BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

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BMT CTN PROTOCOL 1203
Version 3.0
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PROTOCOL SYNOPSIS – BMT CTN 1203 PROTOCOL

A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

Co-Principal Investigators: Javier Bolaños -Meade, MD; John Koreth, MBBS, DPhil; Ran Reshef, MD

Study Design: The study is designed as a Phase II, multicenter trial that randomizes patients to one of three GVHD prophylaxis approaches comparing each to a contemporary control.

Primary Objective: The primary objective of the randomized trial is to compare one year GVHD/relapse or progression-free survival (GRFS) after hematopoietic stem cell transplantation (HSCT) between each of three novel GVHD prophylaxis approaches and a contemporary control from the Center for International Blood and Marrow Transplant Research (CIBMTR) database. An event for this time to event outcome is defined as grade III-IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse or progression, or death by any cause..

Secondary Objectives: Secondary objectives are to describe for each treatment arm: rates of grade II-IV and III-IV acute GVHD, visceral acute GVHD, chronic GVHD, immunosuppression-free survival at one year, hematologic recovery (neutrophil and platelet), donor cell engraftment, disease relapse or progression, transplant-related mortality, rates of Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; incidence of infections; immune reconstitution and overall survival.

Eligibility Criteria: Eligible patients are between 18 and 75 years undergoing HSCT for treatment of acute leukemia, chronic myelogenous leukemia or myelodysplasia with no circulating blasts and with less than 5% blasts in the bone marrow; chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma; marginal zone lymphoma; Hodgkin's Lymphoma, diffuse large B cell lymphoma or, mantle cell lymphoma sensitive to chemotherapy who are eligible for an allogeneic transplant. **Patients must have a related or unrelated peripheral blood stem cell donor. Sibling donor must be a 6/6 match for HLA-A and -B at intermediate (or higher) resolution, and -DRB1 at high resolution using DNA-based typing, and must**

	be willing to donate peripheral blood stem cells and meet institutional criteria for donation. Unrelated donor must be a 7/8 or 8/8 match at HLA-A, -B, -C and –DRB1 at high resolution using DNA-based typing. Unrelated donor must be willing to donate peripheral blood stem cells and be medically eligible to donate stem cells according to NMDP criteria. Patients are eligible only if receiving a reduced intensity conditioning (RIC) regimen.
Treatment Description:	Patients will be randomized to receive one of the three specified regimens: Tacrolimus (Tac)/Methotrexate (Mtx) with bortezomib 1.3 mg/m^2 IV daily Days +1, +4 and +7 post HSCT; Tac/Mtx with maraviroc 300 mg PO twice a day from Day -3 to 30 post HSCT; or cyclophosphamide (Cy) 50 mg/kg Day +3 and +4, followed by Tac and mycophenolate mofetil (MMF). Tac will be maintained at therapeutic doses for a minimum of 90 days in all arms. Methotrexate will be dosed at 15 mg/m^2 Day +1, and 10 mg/m^2 Days +3, 6 and 11 in the maraviroc and bortezomib arms. MMF will be dosed at 15 mg/kg every 8 hours from Day +5 to Day +35 in the Tac/MMF/Cy treatment arm.
Accrual Objective:	The clinical trial will enroll 270 patients or 90 per arm. Patients will be compared to a minimum of 270 controls from the CIBMTR who received Tac/Mtx alone.
Accrual Period:	The estimated accrual period is 30 months.
Study Duration:	Patients will be followed for 1 year following HSCT.
Interim Analysis:	There will be no interim analyses for efficacy. An interim analysis for futility will be conducted based on the 6 month GRFS when 30 patients in each arm have 6 months of follow-up available. If fewer than 14 are alive and GVHD/relapse free among the first 30 patients on an arm, closure of the study arm for futility will be considered.
Stopping Guidelines:	Monitoring of the key safety endpoint of death will be conducted monthly. The rate of mortality will be monitored up to 100 days post-randomization separately in each of the three treatment arms. At least three events must be observed in order to trigger review for consultation with the DSMB.

STUDY SCHEMA

Aim: To determine if any of three new GVHD prophylaxis approaches improves the rate of GVHD and relapse free survival at one year after transplant.

