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Adoptive Immunotherapy in Patients with Relapsed Hematological Malignancy: Effect of Duration and Intensity of Early GVHD Prophylaxis on Long-Term Clinical Outcomes
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Virginia Commonwealth University Massey Cancer Center

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Adoptive Immunotherapy in Patients with Relapsed Hematological Malignancy: Effect Of Duration and Intensity of Early GVHD Prophylaxis on Long-Term Clinical Outcomes

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REVISION HISTORY

Version 2, Version Date 06/23/2017

- The date and version number were updated on the cover page and throughout the protocol.
- Dr. Gary Simmons was added as a Co-Investigator on the cover page.
- A Revision History page was added.
- The List of Abbreviations was updated.
- Clarifications were made in the Background in Section 1.1 and text regarding G-CSF and GM-CSF was re-arranged in Section 1.2.
- A study goal of comparing the survival rate of patients with multiple myeloma in either study cohort with historical control patients was added to the study. Text was added in the following sections to address this goal: Rationale (Section 1.2); Exploratory Objectives (Section 2.3.5); and Statistical Considerations (Sections 13.3.3).
- The secondary endpoints (Section 3.3.1) were rearranged to improve their organization.
- Text describing the stratification factors based on diagnosis was revised in the Schema and in Sections 1.4, 3.1, and 13.2 to include the malignancies added in eligibility (see below).
- The types of eligible hematologic malignancies were expanded to include patients with acute lymphocytic leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome (Section 4.1.1).
- The note regarding HLA-matched stem cells in unrelated donors was clarified (Section 4.1.4).
- The age of the eligible patient population was expanded to include patients with an age of 40-49 years (Section 4.1.5).
- The note regarding substitutions for infection prophylaxis was expanded to allow substitutions if toxicities develop (Section 6.5).
- The instructions regarding tacrolimus were revised to allow adjustment in target tacrolimus levels for drug toxicity (bullet 1, Section 6.7.1).
- The instruction regarding the duration of MMF-15 and MMF-30 was clarified (Sections 6.8, 6.8.1, and 6.8.2).
- The description regarding relapse prevention interventions was revised to allow relapse prevention therapy to be given after day 60 in patients who are at high risk for relapse (Section 6.11.1).
- Exceptions to the requirement for recording AEs (AEs expected with stem cell transplant) were added in Section 8.4.
- The relapse criteria text in Section 10.5.3 was revised to include the malignancies added in the inclusion criterion in Section 4.1.1 as noted above.

- The study calendar was corrected by removing 2 time points for collection of flow cytometry samples from Table 4 (row 22, columns 2 and 3).
- The permitted window of time for tests/assessments was revised in footnote C of Table 4 to provide more flexibility after 6 months.
- Text was added in footnote P of Table 4 to explain the purpose of pre-transplant genotyping for chimerism determination.

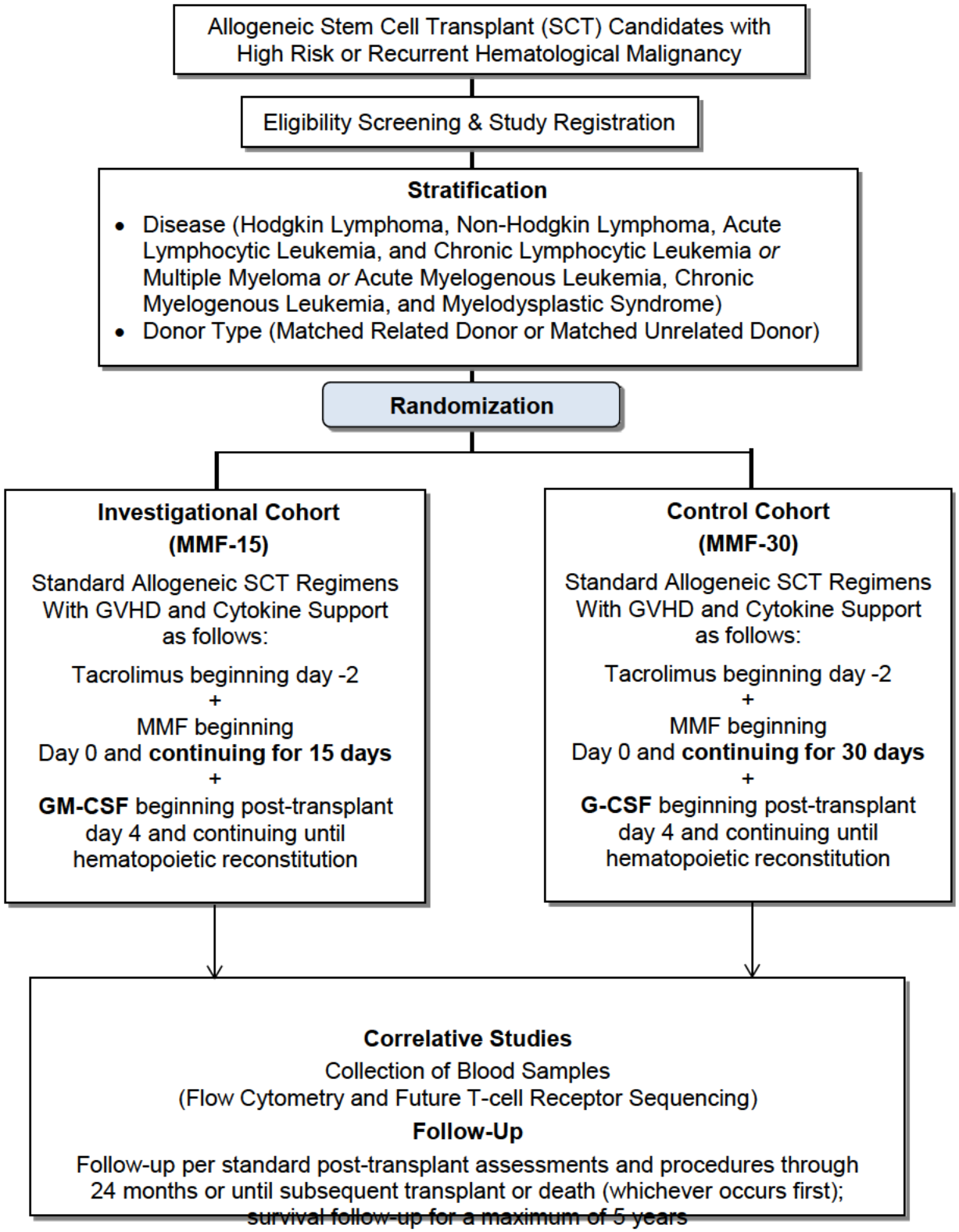
Version 1, Version Date 07/23/2015

Initial version of the protocol.

LIST OF ABBREVIATIONS

AE	adverse event
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
AST	aspartate aminotransferase
ATG	rabbit, anti-thymocyte globulin (Thymoglobulin; Sanofi-Aventis)
AUC	area under the curve
BID	twice per day
BMT	bone marrow transplant
BP	blood pressure
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	chronic myelogenous leukemia
CRF	case report form
CTCAE v4.0	Common Terminology Criteria for Adverse Events Version 4.0
cGVHD	chronic graft versus host disease
ddCD3	donor-derived $CD3^+$ (cell count)
DLCO	diffusing capacity of the lung for carbon monoxide
DLI	donor lymphocyte infusion
DSMC	Data Safety and Monitoring Committee
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage colony stimulating factor
GVHD	graft versus host disease
HCT	hematopoietic cell transplant
HL	Hodgkin lymphoma
HLA	human leukocyte antigen
IBW	ideal body weight
MCC-VCUHS	Massey Cancer Center-Virginia Commonwealth University Health System
MDS	myelodysplastic syndrome
MM	multiple myeloma
MMF-15	mycophenolate mofetil – 15 day duration
MMF-30	mycophenolate mofetil – 30 day duration
MRD	matched related donor
NHL	Non-Hodgkin lymphoma
OHRP	Office for Human Research Protections
PBSC	peripheral blood stem cells
PO	by mouth
RIC	reduced intensity conditioning
SAE	serious adverse event
SCT	stem cell transplantation
TBI	total body irradiation
TRM	transplant-related mortality
ULN	upper limit of normal
UP	unanticipated problem
URD	unrelated donor
VCU	Virginia Commonwealth University
WBC	white blood cell
WCBP	woman of childbearing potential

STUDY SCHEMA



1 BACKGROUND

1.1 Introduction

The last decade has seen allogeneic stem cell transplantation (SCT) evolve from a single intense therapeutic intervention in young healthy individuals, to a series of adoptive immunotherapy interventions resulting in disease control in older individuals with comorbidities (1-8). In this study, we will utilize a regimen combining low dose total body irradiation (TBI) and rabbit anti-thymocyte globulin (ATG; Thymoglobulin, Sanofi-Aventis) to facilitate SCT with human leukocyte antigen (HLA)-matched related and unrelated donors (9-13). Based on the hypothesis that early treatment interventions have significant late effects in allogeneic SCT, a simple intervention, varying the duration of intense immunosuppression following SCT, will be investigated in this study. Patients will receive graft versus host disease (GVHD) prophylaxis using 2 different immunosuppressive regimens with tacrolimus + mycophenolate mofetil (MMF). Patients randomized to the investigational cohort will receive MMF for 15 days following SCT with cytokine support using granulocyte macrophage colony stimulating factor (GM-CSF) beginning on post-transplant day 4. Patients randomized to the control cohort will receive MMF for 30 days following SCT with cytokine support using granulocyte colony stimulating factor (G-CSF) beginning on post-transplant day 4.

Despite the advancements made in allogeneic SCT over the past few decades, patient survival following allogeneic SCT remains highly unpredictable. The ability to identify unique immunologic profiles for patients with next generation sequencing and recently discovered patterns in genetic variation relating to donors and recipients may be critical tools in the process of furthering the understanding of patient prognosis following allogeneic SCT. A dynamical modeling system approach will be utilized to explore the validity of predicting patient outcomes post-transplant based on analysis of individual immune reconstitution in a trial comparing temporal variation of GVHD prophylaxis.

1.2 Rationale and Previous Work

The rationale for this study is based on the recent findings that transplant outcomes are determined by the rate of T-cell reconstitution and lymphoid recovery in the first 2 months of SCT.

