities or if patient is deteriorating
Grade 2 All Grade 2 Cardiac telemetry and pulse oximetry, consider ECHO	**Hypotension** *Not requiring vasopressors*	• IV fluid bolus of NS 500-1000 mL • If patient requires multiple fluids boluses assess fluid balance and consider tocilizumab. • For hypotension refractory to fluid boluses: tocilizumab 8 mg/kg IV. o For high risk patients *consider* tocilizumab + dexamethasone 10 mg IV x one • If no response, consider redosing tocilizumab 8 mg/kg IV (may be repeated every 8 h for up to 3 doses in a 24 h period) • If hypotension persists after fluids boluses and 1-2 doses of tocilizumab, or if patient is not improving or deteriorating: o Consider dexamethasone 10 mg IV every 6 hours. o Manage as grade 3 CRS (start vasopressors, transfer to ICU and obtain ECHO) • Symptomatic management of constitutional symptoms and organ toxicities
	Hypoxia *(Low-flow nasal cannula → O_2 delivered at ≤ 6 L/min)*	• Supplemental oxygen as needed • Tocilizumab 8mg/kg IV o For high risk patients *consider* tocilizumab + dexamethasone 10 mg IV x one • If hypoxia persists after above interventions; however oxygen requirement is stable, continue close monitoring. • Tocilizumab may be repeated every 8 h for up to 3 doses in a 24 h period • If oxygen requirement increases or patient deteriorates: o Consider dexamethasone 10 mg IV every 6 hours o Manage as Grade 3 CRS • Symptomatic management of constitutional symptoms and organ toxicities
Grade 3	**Hypotension** *Requiring one vasopressor +/- vasopressin*	• IV fluid boluses as needed, vasopressors as needed • Transfer to ICU, obtain ECHO if not performed already • Tocilizumab if not administered previously • Start dexamethasone 10 mg IV every 6 hours if not started previously. Alternatively methylprednisolone 1 mg/kg IV every 12 hours may be used. • Symptomatic management of constitutional symptoms and organ toxicities

	Hypoxia *(High-flow nasal cannula → O_2 delivered at ≥6 L/min)*	• Supplemental oxygen as needed • Tocilizumab if not administered previously • Start dexamethasone 10 mg IV every 6 hours if not started previously. Alternatively methylprednisolone 1 mg/kg IV every 12 hours may be used. • Symptomatic management of constitutional symptoms and organ toxicities
Grade 4	**Hypotension** *Requiring multiple vasopressors*	• Vasopressors, tocilizumab and ECHO as above • Consider changing corticosteroids to high dose methylprednisolone 1000mg/day IV. • Symptomatic management of constitutional symptoms and organ toxicities
	Hypoxia *Requiring positive pressure*	• Supplemental oxygen requiring positive pressure ventilations: (CPAP, BiPAP, intubation and mechanical ventilation) • Tocilizumab • Consider changing corticosteroids to high dose methylprednisolone 1000 mg/day IV. • Symptomatic management of constitutional symptoms and organ toxicities

Adapted from Neelapu S, et al. Nat Rev Clin Oncol. 2018;15:47-62, Lee DW, et al. Biol Blood Marrow Transplant. 2018 Dec 25. [Epub ahead of print]

High risk for CRS: bulky disease, co-morbidities, early onset of CRS within 3 days of infusion

Table 3. Dosing

Drug	Dose	Notes
Tocilizumab[1]	8 mg/kg IV over 60 minutes (total volume 100 mL) Up to three doses in 24 hours, up to 4 doses total. Doses a minimum of 8 hours apart Maximum dose of 800 mg	First line treatment for CRS May be used for treatment of ICANS if associated with concurrent grade 2 CRS
Dexamethasone	10 mg IV every 6 hours	Continue until improvement to grade 1 or less and then consider taper
Methylprednisolone	1 mg/kg every 12 hours	Alternative to dexamethasone
High dose methylprednisolone	500 mg IV every 12 hours (1000 mg/day) for 3 days followed by -250 mg IV every 12 hours for 2 days, -125 mg IV every 12 hours for 2 days, -60 mg IV every 12 hours	Taper after improvement to grade 1 CRS or ICANS

APPENDIX II – KARNOFSKY PERFORMANCE STATUS

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

APPENDIX III – TBI GUIDELINES

All patients who have had previous radiation therapy or TBI will be seen by Radiation Oncology prior to entrance on the protocol for approval for additional 200 cGy of TBI. TBI may be delivered by local guidelines provided the effective dose is equivalent to what is recommended in the TBI Guidelines.

Patients ineligible for this protocol include those who have had previous irradiation to areas of the body such that the Radiation Oncologist feels that even a relatively small dose of total body irradiation (TBI) cannot safely be given.

The dose of TBI will be 200 cGy given in a single fraction on Day -1.

The dose rate will be between 10-19 cGy/minute prescribed to the midplane of the patient at the level of the umbilicus.

The TBI will be delivered with right and left lateral fields with the patient semi-recumbent in a semi-fetal position with their arms at their sides.

Based on measurement of transverse thickness, aluminum compensators will be used to ensure that the dose homogeneity across the fields is within 10% of the prescribed dose. Usually head/ neck, leg and lung compensators are used (although based on calculated mid-mediastinal doses, lung compensators are often not needed if the thickness of the arms, which partially shield the lung, are taken into the thickness consideration).

TBI will be delivered with a linear accelerator using 6, 10, or 18 MV photons. The energy used will be based on the calculated dose to midline at points along the patient's torso. The lowest energy that gives 90-100% of the prescriptions point dose will be used.

A beam "spoiler" will be used to ensure a full skin dose.

Half value layer lung and kidney blocks will not be utilized for patients who have not previously received total body irradiation.