Inclusion Criteria	**Exclusion Criteria**
1. Age 18-75 years (patient is older than 18.0 and less than 76.0 years old) 2. Patients with acute leukemia, chronic myelogenous leukemia, or myelodysplasia with no circulating blasts and with less than 5% blasts in the bone marrow. 3. Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma; follicular, marginal zone, diffuse large B-cell, Hodgkin's Lymphoma, or mantle cell lymphoma with chemo-sensitive disease at time of transplant. 4. Recipients of reduced intensity conditioning. 5. Patients must have a related or unrelated peripheral blood stem cell donor. Sibling donor must be a 6/6 match for HLA-A and -B at intermediate (or higher) resolution, and -DRB1 at high resolution using DNA-based typing, and must be willing to donate peripheral blood stem cells and meet institutional criteria for donation. Unrelated donor must be a 7/8 or 8/8 match at HLA-A, -B, -C and –DRB1 at high resolution using DNA-based typing. Unrelated donor must be willing to donate peripheral blood stem cells and be medically cleared to donate stem cells according to NMDP criteria. 6. Cardiac function: Ejection fraction $\geq$ 45% 7. Estimated creatinine clearance greater than 50 mL/minute (using the Cockcroft-Gault formula and actual body weight) 8. Pulmonary function: DLCO $\geq$ 40% (adjusted for hemoglobin) and FEV1 $\geq$ 50% 9. Liver function: total bilirubin < 1.5x the upper limit of normal and ALT/AST < 2.5x the upper normal limit. Patients who have been diagnosed with Gilbert's Disease are allowed to exceed the defined bilirubin value of 1.5x the upper limit of normal. 10. Female subjects (unless postmenopausal for at least 1 year before the screening visit, or surgically sterilized), agree to practice two effective methods of contraception or agree to complete abstain from heterosexual intercourse from the time of signing the informed consent through 12 months post transplant. 11. Male subjects (even if surgically sterilized), of partners of women of childbearing potential must agree to practice effective barrier contraception or abstain from heterosexual intercourse from the time of signing the informed consent through 12 months post transplant. 12. Signed informed consent.	1. Prior allogeneic transplant 2. Karnofsky Performance Score < 70% 3. Active CNS involvement by malignant cells 4. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment. 5. Presence of fluid collection (ascites, pleural or pericardial effusion) that interferes with methotrexate clearance or makes methotrexate use contraindicated 6. Patients with transformed lymphoma (e.g., Richters transformation arising in follicular lymphoma or chronic lymphocytic leukemia). 7. Patients seropositive for the human immunodeficiency virus (HIV). 8. Patient with active Hepatitis B or C determined by serology and/or NAAT. 9. Patients with hypersensitivity to bortezomib, boron or mannitol. 10. Patients with $\geq$ grade 2 sensory peripheral neuropathy. 11. Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure (see Appendix D), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant 12. Female patients who are lactating or pregnant 13. Patients with a serious medical or psychiatric illness likely to interfere with participation in this clinical study 14. Patients with prior malignancies, except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent $\geq$ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the Protocol Officer or one of the Protocol Chairs. 15. Planned use of ATG or alemtuzumab in conditioning regimen. 16. Planned post-transplant therapy (including use of TKIs) 17. Inability to withhold agents that may interact with hepatic cytochrome P450 enzymes (CYP3A4), or glutathione S-transferases involved in bortezomib and/or busulfan metabolism during day -5 through day +7. It is acceptable to use alternative non-interacting medications during this period, and then resume prior medications. 18. Patients with secondary acute myeloid leukemia arising from myeloproliferative disease, including CMML, with evidence of active myeloproliferative features or myelofibrosis in the background.

***Immunosuppression Taper*:**
Patients without GVHD
Tacrolimus
- Taper to initiate at least Day 90 and completely off at Day 180.

MMF
- Discontinued on Day +35 without a taper.

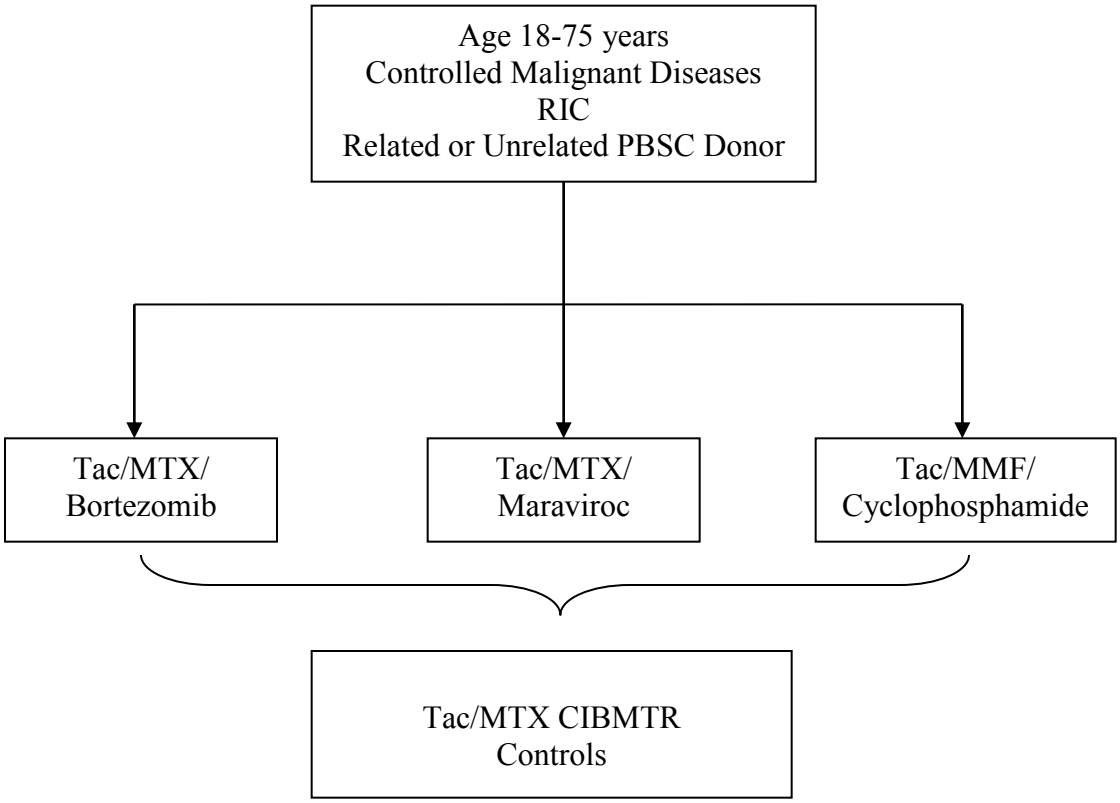
Primary endpoint:
- GVHD/relapse or progression-free survival (GRFS) by 1 year: this time to event outcome is defined as grade III-IV acute GVHD, chronic GVHD requiring systemic treatment, disease relapse or progression, or death by any cause.