Donor-derived T cells exert a powerful anti-malignancy effect in patients with acute and chronic myeloproliferative and lymphoproliferative disorders. However, these disorders largely affect an elderly population where patients are unable to tolerate complications of SCT resulting from alloreactivity between donors and recipients, specifically GVHD. Adoptive immunotherapy interventions, such as reduced intensity conditioning and SCT followed by DLI, have resulted in disease control in older individuals. While this has enabled clinicians to pursue SCT in large numbers of elderly patients with hematological malignancy, GVHD remains a major complication of transplantation and continues to take a heavy toll on these patients.

Further complicating matters is the unpredictability in the likelihood of GVHD developing in HLA-matched individuals transplanted using identical preparative regimens. Ability to predict clinical outcomes in patients as they go through the transplant process would be a

major advance in the clinical management of these patients. Clinical medicine is replete with phenomenon where interventions produce predictable results in a majority of instances. Examples of this may be seen most readily in cardiovascular and pulmonary medicine, where administration of a beta-blocker may slow down a tachycardic rhythm or administration of a beta-agonist relieves bronchospasm. In both these instances, administration of a drug, which interrupts or facilitates passage of an ionic current across cell membranes, yields an outcome, which may be predicted with a fair measure of confidence in most patients. Indeed these systems may be considered analogous to dynamical systems often encountered in the physical sciences, where a measurable change of state is produced over time as the variables determining that state undergo change, for example, change in velocity as an object accelerates. Thus, by reducing the excitability of the cardiac conduction system, beta-antagonists can stabilize a chaotic cardiac rhythm and restore normal sinus rhythm.

Unlike the clinical situations described above, survival likelihood following allogeneic SCT remains probabilistic despite decades of clinical refinement and advances. Attempts to predict outcomes in individuals undergoing this life-saving, albeit dangerous, procedure are limited to calculations of survival odds derived from population-based studies. Although generalities such as HLA matching, availability of a family donor, application of certain pharmacological interventions, or others do predict for better results when cohorts of patients are examined, foretelling the course of an individual transplant recipient remains impossible. This has led to stochastic modeling of transplant interventions, which though valuable in identifying factors contributing to improved population outcomes, fails to yield mechanistic insights into transplant immunobiology when examined in an ‘isolated’ donor-recipient pair.

Recently, application of next generation sequencing has led to the unveiling of a remarkably complex immune repertoire in allogeneic transplant recipients following transplantation. While on the surface this complexity is chaotic and disorganized, it does offer an excellent opportunity to explore the unique patterns that may characterize each individual’s immunologic repertoire during reconstitution (14). Furthermore, the genetic variation demonstrated between individual transplant donors and recipients displays a corresponding degree of complexity to that of the post-transplant immune repertoire, making it entirely plausible that the latter is predicated upon the former (15, 16). If this is the case, then SCT may be considered to be a dynamical system; as such, SCT may be susceptible to the interpretation and analysis applicable to a dynamical system if all the variables determining the evolution of the system following SCT can be identified and quantified (17).

Several lines of evidence suggest that early interventions during the course of SCT have a profound influence on long-term outcomes in transplant recipients. This is analogous to certain types of dynamical systems, where minor modifications in the state of the system at an early time point can produce large variation in later outcomes. Extrapolating this logic to SCT suggests that it is likely that interventions made early in the course of transplant may have profound effects on the later stages of immune reconstitution. The progression of immune reconstitution following SCT appears to follow the same dynamics that govern the growth of biological systems. These growth dynamics are described by the logistic equation describing sigmoidal growth (18), which models initial slow growth followed by exponential expansion, eventually culminating in a stable population. The parameters

describing the lymphocyte reconstitution curve in each individual are associated with clinical outcomes.

The next generation sequencing work done by our group also reveals a previously undescribed magnitude of alloreactivity potential between SCT donors and recipients. This provides an explanation for drugs such as ATG that can ameliorate the risk of GVHD. In a recently concluded trial, our group demonstrated that it is feasible to combine ATG with low dose TBI. A lower dose of ATG results in reliable T-cell engraftment with low risk of GVHD. However, disease relapse remains a problem and is more prevalent when the rate of immune reconstitution is low. The dynamical system nature of immune reconstitution would imply that relatively minor changes in treatments earlier in the course of SCT will result in significant long-term therapeutic effects in patients. Therefore, a clinical trial comparing 2 cohorts of patients treated uniformly with a background of ATG and TBI, except for small differences in early post-transplant immunosuppression, would be informative in this regard. Further, in addition to optimizing clinical outcomes, such a study may yield important mechanistic insights into the interaction between the kinetics of immune reconstitution and clinical outcomes.

G-CSF (filgrastim) and GM-CSF (sargramostim) are regulatory glycoproteins that stimulate the proliferation, differentiation, and functional activity of neutrophils. While G-CSF is a late-acting hematopoietin restricted to the neutrophil lineage, GM-CSF is a multi-lineage hematopoietin essential for production of granulocytes, monocytes, and macrophages (19). We have recently shown that early monocyte recovery is associated with faster T-cell reconstitution in ATG-conditioned patients (20). Thus, we hypothesize that using GM-CSF following transplantation would enhance monocyte recovery and subsequent T-cell reconstitution. While experience with GM-CSF following allogeneic SCT is more limited than experience with G-CSF, several randomized, double-blind trials have shown significantly reduced time to achieve neutrophil recovery with the use of GM-CSF after bone marrow or peripheral blood stem cell (PBSC) transplantation (21-24). Additionally, a large meta-analysis identified no significant increase in the risk of acute or chronic GVHD following treatment with GM-CSF (25).

A further goal of this study will be comparison of clinical outcomes achieved with allografting in patients with multiple myeloma. Allografting for myeloma is a therapeutic conundrum given the competing risks of disease relapse and non-relapse mortality from GVHD and immune compromise. Given the focus of this trial on ameliorating GVHD and consequently minimizing immunosuppression, it is logical that, compared to standard allografting approaches, myeloma patients will experience an improvement in survival because of the reduction in non-relapse mortality. In order to accomplish these comparisons, we will conduct an analysis comparing outcomes in myeloma patients transplanted on this trial with historical outcomes in patients matched for clinical characteristics, but who did not undergo allografting.

1.3 Preliminary Data

The clinical trial we propose is based on an allogeneic SCT regimen incorporating rabbit anti-thymocyte globulin (ATG) and low dose (450 cGy) TBI. This regimen is based on the preclinical model of using anti-T-cell antibodies prior to SCT to achieve a tolerant platform on which to perform adoptive immunotherapy with DLIs.

The rationale for the use of ATG in this regimen is to facilitate engraftment and deplete donor T cells capable of causing acute and chronic GVHD (26, 27). The combination of ATG and TBI has further been shown to reduce GVHD by altering residual host T-cell subsets to favor regulatory natural killer T cells (12, 28). These specific T cells may suppress GVHD by polarizing donor conventional T cells toward secretion of non-inflammatory cytokines such as IL-4 and promoting expansion of donor T regulatory cells.

Given that reduced intensity conditioning (RIC) relies on the graft vs malignancy effect mediated primarily by donor T cells, there is concern the use of ATG may increase relapse in this setting. In 2011, a large retrospective registry analysis from the Center for International Blood and Marrow Transplant Research (CIBMTR) was published (29). This analysis examined outcomes of adult patients with hematologic malignancies who received RIC from 2000 to 2007 and included 879 patients who did not receive ATG and 584 patients who received varying doses and preparations of ATG. In the multivariate analysis, relapse rates at 3 years were higher in the ATG group vs non-ATG group (49% vs. 38%, p <0.01), negatively impacting overall survival. While the results of this trial raise important questions regarding the use of ATG in RIC, we do not believe the findings of this analysis can be applied to our trial design. The median dose of rabbit ATG administered to patients included in the CIBMTR report was high at 7mg/kg and administered closer to the time of stem cell infusion based on the most common conditioning regimens reported (fludarabine and busulfan, fludarabine and melphalan, and fludarabine and cyclophosphamide). The ATG dose proposed in our trial is lower at 5.1 mg/kg and administered early (days -9 through -7), limiting effects on donor T cells. In a similar study of total lymphoid irradiation and ATG conducted by Lowsky and colleagues, ATG was administered early prior to allogeneic SCT on days -11 through -7. Serum levels of active ATG (capable of binding CD3+ T cells) were measured and were nearly undetectable on the day of transplantation and absent beyond day +7 (30). Finally, the relapse results noted in the CIBMTR registry report are also limited by the lack of data on immune reconstitution and use of DLI.

The ATG+TBI regimen is followed by tacrolimus and MMF for GVHD prophylaxis. In earlier versions of this regimen, a schedule of ATG (10 mg/kg) given from day -10 to day -7 prior to blood stem cell infusion was found to yield superior T-cell recovery when compared with ATG administered more proximal to SCT (31).

In a follow-up trial to determine the optimal dose of ATG, a schedule of 5.1 mg/kg delivered on day -9 to -7 was found to accomplish superior T-cell engraftment when compared with a 7.5 mg/kg dose in patients with hematological malignancies (32). In the cohorts treated to date using this regimen, classical onset of grade III-IV acute GVHD has not occurred, nor has day 100 treatment-related mortality. Higher rates of mixed chimerism and the need for DLI (4/19 and 10/22 in ATG5 and ATG7.5, respectively) were recorded in the higher dose ATG arm. Patients with higher donor-derived T-cell counts (ddCD3) at 8 weeks post-transplant were more likely to achieve full donor chimerism and have a lower relapse rate, but sustained a higher frequency of GVHD (33). With 41 patients enrolled in this randomized phase 2 trial stratified for donor type (matched related donor [MRD] [n=19] vs unrelated donor [URD] [n=22]), overall survival at 2 years in the 2 arms was similar (68±1% vs 63±1%, p=NS) (Figure 1). Relapse occurred in 32% (6/19) vs 46% (10/22) of the ATG5 and ATG7.5 patients, respectively (Chi-square P=0.364).