Secondary endpoints:
- Grades II-IV and III-IV acute GVHD
- Incidence of visceral GVHD (liver or gut)
- Chronic GVHD
- Immunosuppression-free survival at 1 years
- Hematologic recovery (neutrophil and platelet)
- Donor cell engraftment
- Disease relapse or progression
- Transplant-related mortality
- Toxicity and rates of infections
- Disease-free and overall survival

Conditioning Regimens	
Reduced Intensity/Non-myeloablative*	
Flu/Bu (≤ 8 mg/Kg) Flu/Mel (≤ 150 mg/m^2)	Flu/Cy/TBI Flu/TBI (200cGy) Flu/Cy

*No anti-thymocyte globulin or alemtuzumab is allowed in the conditioning regimen

Outline of Treatment Plan



CIBMTR control eligibility
Transplants performed in the U.S.
Centers not participating in BMT CTN 1203 and agree to provide supplemental information
Age 18-75 years
Transplants for malignant disease using RIC and a PBSC graft
GVHD prophylaxis with Tac/MTX without additional agents

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Introduction

Acute Graft-versus-Host-Disease (GVHD) is an important cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). Clinically significant grade II-IV acute GVHD occurs in 34-40% of patients undergoing HLA-matched related donor HSCT, 47-52% of HLA-matched unrelated donor HSCT, and is further increased in those lacking HLA-matched donors.[1, 2, 3, 4]

GVHD is thought to be mediated by donor-derived T cells that are reactive against recipient antigens expressed in the context of the major histocompatibility complex (MHC or HLA). These antigens, termed minor histocompatibility antigens (mHA), are small peptides with immunogenic single nucleotide polymorphisms (SNPs) capable of eliciting potent T cell immune responses upon presentation by antigen presenting cells (APCs). A number of these mHAs have been identified.[5] In fact, mismatches of known mHA among HLA identical donor-recipient pairs have been associated with the development of GVHD after stem cell transplantation.[6]

Approximately 40% of patients with acute GVHD will have durable responses to corticosteroid therapy; there has been little change in this response rate over the past 20 years, despite addition or substitution of other immunosuppressive drugs to GVHD treatment regimens.[7] The prognosis of the 60% of patients without long-lasting response is poor.[8] A strategy that minimizes the incidence of GVHD, without other adverse effects, would be an effective approach to improve survival after allogeneic transplantation.

GVHD incidence can be decreased with various pharmacologic agents. Early transplants were done using post-transplant methotrexate to prevent GVHD; in the 1980s cyclosporine was shown to be superior to methotrexate and in 1986 the combined use of cyclosporine and methotrexate was shown to be superior to single agent prophylaxis.[9] More recently, other calcineurin-inhibitors, such as tacrolimus have been developed as GVHD prophylactic agents due to favorable toxicity profiles in comparison with cyclosporine.[10, 11]

Phase III trials comparing tacrolimus/methotrexate versus cyclosporine/methotrexate for related and unrelated donors have been performed. In the unrelated donor setting, the incidence of grade II-IV acute GVHD was 56% among the 46 patients randomized to tacrolimus arm versus 74% among the 63 patients randomized to cyclosporine arm.[12] The combination of tacrolimus/methotrexate remains a standard for GVHD prophylaxis, despite its limited efficacy.