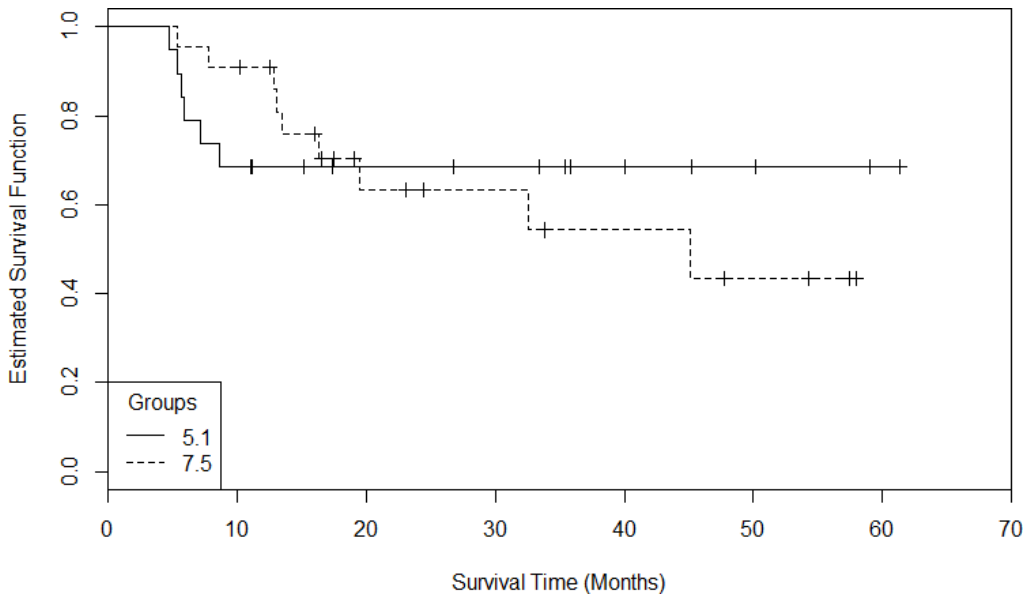
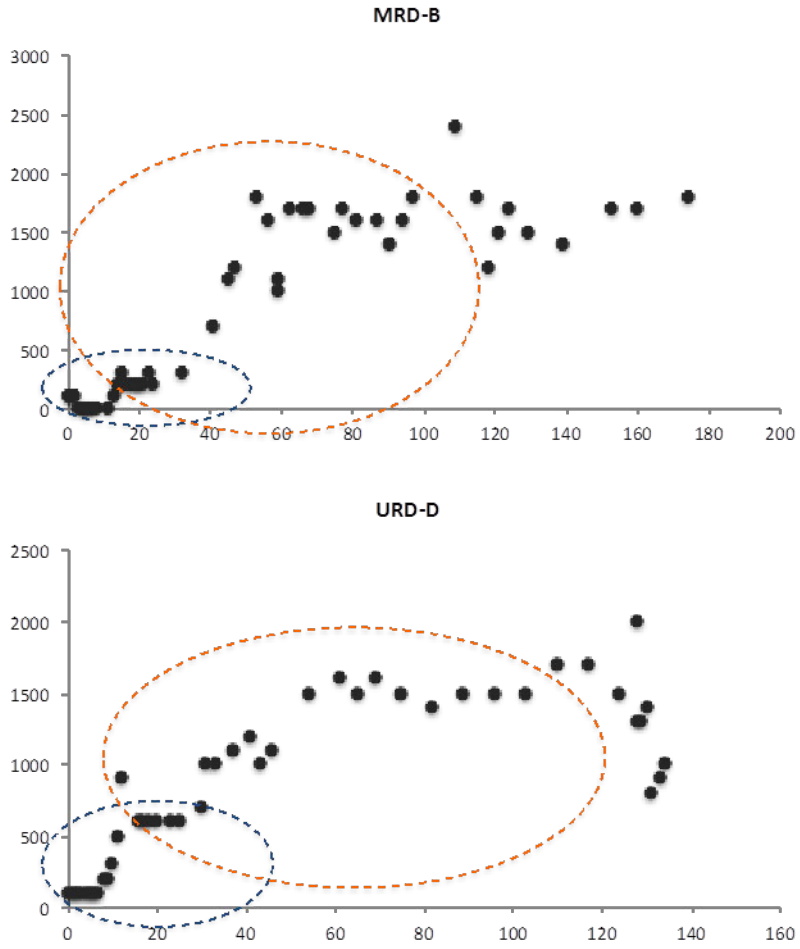


Figure 1. Comparison of overall survival in ATG TBI conditioned patients randomized to 2 ATG doses (P=0.7)

Given the importance of donor-derived T cells in terms of clinical outcomes, the T-cell receptor β repertoire was studied using high throughput sequencing of the T-cell receptor β. This revealed that rather than a random collection of T-cell clones, the immune repertoire in normal donors and SCT recipients had a fractal organization. Furthermore, when the genomic differences between donors and recipients of SCT were determined using whole exome sequencing, a very large amount of protein coding variation was observed. This variation across the exome, when translated to HLA-binding oligopeptides, demonstrated a HLA-binding affinity profile that mirrored the T-cell repertoire organization (34). This observation suggests that SCT represents an example of a dynamical system, albeit a very complex system, where T-cell clonal expansion mimics population growth and may be modeled using the logistic equation.

Absolute lymphocyte count recovery was defined as an average representation of T-cell clonal recovery and plotted for each individual patient following SCT (Figure 2). Notably, several individuals demonstrated a biphasic logistic growth curve. The first phase of exponential lymphocyte growth was observed coincident with engraftment around day 15-20 post-transplant and a second exponential growth phase was observed after cessation of MMF around day 40-50. This is consistent with the observation that the day 60 ddCD3 count has prognostic significance. It also provides an important clue regarding the optimal timing of immunological intervention following SCT.

A.



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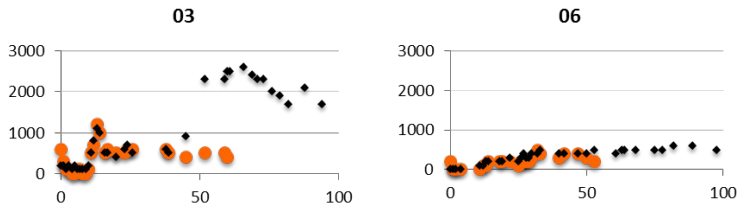

Figure 2. (A) Absolute lymphocyte count (μL^{-1}) recovery following ATG+TBI and either MRD or URD SCT; (B) Association of early monocyte recovery with late lymphocyte recovery

In (A) of Figure 2, two periods of logistic growth are seen: from day 0-30 when patients are on MMF (blue outline) and from day 20 to approximately day 120 (orange outline). Each of these periods demonstrates an initial phase of slow growth followed by exponential expansion before finally leveling out with relatively stable counts until tacrolimus is discontinued. In (B) of Figure 2, two different patterns of monocyte recovery are associated with different lymphocyte recovery kinetics (20).

1.4 Proposed Study

In this trial we will attempt to optimize post-transplant immunosuppression in a cohort of patients conditioned using an ATG-based regimen, with the goal of improving long-term immune reconstitution. This will likely reduce the risk of opportunistic infections, graft loss, and relapse in patients undergoing reduced intensity conditioning with a regimen incorporating ATG. Abbreviating the course of MMF will allow faster T-cell reconstitution. Additionally, we have recently shown that early monocyte recovery is associated with faster T-cell reconstitution in ATG-conditioned patients. Using GM-CSF would enhance monocyte recovery in patients, potentially improving T-cell reconstitution.

In a series of trials investigating ATG use with low dose TBI, the optimal dose and schedule of ATG has been determined (31, 33). In the first trial the optimal schedule for ATG dosing with low dose TBI was determined; in the follow-up trial the dose of ATG to be given was selected. In the proposed study we will utilize the regimen combining rabbit anti-thymocyte globulin (ATG; Thymoglobulin, Sanofi-Aventis) 1.7 mg/kg/day given on day -9 through day -7, and 450 cGy TBI delivered in 3 fractions of 150 cGy each on day -1 and day 0. SCT will be with blood stem cells or marrow from HLA-matched related and unrelated donors.

Based on the hypothesis that early treatment interventions have significant late effects in allogeneic SCT, the main interventions to be investigated in this study are: 1) varying the duration of intense immunosuppression following SCT and 2) administering different cytokines for hematopoietic reconstitution. Patients will receive GVHD prophylaxis with 2 different immunosuppressive regimens using tacrolimus + MMF. Patients in the control cohort will receive MMF for 30 days following SCT and, in the investigational cohort, MMF will be given for 15 days post SCT. The control arm patients will receive G-CSF 5 mcg/kg/day (filgrastim) for hematopoietic reconstitution, while the patients in the investigational arm will receive 250 mcg/m^2/day of GM-CSF (sargramostim) (35).

An adaptive trial design will be used, with the study endpoint for adaptive allocation on the 2 study cohorts being donor-derived T-cell recovery at post-transplant day 60. Patients will be stratified by diagnosis (Hodgkin lymphoma [HL], Non-Hodgkin lymphoma [NHL], acute lymphocytic leukemia [ALL], and chronic lymphocytic leukemia [CLL] *or* multiple myeloma [MM] *or* acute myelogenous leukemia [AML], chronic myelogenous leukemia [CML], and myelodysplastic syndrome [MDS]) and by donor type (matched related *or* matched unrelated). Following adaptive allocation, patients will be eligible to undergo disease-specific relapse prevention therapies according to MCC-VCUHS BMT Program standards. Subsequent to this, patients will be followed for survival, relapse, GVHD, and immune reconstitution endpoints.

The impact of variation in the duration and intensity of early post-transplant GVHD prophylaxis in patients conditioned with ATG 5.1 mg/kg and low dose TBI will be studied. Lymphoid recovery following SCT appears to follow a bilogistic pattern with the current GVHD prophylaxis regimen. It appears that the one month long course of MMF following SCT delays T-cell reconstitution and may delay the establishment of full donor T-cell chimerism in ATG-based reduced intensity conditioning regimens. Because the first phase of exponential lymphoid expansion was observed around the time of engraftment and

because in the dynamical system model the very first phase of the T-cell clonal growth will be critical for the long-term outcome, the investigational arm will have MMF discontinued at day 15 to allow uninhibited growth of T-cell clonal populations. This will likely be reflected in ddCD3 recovery at 8 weeks post SCT. Hypothetically, the relapse rate and opportunistic infection incidence will be reduced in these patients as compared to the control cohort.

Two post-transplant outcomes will be studied in this randomized phase 2 SCT trial: clinical outcomes and immune reconstitution in the background of genetic variation between donors and recipients. The ddCD3 cell count at 8 weeks post-transplant will be used to adaptively allocate patients to the 2 study arms, which will compare post-transplant GVHD prophylaxis with MMF given for either 15 days or 30 days. As noted above, in the previous trials a marked increase in lymphocyte counts following the cessation of MMF was frequently observed. This makes it plausible that discontinuation of MMF earlier will hasten lymphocyte recovery and lead to improved clinical outcomes.

Patients with hematological malignancies will be conditioned using ATG 5.1 mg/kg given in divided doses from day -9 thru -7, followed by 450 cGY TBI in 3 fractions administered on day -1 and day 0. Blood stem cells from HLA-A, -B, -C, and -DRB1 8/8 matched related or unrelated donors will be provided and post-graft GVHD prophylaxis will be administered using tacrolimus (day -3 to day 120; tapered thereafter depending on donor-derived T-cell count) and MMF.

The randomization of the stratified cohorts will be between MMF 15 mg/kg administered twice daily from day 0 to day 30 in the control cohort (MMF-30) and day 0 to day 15 in the investigational cohort (MMF-15). The MMF-30 arm is similar to the regimen used in MCC-11561 and will serve as the control arm, whereas the investigational arm will be MMF-15, where MMF will be discontinued closer to the time of myeloid engraftment. Patients in the investigational arm (MMF-15) will also receive sargramostim (GM-CSF) for hematopoietic reconstitution with the hypothesis that this will lead to more robust monocyte recovery and consequently rapid lymphocyte reconstitution. Patients randomized to the control cohort (MMF-30) will receive filgrastim (G-CSF). Presumably, this will result in faster and more robust eventual T-cell reconstitution, helping reduce relapse and infection risk without affecting GVHD risk.

1.5 Investigational Regimen

1.5.1 MMF

MMF is a potent uncompetitive inhibitor of inosine monophosphate dehydrogenase and, therefore, inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas, other cell types can utilize salvage pathways, the active component of MMF (mycophenolic acid [MPA]) has potent cytostatic effects on lymphocytes. MPA also inhibits proliferative responses of T and B cell mitogens, antibody formation by B cells, and prohibits glycosylation of glycoproteins that mediate adhesion.

MMF is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants. In experimental animal models, MMF has been demonstrated to prolong the survival of allogeneic transplants

(e.g., kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow). MMF has been extensively studied in clinical trials following bone marrow transplantation and has been included in GVHD prophylaxis following blood and bone marrow transplant for more than 15 years.

Gastrointestinal adverse reactions including diarrhea, nausea/vomiting, and mucositis have been reported. Constitutional symptoms include pain, fever, headache, and asthenia. Hematological toxicities, such as anemia and leukopenia, occur in 25% of patients. Peripheral edema has also been reported.

Previous clinical studies in patients after renal allografting suggested that the principal adverse reactions associated with the administration of MMF include diarrhea, leukopenia, sepsis, vomiting, and a higher incidence of certain viral infections, e.g., cytomegalovirus (CMV), varicella zoster virus, and herpes simplex virus.

1.5.2 Cytokine Support following SCT

The cytokine to be used for hematopoietic reconstitution will be specified as part of the randomized treatment regimen. The investigational cohort (MMF-15) will receive GM-CSF (sargramostim) to potentially provide more robust monocyte recovery and consequently rapid lymphocyte reconstitution. The control cohort (MMF-30) will receive granulocyte colony stimulating factor (G-CSF; filgrastim). Both colony stimulating factors have been used extensively in the treatment of patients receiving myelosuppressive therapies since initial approval by the Food and Drug Administration (FDA) in 1991.

1.6 Potential Risks and Benefits of the Investigational Regimen

1.6.1 Potential Risks

The potential risks associated with the study design include a higher risk of acute and/or chronic GVHD and higher risk of engraftment syndrome in the investigational cohort. These potential risks are included in the stopping criteria described in Section 13.5.

1.6.2 Potential Benefits

As described previously, reducing the intensity of the GVHD prophylaxis by shortening the duration of MMF will potentially result in faster and more robust eventual T-cell reconstitution, helping reduce relapse and infection risk.

1.7 Correlative Studies

To allow for mathematical modeling changes over time, additional blood samples for flow cytometry to assess monocytes, T-cell subset, B cell, and natural killer (NK) cell recovery will be drawn (4 mL) at 2, 6, and 10 weeks (in addition to the standard time points of 4, 8, 12, 24, and 52 weeks). Additional blood samples will be drawn (4 mL) pre-transplant, about 30 days and 100 days post-transplant, and at the time of GVHD diagnosis. These will be processed and stored for future T-cell receptor (TCR) sequencing. Cryopreserved

peripheral blood mononuclear cells (PBMCs) will be obtained and stored through the VCU Tissue and Data Acquisition and Analysis Core (TDAAC).

2 OBJECTIVES

2.1 Primary Objective

To determine the difference in the relapse-free/DLI-free survival rate between patients randomized to MMF-30 (control cohort) and MMF-15 (investigational cohort)

2.2 Secondary Objectives

2.2.1 To determine the difference between patients randomized to MMF-30 (control cohort) and MMF-15 (investigational cohort) in the following:

2.2.1.1 Day 60 ddCD3

2.2.1.2 Overall survival (OS)

2.2.1.3 Rate of acute GVHD

2.2.1.4 Rate of chronic GVHD

2.2.1.5 Rate of opportunistic infection

2.2.1.6 Rate of graft loss

2.2.1.7 Rate of engraftment syndrome

2.2.1.8 Rate of achieving donor chimerism

2.2.1.9 T-cell recovery kinetics following SCT

2.3 Exploratory Objectives

2.3.1 To evaluate dynamic exposure to immunosuppressive therapies

2.3.2 To determine HLA-specific alloreactivity potential between HLA-identical transplant recipients

2.3.3 To determine T-cell receptor beta and alpha repertoire restoration kinetics following SCT

2.3.4 To explore the association and relationship between T-cell recovery kinetics, dynamic exposure to immunosuppressive therapies, HLA-specific alloreactivity potential between HLA-identical transplant recipients, and T-cell receptor beta and alpha repertoire restoration kinetics

2.3.5 To determine the difference in survival rate between patients with multiple myeloma in either study cohort (MMF-15 or MMF-30) and historical control patients with multiple myeloma who have relapsed but have never received an allogeneic transplant

3 STUDY DESIGN

3.1 General Description

This is a randomized phase 2 trial for patients with high risk or recurrent hematological malignancies who are candidates for reduced intensity allogeneic stem cell transplantation. All transplant-related treatment interventions are performed according to standard transplant procedures with the exception of the duration (15 days vs 30 days) of MMF, an agent routinely included in GVHD prophylaxis. The agent used for cytokine support for the investigational cohort (MMF-15) will be GM-CSF; G-CSF will be included in the treatment regimen for the control cohort (MMF-30). Both cytokines are routinely used following allogeneic SCT.

Patients enrolled in the study will undergo randomization stratifying them according to diagnosis (HL/NHL/ALL/CLL or MM or AML/CML/MDS) and donor type (matched related donor or matched unrelated donor [MRD or URD]). A total of 60 patients will be accrued in the study over a period of 5 years.

3.2 Primary Endpoint

The proportion of patients with event-free survival in the investigational cohort compared to the proportion of patients with event-free survival in the control cohort where the conditional events are the occurrence of relapse or DLI.

3.3 Secondary Endpoints

3.3.1 Secondary endpoints for the objective to determine the differences between patients randomized to MMF-30 (control cohort) and MMF-15 (investigational cohort)

3.3.1.1 ddCD3 counts measured on day 60

3.3.1.2 Overall survival (days to event)

3.3.1.3 Diagnosis of acute GVHD

3.3.1.4 Diagnosis of chronic GVHD

3.3.1.5 Diagnosis of an opportunistic infection

3.3.1.6 Diagnosis of graft loss

3.3.1.7 Diagnosis of engraftment syndrome

3.3.1.8 Donor chimerism

3.3.1.9 Number of T cells indicating recovery following SCT

4 PATIENT SELECTION

4.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible to participate in the study.

4.1.1 Any of the following high risk or recurrent hematological malignancies:

- Hodgkin lymphoma (HL)
- Non-Hodgkin lymphoma (NHL)
- Chronic lymphocytic leukemia (CLL)
- Multiple myeloma (MM)
- Acute myelogenous leukemia (AML)
- Acute lymphocytic leukemia (ALL)
- Chronic myelogenous leukemia (CML)
- Myelodysplastic syndrome (MDS)

Note: Determination that the malignancy is high risk will be made by the investigator.

4.1.2 Investigator determination that the patient is an appropriate candidate for reduced intensity allogeneic SCT with the standard MCC-VCUHS BMT Program regimen employed in this trial

4.1.3 Patients with or without previous myeloablative autologous transplant

4.1.4 HLA-matched stem cell donor, either related (6/6 or 5/6 loci matched) or unrelated (8/8 or 7/8 loci matched)

Note: Unrelated donors should be matched at HLA-A, -B, -C, and -DRB1 loci. However, a single locus mismatch will be acceptable in the event a more closely matched donor is not available.

4.1.5 Age ≥ 40 to < 75 years; patients 18 to 39 years of age will be eligible only if the investigator has determined that the patient has comorbidity(ies) precluding conventional allogeneic transplantation with full intensity myeloablative conditioning

4.1.6 Karnofsky Performance Status of 70-100%

4.1.7 Negative serology for HIV

4.1.8 Women who are not postmenopausal or have not undergone hysterectomy must have a documented negative serum pregnancy test per standard MCC-VCUHS BMT Program guidelines

4.1.9 Ability to understand and the willingness to sign a written informed consent document

Note: The consent form must be signed and dated prior to initiation of SCT preparative treatments (see Section 6.4).

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria is ineligible to participate in the study.

4.2.1 Previous therapeutic radiation therapy (RT) that exceeds critical structure tolerance doses as determined by a radiation oncologist

4.2.2 Uncontrolled viral, fungal, or bacterial infection

4.2.3 Active meningeal or central nervous system disease

4.2.4 Previous therapy with rabbit anti-thymocyte globulin (ATG); previous treatment with equine ATG is allowed if more than 3 months ago

Note: Previous myeloablative autologous transplant is permitted but not required.

4.2.5 Pregnancy or breastfeeding

4.2.6 Medical, psychological, or social condition that, in the opinion of the investigator, may increase the patient's risk or limit the patient's adherence with study requirements

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Study Entry Procedures

5.1.1 Required Pre-Registration Screening Tests and Procedures

Refer to the study calendar in Section 12 for the screening tests and procedures that are required prior to registration, and for the timing of these events relative to the start of the SCT preparative regimen.

5.1.2 Study Enrollment

The following are needed for patient registration:

- Completed, signed, and dated eligibility checklist
- Signed and dated consent form

The patient's initial enrollment data (e.g., demographics, consent, eligibility, on study, treatment assignment) will be entered into the OnCore database within 24 hours of registration and before treatment begins.

5.2 Randomization Procedures

Upon registration, patients will be randomized to either the investigational cohort (MMF-15 with GM-CSF) or to the control cohort (MMF-30 with G-CSF) according to a pre-specified randomization assignment provided by the statistician (see Section 13.1).