However, improved GVHD prophylaxis remains a significant clinical need in HSCT. The current clinical trial will test three novel GVHD prophylaxis approaches: tacrolimus/methotrexate and bortezomib (Tac/MTX/Bort), tacrolimus/methotrexate and maraviroc (Tac/MTX/MVC) and tacrolimus/mycophenolate mofetil and cyclophosphamide (Tac/MMF/Cy). This randomized Phase II clinical trial will compare each intervention arm with a Tac/MTX control.

1.2. Tacrolimus, Methotrexate and Bortezomib (Tac/MTX/Bort)

1.2.1. Bortezomib

Bortezomib for Injection is a small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy.

1.2.2. Bortezomib Mechanism of Action

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The antineoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration, and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays.[13] In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation.[14,15,16,17,18,19,20,21,22,23,24,25,26] Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.[27]

The mechanisms of action leading up to apoptosis have been more clearly defined and include initiation of the unfolded protein response and direct/indirect effects on various molecular targets including cell cycle control proteins p27 and p21, cyclins, signal transduction molecules, transcription factors c-jun and HIF1-α, tumor suppressor protein p53, angiogenesis factors, and many others. Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.[28,29,30,31,32,33,34,35]

Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.[36] Bortezomib also has immunomodulatory effects relevant to allogeneic HSCT. The proteasome, acting via NF-kB, plays an important role in cytokine signaling and the generation of cell mediated immune responses via T cell activation, proliferation and apoptosis.[37, 38, 39] Bortezomib also attenuates TLR4 mediated antigen-presenting cell activation, with reduced cytokine production and immunostimulatory activity.[40] In the allogeneic setting, bortezomib preferentially and specifically depletes alloreactive T lymphocytes.[41] It however spares human regulatory T cells (Treg) that act to suppress inappropriate immune responses underlying GVHD.[42] Given the immunomodulatory effects of bortezomib on APCs, alloreactive T lymphocytes and Tregs, as

well as its anti-tumor effects and its lack of hematopoietic stem cell toxicity, it is an attractive candidate for control of GVHD after allogeneic transplantation.

1.2.3. Bortezomib and Graft-versus-Host-Disease: Preclinical Data

In murine models of severe acute GVHD involving fully-HLA mismatched myeloablative HSCT, bortezomib administered early after stem cell infusion protected against GVHD without impairing engraftment.[43, 44] In a model intended to induce less severe GVHD, mice receiving bortezomib had 100% survival with no animal developing GVHD, while control animals all succumbed to GVHD prior to Day 50 post-transplantation.[43]

Additionally, in other in-vivo murine models combination bortezomib/sirolimus synergistically reduced GVHD risk without hampering graft-versus-leukemia effect.

1.2.4. Bortezomib Clinical Pharmacokinetics and Pharmacodynamics

The clinical pharmacology characterization of bortezomib has been determined from Phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in Phase 2 studies in subjects with multiple myeloma.

Bortezomib demonstrates multi-compartmental pharmacokinetics. Following intravenous administration of 1.0 mg/m^2 and 1.3 mg/m^2 dose, the mean first-dose maximum observed plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively in 11 patients with multiple myeloma and creatinine clearance values >50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multi-dose regimen in humans.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

The time course of proteasome inhibition in subjects is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity. On the Day 1, 4, 8, and 11 schedule variable (10%–30%) levels of proteasome inhibition have been observed at next scheduled dosing. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.

The relationship between bortezomib plasma concentrations and proteasome inhibition can be described by a maximum effect (E_{max}) model. The E_{max} curve is initially very steep, with small changes in plasma bortezomib concentration over the range of 0.5 to 2.0 ng/mL relating to large increases in the percent inhibition (0–60%). After that, a plateau occurs where marginal increases of proteasome inhibition are observed in spite of large changes in plasma bortezomib concentrations.[45]

1.2.5. Clinical Experience with Bortezomib

To date, more than 436,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

1.2.6. Clinical Experience with Bortezomib for GVHD Prophylaxis

In a Phase I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.[46] The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy in patients with advanced solid tumors, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.[45]

In the allogeneic HSCT context, a Phase I/II clinical trial (DFCI protocol 06-065) of a regimen of bortezomib plus standard tacrolimus/methotrexate for GVHD prophylaxis after fludarabine/busulfan-based RIC HSCT with 1-2 locus HLA-mismatched donors (HLA-A, -B, -C; -DQB1, -DRB1). Bortezomib MTD was 1.3 mg/m^2 administered on Days +1, +4 and +7 after stem cell infusion. Phase I results indicated minimal toxicity (rapid engraftment, zero non-relapse mortality in the first year) and excellent acute GVHD control with the bortezomib-based regimen.[47] Phase I/II results demonstrated that the grade II-IV acute GVHD rate at Day 180 was 22% and no patients developed grade IV acute GVHD. Additionally, 2-year probabilities of non-relapse mortality and relapse were 11% and 38% respectively in a population receiving HLA-mismatched unrelated donor HSCT.[48] Consequently, the combination of bortezomib, tacrolimus and methotrexate appears suitable for prospective multicenter evaluation.

1.3. Tacrolimus, Methotrexate and Maraviroc (Tac/MTX/MVC)

1.3.1. CCR5 and CCR5 inhibitors

CCR5 is a chemokine receptor. Its natural ligands are CCL3, CCL4 and CCL5, also known as macrophage inflammatory protein-1-alpha (MIP-1α), MIP-1β and regulated and normal T cell expressed and secreted (RANTES). CCR5 is expressed on subsets of T-cells, dendritic cells and macrophages. It is a G-protein coupled receptor with 7 transmembrane domains.[49] CCR5 is a major co-receptor for HIV entry into host cells,[50, 51] and a common polymorphism (Δ32-CCR5) results in deletion and frame-shift and a non-functional receptor, leading to protection against HIV infection.

1.3.2. Maraviroc

Maraviroc (SELZENTRY™ – Pfizer, formerly UK-427,857) is the first FDA-approved drug in its class of CCR5-antagonists. It is a highly specific small molecule antagonist of CCR5, developed for the treatment of HIV-1 infection. Two pivotal Phase III trials (MOTIVATE-1 and MOTIVATE-2) have shown that in HIV patients maraviroc was able to produce a significant decrease in viral load and an increase in CD4 count.[52, 53, 54]

1.3.3. Maraviroc Mechanism of Action and Safety Studies

Maraviroc is a true antagonist of the CCR5 receptor. It creates an allosteric conformational change in the extracellular domain of the receptor and prevents binding of all 3 ligands (CCL3-5). It is not a partial agonist and does not trigger any calcium influx or internalization of the receptor. Pharmacokinetic studies showed that drug absorption is rapid, bioavailability is 23-33% due to a 1st pass effect in the liver with maximum concentrations achieved 1–4 h after dosing. Absorption is decreased with food but no efficacy data determined any difference in outcome so the drug is given without food restrictions.[55]

Maraviroc is a substrate of cytochrome P450, family 3, subfamily A4. Its level is affected by inducers and suppressors of the cytochrome P450 such as rifampin, antiretroviral medications and certain azoles, mainly ketoconazole and itraconazole. The drug itself is not a significant inhibitor or inducer of any known metabolic pathway, and studies were conducted to guide the dosing in patients who are taking inhibitors or inducers of CYP3A4[55]. Therefore, the recommended dose is determined by concomitant medications. Patients on strong inhibitors of CYP3A4 should take 150 mg bid, patients on strong inducers of CYP3A4 should take 600 mg bid and all other patients should take 300 mg bid.

Phase I trials showed postural hypotension to be a dose-limiting side effect when a 600 mg dose was given to healthy volunteers. No effects on blood counts, immunoglobulin levels or lymphocyte subset numbers were observed in Phase I/II studies.

The safety of maraviroc has not been specifically studied in patients with significant underlying liver disorders. Several cases of hepatotoxicity and hepatic failure with allergic features have been reported in association with maraviroc, including one case in a study of healthy volunteers.

Phase III studies in HIV patients showed mild side effects. Liver enzyme and bilirubin elevation occurred in 9.2% as opposed to 6.2% in the placebo groups. These findings, together with reports of hepatotoxicity with other CCR5 antagonists, led the FDA to mandate a black box warning for hepatotoxicity. Discontinuation of maraviroc should be considered in any patient with signs or symptoms of acute hepatitis, in particular if drug-related hypersensitivity is suspected or with increased liver transaminases combined with rash or other systemic symptoms of potential hypersensitivity (e.g. pruritic rash, eosinophilia or elevated IgE). There are limited data in patients with hepatitis B/C infection, although such patients were not excluded from clinical trials in HIV patients. Special caution should be exercised when treating these patients with maraviroc.

A study compared the pharmacokinetics of a single 300 mg dose of maraviroc in subjects with severe renal impairment (CLcr < 30 ml/min, n=6) and end-stage renal disease (ESRD) to healthy volunteers (n=6). Results show that dialysis had a minimal effect on exposure in subjects with ESRD. Exposures observed in subjects with severe renal impairment and ESRD were within the range observed in single maraviroc 300 mg dose studies in healthy volunteers with normal renal function. Therefore, no dose adjustment is necessary in patients with renal impairment receiving maraviroc without a potent CYP3A4 inhibitor. Dose adjustment is necessary in patients with renal impairment receiving maraviroc with potent CYP3A4 inhibitors.

Maraviroc does not affect any major metabolic pathway. In particular, it does not affect the levels of drugs that are metabolized by the CYP450-3A4 system. In the phase I/II study, no significant interaction was noted with tacrolimus and tacrolimus dosing was standard.

The drug is available in oral form only. The commercially-available formulation is in pill form and a maraviroc solution is available for clinical research, although the solution will not be available for the BMT CTN 1203 study.