5.3 Study Withdrawal

A patient will be removed from the study for any of the following reasons:

- Consent withdrawal for study treatment and study procedures
- If, in the opinion of the investigator, it is in the best interest of the patient to do so
- The study has been closed by the Principal Investigator
- The study has been closed by the study sponsor

The reason for withdrawal from the study and the date the patient was removed from the study must be documented in the case report form.

6 TREATMENT PLAN

6.1 Treatment Randomization

Eligible patients who consent to participate in the study will undergo randomization between 2 GVHD prophylaxis cohorts.

6.1.1 MMF-15 Cohort

The investigational cohort will receive MMF orally at a dose of 15 mg/kg BID from **day 0 to day 15.** GM-CSF will be administered by subcutaneous injection to support hematopoietic reconstitution.

6.1.2 MMF-30 Cohort

The control cohort will receive MMF orally at a dose of 15 mg/kg BID from **day 0 to day 30.** G-CSF will be administered by subcutaneous injection to support hematopoietic reconstitution.

6.2 HLA Typing

All HLA typing will be confirmed according to the standard procedures of the MCC-VCUHS BMT Program.

6.3 Peripheral Blood Stem Cell (PBSC) Mobilization

Donors should be mobilized using a standard stem cell mobilization protocol as follows:

- Filgrastim (G-CSF) 10 mcg/kg/day administered by subcutaneous injection beginning on day 1 of the stem cell mobilization protocol and continuing through day 5
- Apheresis performed on days 4 and 5; a CD34+ cell dose of at least 5 x 106 CD34+ cells/kg recipient body weight will be obtained, if possible.

For unrelated donors at National Marrow Donor Program (NMDP) centers, although PBSC will be the first choice, bone marrow will be acceptable based on donor choice if no other donors are available.

6.4 Preparative Regimen

6.4.1 ATG

All patients will receive rabbit ATG (Thymoglobulin, Sanofi-Aventis) at a dose of 1.7 mg/kg/day for 3 days (5.1 mg/kg total). ATG will be administered intravenously over 10-12 hours, starting on day -9 and continuing daily through day -7.

Patients who weigh greater than 125% of their ideal body weight (IBW) will have their ATG dose calculated using adjusted weight according to MCC-VCUHS BMT Program practice:

Adjusted Weight (KG) = [(Weight - IBW) × 0.4] + IBW

6.4.2 Premedications for ATG

ATG-related premedications should be administered as follows:

- Benadryl 50 mg IV, acetaminophen 650 mg PO, and methylprednisolone 2 mg/kg IV will be given on each day as a premedication for ATG.
- Repeat the methylprednisolone at the same dose halfway through each ATG infusion.

Patients will be monitored according to standard procedures of the MCC-VCUHS BMT Program for infusion-related side effects.

6.4.3 Total Body Irradiation (TBI)

TBI will be administered twice on day -1 and once on the morning of day 0 with an AP-PA technique, prior to hematopoietic cell infusion. The total dose of radiation is 450 cGy given in 3 fractions of 150 cGy/fraction and at a dose rate of 10-15 cGy/minute prescribed at the midpoint (central axis). No lens or lung shielding will be used.

6.5 Infection Prophylaxis

A standard regimen for infection prophylaxis will be followed as described below **beginning on day -9 (or earlier, if necessary per investigator's discretion)**.

Note: Investigators may substitute appropriate medications for patients who have an allergy history or if toxicities develop related to the medications listed.

- All patients will receive:
  - Voriconazole 200 mg PO every 12 hours or 4 mg/kg IV every 12 hours; may be discontinued when tacrolimus is stopped. Patients intolerant of voriconazole may receive fluconazole 400 mg PO daily.
  - Levofloxacin 500 mg/day PO; continue until neutrophil engraftment.
  - Bactrim DS once daily on 3 days a week; continue for 6 months post-transplant
- For CMV-seropositive donor or recipient:
  - Valacyclovir at 1000 mg TID for CMV prophylaxis; continue for 12 months post-transplant
- For CMV-seronegative donor *and* recipient:
  - Acyclovir 400 mg PO BID for HSV prophylaxis

Appropriate therapeutic substitution may be made in the event of drug intolerance or toxicity.

6.6 Transplant

- Peripheral blood stem cells/bone marrow will be infused intravenously according to standard procedures for the BMT Program at MCC-VCUHS on day 0, after the last TBI treatment.
- ABO-incompatible marrow will be red-cell depleted.
- Corticosteroids will **NOT** be routinely used to support cell infusion.

6.7 GVHD Prophylaxis

Two agents, tacrolimus and MMF, will be used for GVHD prophylaxis in all patients as follows:

6.7.1 Tacrolimus

- Tacrolimus will be initiated orally at 0.04 mg/kg/day in divided doses beginning on day –2 and continuing until day 90 maintaining levels of approximately 10-14 ng/μL in the first month after transplant and 8-12 ng/μL in the next 2 months after transplant. Target tacrolimus levels may be adjusted for drug toxicity at the investigator's discretion.

- Tacrolimus taper will begin at day 90 over a 2-month period at the transplanter's discretion. The tacrolimus taper schedule may be modified by the transplant attending physician according to clinical judgment based on relapse or GVHD risk or engraftment status.

6.7.2 MMF

- MMF will be taken orally at a dose of 15 mg/kg BID; the patient's adjusted weight will be used for dose calculation (see Section 6.4.1 for the formula for calculating adjusted weight).
- The dose may be rounded to the nearest capsule size (250 mg).
- If the patient cannot tolerate oral MMF, MMF may be administered IV using an equivalent IV dose.
- The duration of MMF will be per randomized cohort.
  - Patients randomized to the investigational cohort (MMF-15) will take MMF from day 0 to day 15.
  - Patients randomized to the control cohort (MMF-30) will take MMF from day 0 to day 30.

The randomized assignments for the duration of MMF and for the post-transplant cytokine support are illustrated in Figure 3.

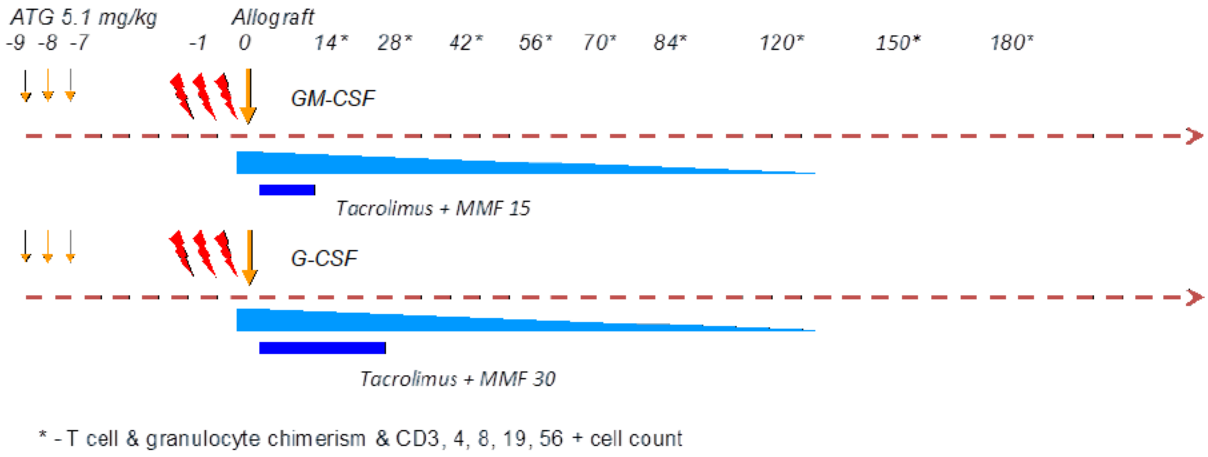

Figure 3. Overview of the randomized temporal variation of GVHD prophylaxis and randomized agent for cytokine support

6.7.3 Corticosteroids

Corticosteroids will not be used for GVHD prophylaxis and their use will be avoided as much as possible during the first month following SCT. However, corticosteroids may be used if clinically indicated.

6.8 Post-transplant Cytokine Support

Cytokine support will begin on post-transplant day 4 and continue at least until neutrophil engraftment, defined as an ANC > 500/µL on 3 consecutive days. The first of the 3 days is the day of engraftment.

6.8.1 Investigational Cohort (MMF-15)

Patients in the MMF-15 cohort will receive sargramostim (GM-CSF) 250 mcg/m^2/day beginning on post-transplant day 4 and continuing at least until neutrophil engraftment.

Patients receiving GM-CSF will also receive inhaled corticosteroids, fluticasone (Flovent) 2 puffs twice daily, starting on post-transplant day 4 and stopping after cessation of GM-CSF, to diminish the risk of pneumonitis.

Note: At investigator discretion, patients in the MMF-15 cohort who have preexisting pulmonary risk factors, will be permitted to receive G-CSF.

6.8.2 Control Cohort (MMF-30)

Patients in the MMF-30 cohort will receive filgrastim (G-CSF) 5 mcg/kg/day beginning on post-transplant day 4 and continuing at least until neutrophil engraftment.

6.9 Treatment of Acute GVHD

- Treatment of > grade II acute GVHD (see Section 10.6) will be initiated promptly with methylprednisolone until control is obtained, which will be determined by the investigator.
- Patients with steroid-refractory acute GVHD will be treated according to standard GVHD therapy protocols for the MCC-VCUHS BMT Program.

6.10 Post-Treatment Evaluation

- All patients will undergo standard blood tests for granulocyte and T-cell chimerism at approximately 2, 4, 6, 8, 12, 24, and 52 weeks following transplant.
- Flow cytometry to assess monocytes, T-cell subset, B cell, and NK cell recovery will be performed at 4, 8, 12, 24, and 52 weeks post-transplant. These assessments will also be performed at weeks 2, 6, and 10 for the correlative studies (Section 1.7).
- Relevant and disease-specific restaging studies will be performed per standard procedures of the MCC-VCUHS BMT Program following transplantation at approximately 3, 6, and 12 months post-transplant or earlier if clinically indicated.

6.11 Management of Mixed Chimerism/Relapse

6.11.1 Eligibility to Discontinue Immunosuppression and Administer DLI or Other Intervention

Patients demonstrating ≤ 90% donor chimerism (mixed chimerism) at any time point beyond approximately 8 weeks post-transplant and patients with residual/relapsing disease on restaging studies in the absence of GVHD at any time following transplant, will be eligible to discontinue immunosuppression and receive DLI or other relapse prevention intervention such as azacitidine (AML patients), rituximab (CD20-positive NHL), brentuximab (CD30-positive HL or ALCL), or lenalidomide (MM) along with tapering of tacrolimus at investigator discretion. For patients at high risk for relapse, relapse prevention therapy may be given after day 60.

Immunosuppression should be stopped or tapered before administration of DLI. DLI may be given the day following cessation of immunosuppression at the discretion of the investigator.

Active (i.e., ongoing or unresolved) grade 3 acute GVHD or moderate chronic GVHD is a contraindication for DLI. Caution should be exercised in DLI administration to patients with a previous history of steroid-refractory GVHD and grade III-IV active GVHD as well as extensive chronic GVHD.

6.11.2 Donor Lymphocyte Infusion (DLI)

- Donor lymphocytes will be collected with either G-CSF or without any stimulation, using standard apheresis techniques.
- In the absence of disease relapse, the first infusion will generally consist of 5 x10^6 CD3+ cells /kg recipient body weight. Dose escalation from 1 to 10 x10^7 CD3+ cells /kg is allowed for subsequent infusions. Four to 8 weeks will be allowed between infusions.
- Chimerism studies will be obtained at 4 weeks following DLI, and as clinically indicated thereafter. Disease restaging will be done as clinically indicated.

6.12 Graft Failure

Patients with failure to engraft the allogeneic stem cell graft beyond day 28 (or earlier at the discretion of the investigator) will be eligible to receive a hematopoietic stem cell (HSC) boost from the donor.

6.13 Additional Treatment Modalities

- Medications for the prevention of GVHD, other than those specified in this protocol, are **not** permitted.
- Appropriate therapeutic substitution for other transplant-related interventions may be made in the event of drug intolerance or toxicity.

6.14 General Concomitant Medication and Supportive Care Guidelines

Standard transplant-related supportive medications, other than non-protocol medications for the prevention of GVHD and cytokine support, may be administered at the investigator's discretion.

6.15 Follow-Up Period

The patient's follow-up status will be recorded in the source documents and the CRFs. Study follow-up will be conducted as follows:

6.15.1 Evaluation of Adverse Events (AEs)

Patients will continue to be evaluated for AEs until 6 months post-transplant or until the time of relapse, whichever occurs first.

6.15.2 Relapse-Free Survival

Follow-up for relapse-free survival will continue for 5 years following transplantation per standard post-transplant procedures or until subsequent transplant or death.

6.15.3 Survival

Patients will be followed for survival for 5 years.

7 DOSING DELAYS/DOSE MODIFICATIONS

There are no study-required dosing delays or dose modifications for any of the agents included in the SCT preparatory, GVHD prophylaxis, infection prophylaxis, or transplantation regimens. Dose modifications and delays, if needed for patient support and safety, will be per investigator discretion.

8 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

8.1.2 Serious AE (SAE)

An AE is considered “serious” if, in the view of the investigator, it results in any of the following outcomes:

- death,
- a life-threatening AE (An AE is consider “life-threatening” if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- inpatient hospitalization or prolongation of existing hospitalization,

  Planned inpatient hospitalizations are exempt from SAE reporting. Events that prolong hospitalization beyond the expected period of time and otherwise meet reporting criteria are, however, subject to SAE reporting requirements.
- 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 and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the patient 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 patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.4 AE Description and Grade

The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) will be utilized for AE reporting.

8.1.5 AE Expectedness

AEs can be 'Unexpected' or 'Expected'. Refer to Section 8.2 regarding expected AEs. Unexpected AEs are those AEs occurring in one or more patients participating in the study, the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease, disorder, or condition of the patient(s) experiencing the AE and the patient's predisposing risk factor profile for the AE.

8.1.6 AE Attribution

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

8.2 Known AEs Related to MMF, GM-CSF, and G-CSF

Patients randomized to the investigational cohort will receive MMF and GM-CSF. The control cohort will receive MMF and G-CSF. All 3 agents are routinely used in the clinical management of patients undergoing SCT. Refer to the current FDA-approved prescribing information for MMF, GM-CSF, and G-CSF.

8.3 Recording AEs, SAEs, and UPs

All AEs to be collected per protocol, all SAEs, and all UPs will be recorded per standard practice in the MCC-VCUHS BMT Program. In most cases, it is acceptable to record only the highest grade of a toxicity occurring during a particular study segment when an event has serial fluctuations in grade over time.

SAE's will be entered into the OnCore SAE domain. UPs will be entered into the OnCore Deviations domain. An SAE that is both an SAE and a UP will be entered in both domains. For all SAEs, a corresponding entry should be made in the routine AE record to match the event entries in the SAE domain. Additionally, events related to stopping criteria will be entered in OnCore as an event of special interest.

8.4 Time Period and Grade of AE Capture

AEs ≥ grade 3 including those expected with SCT (e.g., diarrhea, hematuria, hemorrhage, hypoxia, sepsis, mental status changers, pneumonitis, and veno-occlusive disease) will be recorded for study tabulation and analysis beginning on day 0 and continuing until day 180. Exception: Expected ≥ grade 3 cytopenias and changes in electrolytes (e.g., magnesium, potassium, phosphorus, and calcium) will **not** be recorded.

Toxicity assessments will include a review of all toxicities experienced during each assessment period. The highest grade of each ≥ grade 3 toxicity will be recorded.

8.5 AEs Requiring Expedited Reporting

All patients in this study will be receiving potentially toxic preparative therapy, therefore, significant regimen-related toxicity is anticipated, i.e., expected AEs.

8.5.1 Expedited Reporting Requirements

All grade 3, 4, and 5 ***unexpected*** AEs regardless of attribution will be reported in an expedited manner from the first dose of MMF (on day 0) until post-transplant day 180. (Refer to Section 8.5.2 for AEs that should NOT be considered unexpected.)

8.5.2 Expedited Reporting Exceptions

The following ≥ grade 3 toxicities/events are **expected** AEs:

- All laboratory abnormalities regardless of grade
- Hospitalization including hospitalization for the transplant procedure
- Infection
- GVHD
- Graft failure
- Progression or relapse
- Death
- Adverse events that are commonly observed after hematopoietic cell transplantation including anemia, minor bleeding episodes (e.g., epistaxis), hepatic veno-occlusive disease (VOD), and thrombotic microangiopathy (TMA)

8.6 Expedited Reporting Procedures for SAEs, and UPs

Refer to the table below for expedited reporting requirements.

Table 1. Expedited Reporting Requirements

SAEs	UPs
Principal Investigator[A] Amir A. Toor, MD Phone: 804-828-4360 Email: atoor@vcu.edu	**Principal Investigator**[A] Amir A. Toor, MD Phone: 804-828-4360 Email: atoor@vcu.edu
Study Coordinator[A] Catherine H. Roberts, PhD Phone: 804-828-1292 Email: croberts2@vcu.edu	**Study Coordinator**[A] Catherine H. Roberts, PhD Phone: 804-828-1292 Email: croberts2@vcu.edu
	DSMC[B] Email: masseydsmc@vcu.edu
	IRB[C]

A. Report event within 1 business day of becoming aware of the occurrence.

B. Report event within 5 business days of becoming aware of the occurrence.

C. Each UP must be reported to the VCU IRB within 5 business days of becoming aware of the occurrence.

9 PHARMACEUTICAL INFORMATION

Refer to the current FDA-approved prescribing information for the pharmaceutical information for all of the agents, including MMF, GM-CSF, and G-CSF, used in the management of patients enrolled on the study.

10 MEASUREMENT OF EFFECT

10.1 Engraftment

Hematopoietic engraftment is defined as all of the following:

- Recovery from post-transplant cytopenia with an absolute neutrophil count of ≥ 0.5 x 10^9 /L for 3 consecutive measurements or ≥ 1.0 x 10^9 /L for 1 day;
- Platelet count of ≥ 20 x 10^9 /L for 7 days without transfusion; and
- Evidence by chimerism studies that hematopoiesis is of donor origin (≥ 95% donor DNA by short tandem repeat (STR) analysis in whole blood, myeloid, and lymphoid lineages).

10.2 Complete Remission

Complete remission is defined as engraftment along with attainment of a normocellular marrow with trilineage hematopoiesis and without evidence of residual disease by conventional, cytogenetic, or molecular criteria (i.e., flow cytometry, fluorescence in situ hybridization [FISH], and polymerase chain reaction [PCR] for relevant disease-specific markers). CT scans should demonstrate normalization with any residual masses being negative by PET scanning in patients with lymphoma. Patients with myeloma should have a negative immunofixation.

10.3 Length of Relapse-Free/DLI-Free Survival and Survival

All study patients including those removed from the treatment protocol will be followed for survival every 3 months.

- Length of relapse-free/DLI-free survival is measured from transplant to relapse, DLI, death, or time of last contact, censoring for patients alive and relapse-free/DLI-free at the time of last contact.

- Length of survival is measured from transplant to death or time of last contact, censoring for patients alive at time of last contact.

10.4 Treatment Failure

Treatment failure is defined as death from toxicities associated with transplant procedure, relapse or progression of malignancy, or autologous hematopoietic recovery with loss of donor chimerism.

10.5 Relapse from Remission

10.5.1 Multiple Myeloma

In patients with multiple myeloma increase in the plasmacytosis to greater than 5% plasma cells and/or 25% or greater increase in paraproteinemia, appearance of new extramedullary or skeletal disease, will define relapse.

10.5.2 Hodgkin Lymphoma and NHL

In patients with Hodgkin lymphoma or NHL, 25% or greater increase in involved lymph nodes and histologically documented relapse at another site will be indicative of relapse or PET scanning with an SUV >4.

10.5.3 Acute Lymphocytic Leukemia, Acute and Chronic Myelogenous Leukemia, and Myelodysplastic Syndrome

Patients with ALL, AML, CML, and MDS will be considered as having relapsed if there is an increase in blast count to beyond 5% or recurrent cytogenetic abnormalities or molecular aberration defined by an abnormal FISH or PCR.

10.5.4 CLL

Patients who present in complete remission prior to transplantation may fulfill the relapse definition if there is reappearance of circulating malignant cells that are phenotypically characteristic of CLL.

10.6 GVHD Staging and Grading

Acute graft vs. host disease will be graded according to the CIBMTR acute GVHD system. The staging and grading criteria for GVHD are outlined on Table 2 and Table 3.