1.3.4. CCR5 Inhibition and GVHD

Blocking CCR5 in a GVHD murine model reduced the number of CD8+ lymphocytes that infiltrated the liver and prevented clinical GVHD.[56] The entry of T-cells into Peyer's patches was also dependent on CCR5.[57] GVHD models also support the role of CCR5 ligands in the recruitment of cytotoxic T-cells into tissues.[58]

Retrospective epidemiologic data support an association between CCR5 and GVHD. A European study analyzed 186 recipients and 163 donors of SCT, and revealed that recipient Δ32 was a protective factor for acute GVHD of any grade. Δ32 in the donor did not predict outcome but the combination of Δ32 in both donor and recipient was protective (0/11 patients had GVHD).[59] Another study used the NMDP sample repository and revealed that the H1/H1 haplotype, which leads to high CCR5 expression, was associated with severe GVHD.[60]

1.3.5. Phase I/II Study of Maraviroc in GVHD Prophylaxis

At the University of Pennsylvania, a Phase I/II clinical trial was conducted to study the role of maraviroc when added to conventional GVHD prophylaxis following RIC SCT.[61] The trial enrolled 38 subjects (Table 1.3a), who received a standard RIC regimen of fludarabine and busulfan followed by the infusion of a peripheral blood stem cell (PBSC) graft from either a matched related or unrelated donor. Single-antigen mismatched donors were acceptable. In addition to standard tacrolimus and methotrexate (MTX) prophylaxis, all patients received maraviroc from Day -2 to Day+30.

TABLE 1.3a: PATIENT CHARACTERISTICS

		N=38
Dose levels, n:	150 mg bid 300 mg bid	7 31
Recipient age, median (range)		62 (21-74)
Recipient age>60, n (%)		26 (68)
Recipient gender: M/F, %		60.5 / 39.5
Comorbidity Index, n (%):	Low Intermediate High	21 (55) 13 (34) 4 (11)
Diagnosis, n:	Acute Myelogenous Leukemia Myelodysplastic Syndrome Non-Hodgkin Lymphoma Myeloproliferative Disease/Myelofibrosis Aplastic Anemia/Multiple Myeloma/Hodgkin/Chronic Myeloid Leukemia-Blast Crisis/Chronic Lymphocytic Leukemia	15 6 8 4 1 each
Donor, n(%):	Matched related Matched unrelated Single-antigen mismatched	13 (34) 19 (50) 6 (16)
Donor age, median (range)		38 (20-68)

Maraviroc dose level verification

Studies in normal volunteers and HIV patients have established safe and effective doses of maraviroc and defined the expected drug interactions when the drug is administered together with inducers and inhibitors of CYP450 3A4. In order to verify the dose level in patients undergoing allogeneic SCT, detailed pharmacokinetics and safety data were studied from 13 subjects at 2 dose levels (summarized in Figure 1.3a); the 300 mg bid (n=6) and 150 mg bid (n=7) doses resulted in mean Cavg (AUC/dosing interval) of 536 and 118 ng/ml, respectively. The results for the 300 mg bid dose were high compared to data from HIV trials, likely due to drug interactions; however, 3/7 patients at 150 mg bid did not reach the targeted minimum Cavg (100 ng/ml), while the higher dose level resulted in adequate Cavg in 6/6 patients. Significant drug-related toxicity was not seen in either dose levels. It was concluded that 300 mg bid should be the Phase II dose.

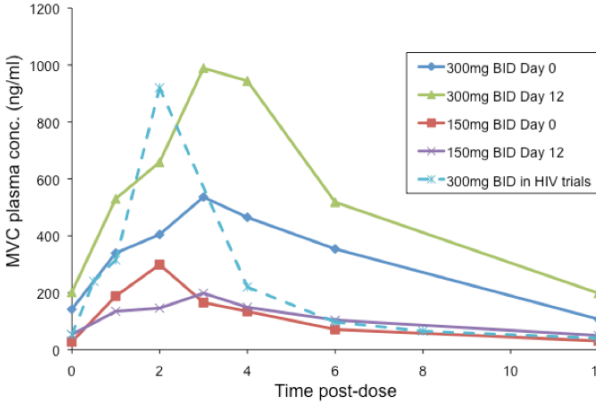


Figure 1.3a Summary of pharmacokinetic data at 2 time points on 2 dose levels in comparison with known data in HIV trials.

Maraviroc safety

Maraviroc was well tolerated and significant drug-related adverse events were not identified. Prompt engraftment was seen in all subjects with no primary graft failures. Four subjects encountered delayed graft failure, three of them due to progressive primary myelofibrosis. The frequency of microbiologically confirmed infections and CMV reactivations was not different than expected. Patterns of donor-recipient chimerism were typical for RIC HSCT.