Table 2. GVHD Staging

Stage	Skin Rash (BSA %)	Gastrointestinal	Liver (Total Bilirubin)
1	< 25%	Diarrhea > 500 mL/day or persistent nausea	2-3 mg/dL
2	25-50%	Diarrhea > 1000 mL/day or persistent nausea	3.1-6 mg/dL
3	> 50%	Diarrhea > 1500 mL/day or persistent nausea	6.1-15 mg/dL
4	Generalized erythroderma with bullae	Large volume diarrhea and severe abdominal pain +/- ileus	> 15 mg/dL
From the Technical Manual of Procedures Version 3.0 of the Blood and Marrow Transplant Clinical Trials Network, 2013.			

Table 3. GVHD Grading

Overall Grade	Skin		Gastrointestinal		Liver
I	Stage 1-2	*and*	0	*and*	0
II	Stage 3	*or*	Stage 1	*or*	Stage 1
III	---	---	Stage 2-4	*or*	Stage 2-3
IV	Stage 4	---	---	*or*	Stage 4
From the Technical Manual of Procedures Version 3.0 of the Blood and Marrow Transplant Clinical Trials Network, 2013.					

11 CORRELATIVE STUDIES

11.1 Participation in Correlative Studies

Plans for the correlative studies are described in Section 1.7. Participation in the correlative studies using collected blood samples is mandatory.

The principal investigator should be contacted in the event that a correlative sample must be missed or is found to be inadequate for submission.

11.2 Processing and Distribution of Blood Samples

The VCUHS Immunopathology Laboratory will receive and process or distribute all correlative blood samples to the laboratories that will be performing the correlative studies.

11.3 Blood Samples for Correlative Studies

Time Points for Collecting Samples

- Blood samples (4 mL at each collection time point) will be collected for the correlative studies at post-transplant weeks 2, 6, and 10.
- Additional blood samples will be drawn (4 mL at each collection time point) pre-transplant and following transplant at 30 days, 100 days, and at the time of GVHD diagnosis. These will be processed and stored for future TCR and whole exome sequencing.

11.4 Labeling for all Blood Samples

Each collected blood sample should be labeled as follows:

- Study number
- Patient study identification number
- Date of sample collection
- Time of sample collection
- Study time point

11.5 Processing of Blood Samples

Samples will be processed, stored, and cataloged by TDAAC until the appropriate time for T-cell sequencing, which will be performed by a commercial laboratory selected for the study.

12 STUDY CALENDAR

12.1 Prior to Randomization

The hospital admission date and other treatments related to the transplant should be scheduled prior to randomization.

12.2 Following Randomization

Treatment should be initiated as soon as possible after randomization.

12.3 Study Calendar

Study-required assessments, tests, and collection of blood samples for correlative studies are outlined on Table 4.

Table 4. Study-Required Tests and Assessments

Assessments/ Other Requirements[A]	Baseline[B]	Transplant Day 0	Post-Transplant Day[C]									
			14	28	42	56	70	84	180	365	730	Years 3- 5 (annually)
Demographics	X											
Medical History	X											
Physical Exam	X	X	X	X	X	X		X	X	X	X	X[D]
Vital Signs including BP	X	X	X	X	X	X		X	X	X		
Performance Status	X							X	X	X	X	
Comorbidity Index Score	X											
Weight & Height	X											
HLA Typing[E]	X											
CBC, Differential, Platelet Count	X	X[F]	X[F]	X[F]	X[F]	X[F]		X	X	X		
Blood Chemistries[G]	X	X	X[H]	X[H]	X[H]	X[H]		X	X	X		
Serum Pregnancy Test	X[I]											
Creatinine Clearance	X											
Infectious Disease Titers[J]	X											
Cardiac Assessment[K]	X											
Pulmonary Function[L]	X								X	X	X	
Chest x-ray or Chest CT	X											
Disease Staging[M]	X											
Toxicity Assessment[N]				X		X		X	X	X	X	
GVHD Assessment[O]			X	X	X	X		X	X	X	X	X[D]
Chimerism[P]	X		X	X	X	X		X	X	X		
Flow Cytometry Samples[Q]			X[R]	X	X[R]	X	X[R]	X	X	X		
Correlative Blood Samples[S]	X[T]			Samples collected on day 30, day 100, and at time of GVHD diagnosis[T]								

Table 4 Footnotes:

A. In addition to the assessments/tests listed on Table 4, other tests and exams may be performed per standard guidelines for the MCC-VCUHS BMT Program and per investigator discretion.

B. Timing prior to randomization should be consistent with the usual MCC-VCUHS BMT Program practices to screen patients for SCT.

C. Following hospital discharge, assessments/tests should be performed within +/- 1 week of the day indicated on the calendar until 6 months; then +/- 3 weeks.

D. For patients who are not able to return for evaluation during years 3-5, follow-up may be performed by telephone contact with the patient or through the patient's referring physician.

E. Donor and recipient.

F. Frequency per standard practice of the MCC-VCUHS BMT Program.

G. Blood chemistries include serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and additional tests per investigator discretion.

H. Blood chemistries performed twice weekly until hospital discharge; performed weekly after hospital discharge until weekly testing is no longer indicated per investigator assessment.

I. For WCBP: At baseline (prior to study enrollment), serum pregnancy test within 30 days prior to initiation of the preparatory regimen.

J. Infectious disease markers include: CMV, EBV, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV-1 and -2 and HTLV-I and –II antibody, varicella zoster, and toxoplasmosis.

K. Cardiac assessments include ECG and left ventricular ejection fraction or shortening fraction by echocardiogram or MUGA.

L. Pulmonary function tests include DLCO (adjusted for hemoglobin), FEV1, and FVC.

M. Relevant and disease-specific staging according to the MCC-VCUHS BMT Program usual practice.

N. Refer to Section 8 for AE reporting requirements and instructions.

O. Performed weekly until Day 63 post-transplant and as indicated on the calendar; assessment will include review of all abnormalities experienced during entire assessment period; highest grade for each abnormality (whether attributed to GVHD or not) will be recorded on the appropriate CRF.

P. Granulocyte and T-cell chimerism. (Chimerism pre-transplant is donor/recipient genotyping to allow for chimerism determination after transplant.)

Q. Blood samples for flow cytometry: T-cell subset, B cells, NK cells.

R. Blood samples collected at weeks 2, 6, and 10 will be used for correlative studies (see Section 11).

S. Blood samples collected for future T-cell receptor sequencing (see Section 11).

T. Baseline sample: after study registration but before SCT; per investigator discretion, the specific timing for collection of the 30- and 100-day samples can be adjusted based on the patient's clinical status; if GVHD is diagnosed, the sample should be collected as soon as possible.

13 STATISTICAL CONSIDERATIONS

13.1 Randomization Scheme

To allocate consented and enrolled patients between treatments, we propose an outcome-adaptive allocation scheme that would increase the probability that patients are allocated to the more effective treatment regimen. We propose the use of the doubly adaptive biased coin design (DBCD) (36) coupled with optimal allocation of continuous outcomes, which has been shown to more greatly reduce treatment failures than other adaptive strategies while simultaneously maintaining power (37). In this set-up, the allocation probability for treatment A (MMF-15) is the function

$$gg\left(\frac{nn_{AA}}{nn}, \rho\right) = \frac{\left(\frac{nn_{AA}}{nn}\right)^{2}\rho}{\left(\frac{nn_{AA}}{nn}\right)^{2}\rho + \left(\frac{nn_{BB}}{nn}\right)^{2}(1-\rho)},$$

where nn_{AA} is the number of patients currently allocated to treatment "A", *n* is the total number of currently accrued patients, *ρ* is the optimal allocation ratio defined as:

$$\rho = \frac{ss_{AA}\bar{xx}_{BB}}{ss_{AA}\bar{xx}_{BB} + ss_{BB}\bar{xx}_{A}} \text{ if } (xx_{A} < \bar{xx}_{BB} \text{ and } ee > 1) \text{ or } (xx_{A} > \bar{xx}_{BB} \text{ and } ee < 1)$$

$$1/2, \text{ otherwise,}$$

where $ee = ss_{AA}\bar{xx}_{A} / ss_{BB}\bar{xx}_{BB}$, and ss_{jj} and $\bar{xx}_{j}$ are the sample standard deviation and sample mean, respectively, in the jth treatment.

Thus, the allocation probability for treatment B (MMF-30) is:

$$gg\left(\frac{nn_{BB}}{nn}, \rho\right) = 1 - gg\left(\frac{nn_{AA}}{nn}, \rho\right).$$

The treatment-specific, day-60 ddCD3 count (33) will be the continuous measure used in the adaptive allocation algorithm listed above, with implications that, as the trial progresses, patients will be increasingly likely to be allocated to the treatment with larger mean ddCD3 count, provided a difference exists between the 2 groups. A two-patient lead-in will be used in both groups, where the allocation ratio is held constant (1:1) until at least 2 patients have provided their day-60 ddCD3 measurements in each group; this will ensure the mean and standard deviations for each group are estimable. As large treatment differences in mean ddCD3 counts between the 2 treatment groups could lead to imbalanced treatment groups, we will perform additional statistical analyses (described below) using patient information from the previous ATG TBI trial whose treatment regimen is identical to that in the MMF-30 group. Note that we anticipate patients allocated to

MMF-30 will have inferior ddCD3 counts compared to patients allocated to MMF-15, on account of the earlier cessation of MMF at day 15 in the MMF-15 group as opposed to day 30 in the control cohort in this study (MMF-30) and as in the previous study (MCC-11561).

13.2 Stratification Factors

Patients will be stratified at the time of randomization according to the following factors:

- Diagnosis (Hodgkin lymphoma, NHL, ALL, CLL *or* MM *or* AML, CML, MDS)
- Donor type (MRD *or* URD)

Adaptive allocation rates will be determined separately within each level/combination of the stratification factors.

13.3 Statistical Methods

13.3.1 Primary Endpoint

The primary outcome in this study is event-free survival, where the conditional events are the occurrence of relapse or DLI.

13.3.2 Secondary Endpoints (with measurement type)

- Overall survival (days to event or survival: time-to-event; survival: categorical)
- Acute and chronic GVHD (days to positive diagnosis: time-to-event; positive diagnosis: categorical)
- Engraftment loss (days to loss: time-to-event; graft loss: categorical)
- Engraftment syndrome (categorical)
- Immune reconstitution (numerical)
- DLI administration (days to administration: time-to-event; administration: categorical)
- Rate of T-cell recovery following SCT

13.3.3 Statistical Analysis

The difference in the survival rate between patients allocated to MMF-30 and MMF-15 will be tested using a log-rank test and will be graphically represented with a Kaplan-Meier step-function for each treatment group; all time-to-event outcomes will be similarly analyzed and will account for the competing hazard of fatality using Gray's test (38). Odds ratios of successful treatment for categorical outcomes between the 2 treatment groups will be estimated using logistic regression with a two-group treatment indicator. Treatment-specific means of numerical measurements will be compared between treatment groups using a one-factor analysis of variance model with 2 levels.

To account for patient demographics and other characteristics, a proportional hazards model will be used for time-to-event measurements, multiple logistic regression will be used for categorical outcomes, and analysis of covariance will be used for numerical outcomes. For repeated-measure numerical outcomes (e.g., immune reconstitution), mixed-effect repeated-measure analysis of variance will be used, where a patient-level random effect will be used to account for intra-

subject dependence, which will be modeled with an autoregressive correlation structure. All categorical measures will be summarized with frequencies, proportions, and 95% confidence intervals for each treatment group, and odds ratios will also be reported. All numerical measures will be summarized with means, and 95% confidence intervals, and standard deviations for each treatment group. Summary measures (proportions, means) and analytic measures (odds ratios, differences in means, hazard ratios) will also be adjusted for patient demographics and characteristics.

All analyses will be conducted in the manner described above in 2 different scenarios: (i) including only patients accrued within this study period, and (ii) including both patients accrued within this study period as well as those allocated to the 5.1-dose group of the previous study (MCC-11561) (n=19). These additional patients will be included in the MMF-30 treatment group, and all analyses will be adjusted by a random cohort effect to account for any between-study differences. These secondary analyses with additional patients will have greater power (see below) than analyses featuring patients solely from the current study, and will help protect against any imbalances caused by the outcome-adaptive allocation mechanism.

Additionally, we will conduct a sub-set analysis consisting of the following: (1) patients diagnosed with multiple myeloma (MM) in both the MMF-15 and MMF-30 groups who have relapsed; (2) a group of historical control patients with MM who have relapsed but have never received an allogeneic transplant. We assume that nearly 1/3 of the 60 patients in the current study (n ≈ 20) will be diagnosed with MM. The historical control group will consist of 20 patients matched for age, gender and race. The difference in the survival rate between patients who received an allogeneic transplant (treated at either MMF-15 or MMF-30) and the group of historical control patients will be tested using a log-rank test and will be graphically represented using a Kaplan-Meier step function in each group.

13.4 Sample Size and Power Determination

The following calculations assume that 12 patients will be accrued per year for 5 years (60 total), that there will be twice the allocated patients (due to the outcome-adaptive allocation algorithm) in the MMF-15 group than in the MMF-30 group, and an event rate of 0.421 (observed rate at 2 years in the MMF-30 group in the previous study [MCC-11561]). Then assuming a 15% reduction in the event rate in the MMF-15 group, we will have 80% power (at 10% significance) to detect a hazard ratio as small as 1.53. If we add the patient information from the previous study into the MMF-30 group (which would help balance the expected sample sizes between treatment groups), then we will have 80% power to detect a hazard ratio as small as 1.50.

13.5 Stopping Criteria

The early stopping criteria will be applied to each treatment group separately once 5 patients within a group have been accrued. The study will be stopped early if the observed number of patients experiencing one of the 4 events listed on Table 5 exceeds the threshold number of events (see Figure 4 and Figure 5), where the threshold number of

events was determined assuming a binomial distribution at the unacceptable rate at the 95% level.

Table 5. Early Stopping Criteria

Criteria	Unacceptable Rate
Engraftment failure	≥ 10% (Figure 4)
Steroid-refractory GVHD	≥ 30% (Figure 5)
Day 100 transplant-related mortality (TRM)	≥ 10% (Figure 4)
Severe engraftment syndrome	≥ 10% (Figure 4)

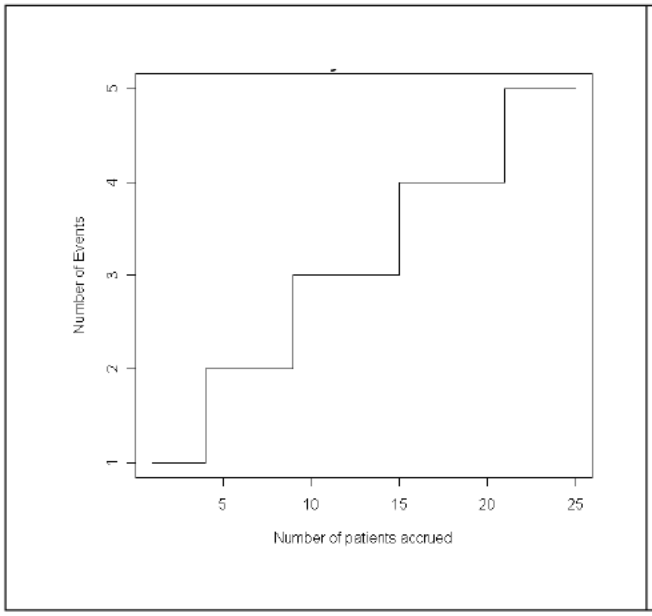

Figure 4. Event (Engraftment Failure, Day 100 TRM, and Severe Engraftment Syndrome) Frequency Threshold for Applying Stopping Criteria at Patient Accrual Milestones

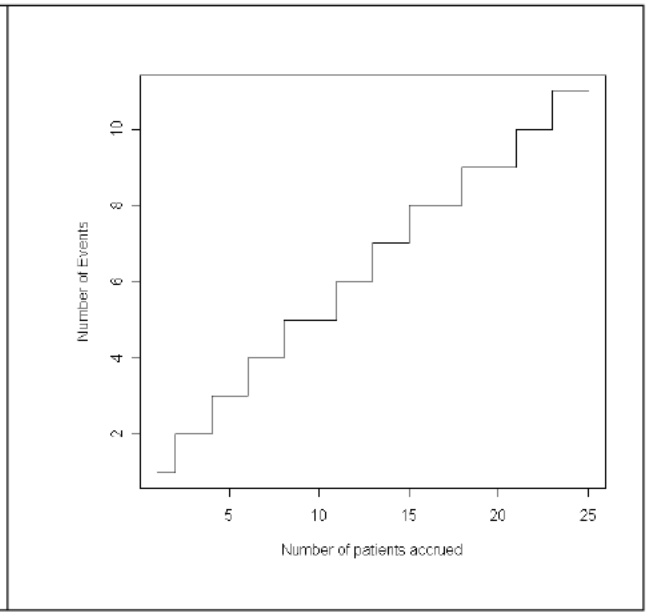

Figure 5. Event (GVHD) Frequency Threshold for Applying Stopping Criteria at Patient Accrual Milestones

The events comprising the stopping rule will be defined as:

- Engraftment failure defined as loss of established donor chimerism or failure to establish stable mixed donor chimerism, with or without autologous reconstitution, despite withdrawal of immunosuppression and DLI beyond day 100. In the absence of progressive disease, an observation period of 8 weeks post DLI will be required prior to declaring engraftment failure.
- Steroid-refractory GVHD defined as biopsy-proven ≥ grade III classic acute GVHD (developing before day 100) requiring therapy with systemic corticosteroids for > 1 week for control.
- Treatment-related day 100 mortality, excluding relapse/progressive disease, i.e., GVHD, sepsis, VOD, pneumonitis, etc.
- Severe engraftment syndrome, defined as fever, rash, hypoxia, pneumonitis, and diarrhea requiring therapy with corticosteroids (methylprednisolone > 2 mg/kg/day) or etanercept.

Patients unable to receive protocol-specified conditioning and GVHD prophylaxis will be excluded from the analysis for early stopping criteria. For example, patients unable to receive either tacrolimus or MMF will not count towards engraftment failure and GVHD analysis. Likewise, the stopping rule for engraftment failure and treatment-related mortality requires that the patients included in the analyses be transplanted.

14 DATA AND SAFETY MONITORING PLAN (DSMP)

The DSMP for this study will consist of the following 3 elements:

14.1 Study Team

The study team minimally consists of the principal investigator, the co-investigators, the study coordinator, the clinical research associate, and the study biostatistician. While patients are on treatment, the principal investigator, the study coordinator, and the clinical research associate will meet at least monthly and will meet at least quarterly with the study biostatistician to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further patient enrollment is addressed. All meetings including attendance are documented.

14.2 Audit Committee

This trial will be audited by the MCC Audit Committee.

14.3 Data and Safety Monitoring Committee (DSMC)

The study will be monitored by the MCC DSMC. The frequency with which the protocol is reviewed will be determined by the Protocol Review and Monitoring Committee.

15 REGULATORY COMPLIANCE AND ETHICS

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979).

15.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards); 21 CFR 312 (IND Application); and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children)

15.3 Institutional Review Board

The VCU IRB, which is registered with the Office for Human Research Protections (OHRP), will review and provide approval for the protocol, the associated informed consent document, material that will be provided to participating patients, and any recruitment material. Any amendments to the protocol, consent form, or other materials will also be approved by the IRB.

15.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the patients and their families. Consent forms describing in detail the study interventions/ products, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting intervention/administering study product. The consent form will be IRB-approved and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. The patient will sign the informed consent document prior to any procedures being done specifically for the study. The patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to patients for their records. The rights and welfare of the patients 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.

15.5 Patient Confidentiality and Access to Source Documents/Data

Patient confidentiality is strictly held in trust by the participating investigators and their staff. This confidentiality includes the clinical information relating to participating patients, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

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

The study monitor or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Management Responsibilities

The principal investigator is responsible for: (i) the overall conduct of the investigation; (ii) ongoing review of trial data including all safety reports; and (iii) apprising participating investigators of any UPs. Participating investigators are responsible for reporting SAEs and UPs as required in Section 8.

Any laboratory conducting correlative studies must maintain the laboratory records and documentation (laboratory notebooks, laboratory protocols, print-outs, recordings, photographs, etc).

16.2 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc) are maintained in the patient's clinical file. Source documents for the correlative studies are maintained in the laboratory conducting the study.

16.3 Case Report Forms

Standard and study-specific case report forms (CRFs) will be used to capture all the information required by the protocol. The CRFs will be created and approved by the study team to ensure the most effective data acquisition. All information on the CRFs will be traceable to the source documents which are generally maintained in the patient's file. All CRFs should be completed and available for collection within a timely manner, preferably no more than 7 days after the patient's visit.

16.4 Study Record Retention

As applicable, study records will be maintained a minimum of 5 years beyond: (i) the publication of any abstract or manuscript reporting the results of the protocol; (2) the submission of any sponsored research final report; or (iii) submission of a final report to clinicaltrials.gov.

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