Adverse events were similar to the expected toxicity of RIC HSCT. One patient died within the first 30 days from septic shock and bacteremia. The drug was briefly held in 7 patients due to grade 3 LFT abnormalities (n=2) or grade 3–4 mucositis (n=5). LFT abnormalities did not recur when the drug was restarted in both patients. The adverse event profile was similar to the expected toxicity observed in patients undergoing RIC HSCT.

Maraviroc efficacy

As of January 2012 the median follow up was 19.6 months (range 13.8 – 34.8). A final analysis for the primary end-point demonstrated that the cumulative incidence rates of acute GVHD grade II-IV and III-IV at Day 100 were 14.7% and 2.9% respectively. By Day 100 all cases of acute GVHD involved only the skin without liver or intestinal involvement. These results were compared with a well-matched cohort of patients (n=48), who underwent RIC HSCT with Tac/MTX prophylaxis but without maraviroc between 2009-2011 at Penn (Reshef, unpublished data). This cohort included patients who underwent RIC HSCT prior to or after the completion

of the maraviroc trial, or during its interim analyses. These comparisons are summarized in Table 1.3b and Figure 1.3b and demonstrate a significant decrease in GVHD of the gut (8.8% vs. 27.1%; P=0.02) and liver (2.9% vs. 14.6%; P=0.05), leading to a lower cumulative incidence of grade III-IV GVHD (5.9% vs. 20.8%; P=0.03). The rates of skin GVHD were unaffected by maraviroc and the cumulative incidence of grade II-IV GVHD was lower but did not reach statistical significance (23.6% vs. 35.4; P=0.24). Significant differences in non-relapse mortality, relapse and survival rates were not observed, but non-relapse mortality was numerically lower (11.7% vs. 19.1%; P=0.35). In summary, this Phase I/II clinical trial showed low rates of GVHD, a significant decrease in visceral GVHD, leading to low rates of severe GVHD without adversely affecting the relapse rate. These results are sufficiently encouraging to proceed to multicenter testing.

TABLE 1.3b: CUMULATIVE INCIDENCE RATES (+/- STANDARD ERRORS) OF ACUTE GVHD IN PATIENTS WHO RECEIVED TAC/MTX+MARAVIROC IN COMPARISON WITH A CONTROL GROUP OF PATIENTS WHO RECEIVED STANDARD PROPHYLAXIS WITH TAC/MTX

	Day 100					**Day 180**				
	Tac/MTX+ maraviroc		**Tac/MTX**		***P***	**Tac/MTX+ maraviroc**		**Tac/MTX**		***P***
	CI Rate	**S.E.**	**CI Rate**	**S.E.**		**CI Rate**	**S.E.**	**CI Rate**	**S.E.**	
Grade II-IV GVHD	14.7	6.2	18.8	5.7	0.62	23.6	7.4	35.4	7	0.24
Grade III-IV GVHD	2.9	2.9	8.3	4	0.27	5.9	4.1	20.8	5.9	**0.03**
Gut GVHD	0	0	12.5	4.8	**0.009**	8.8	5.0	27.1	6.5	**0.02**
Liver GVHD	0	0	8.3	4	**0.04**	2.9	2.9	14.6	5.2	**0.05**
Skin GVHD	14.7	6.2	18.9	5.7	0.62	32.4	8.2	32.6	7.1	0.99

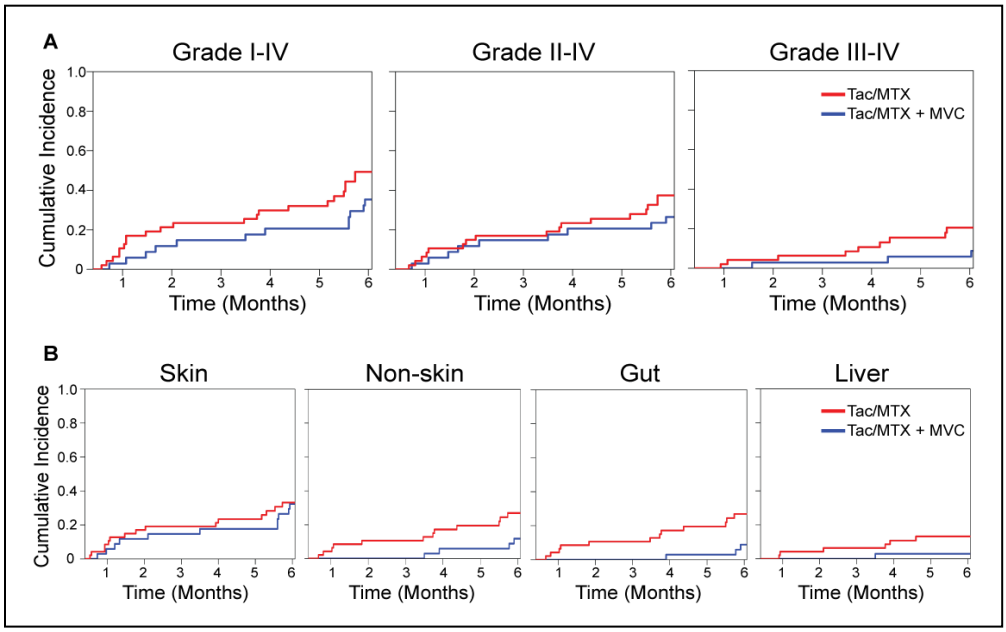


Figure 1.3b Cumulative incidence rates of acute GVHD (panel A) and organ-specific GVHD (panel B) in patients who received maraviroc in addition to standard Tac/MTX (n=35) in a Phase I/II trial in comparison with patients treated with Tac/MTX alone (n=48) during the same time period.

1.4. Tacrolimus, Mycophenolate Mofetil and Cyclophosphamide (Tac/MMF/Cy)

1.4.1. Rationale of Post-transplant Cyclophosphamide

High dose cyclophosphamide is a potent immunosuppressor that has been successfully used to prevent GVHD in unrelated, HLA-matched sibling and haploidentical bone marrow/PBSC transplants in single center as well as in multi-center studies.[62, 63, 64, 65, 66] Cyclophosphamide administered early post HSCT preferentially kills allo-reactive T cells while sparing resting, non allo-reactive T cells leading to suppression of GVHD as well as graft rejection.[67]

1.4.2. Post-transplant Cyclophosphamide in Haploidentical Donor Transplants

Based on promising pre-clinical results at Johns Hopkins, a Phase I/II clinical trial of haploidentical BMT to treat high-risk hematologic malignancies was initiated in 1999. Following a non-myeloablative regimen of fludarabine, cyclophosphamide, and low-dose TBI, GVHD prophylaxis consisted of cyclophosphamide (Cy) given on Days +3 and +4 post-transplant, tacrolimus, and mycophenolate mofetil (MMF).[64] Primary graft failure occurred in 13% of patients, and was fatal due to infection in one patient in whom autologous hematopoiesis failed to occur. In general, complete T-cell engraftment was observed by Day +28 or the grafts were rejected. Cumulative incidences of grades II-IV and grades III-IV acute GVHD by Day 200 were 34% and 6%, respectively. There was lower incidence of extensive chronic GVHD among recipients of two versus one dose of post-transplantation Cy (5% versus 25%; p=.05). There was no difference in the incidence of severe acute GVHD with one or two doses of post-transplant Cy. The cumulative incidences of non-relapse mortality and relapse at 1 year were

15% and 51%, respectively. Actuarial overall and event-free survivals (EFS) at two years after transplantation were 36% and 26%, respectively. Patients with lymphoid malignancies appeared to have an improved EFS compared to those with myeloid malignancies (p=.02).

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) sponsored a multi-center Phase II trial of haploidentical BMT (BMT CTN 0603) for high-risk hematologic malignancies modeled after the Hopkins approach. This was published along with a similar study using cord grafts without post transplant Cy (BMT CTN 0604).[62] The 1-year probabilities of overall and progression-free survival were 54% and 46% after cord transplantation and 62% and 48% after haploidentical bone marrow transplantation. The Day +56 cumulative incidence of neutrophil recovery was 94% after dUCB and 96% after haploidentical marrow. The 100-day cumulative incidence of grade II-IV acute GVHD was 40% with cord blood and 32% with haploidentical bone marrow. The 1-year cumulative incidences of non-relapse mortality and relapse after cord transplantation were 24% and 31%, respectively; corresponding rates after haploidentical bone marrow transplantation were 7% and 45%.

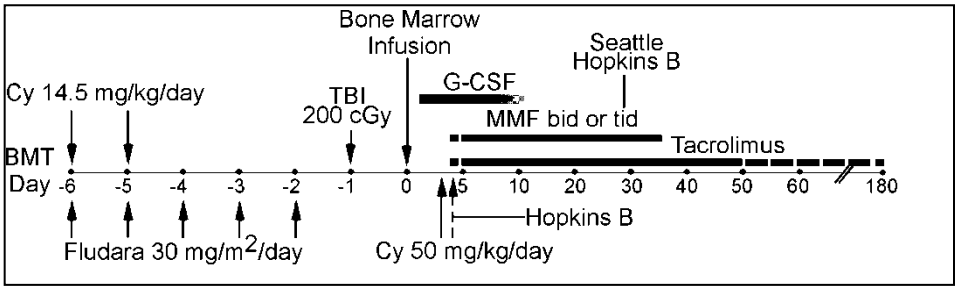


Figure 1.3c: Treatment schema of patients undergoing haploidentical donor transplants in the BMT CTN 0603 clinical trial.

1.4.3. Post-transplant Cy as GVHD Prophylaxis

Post-transplant Cy as GVHD prophylaxis was developed initially for haploidentical bone marrow transplantation after nonablative conditioning but, recently, several small studies have extended the approach to myeloablative conditioning and to PBSC transplantation. To date, haploidentical nonablative transplantation with post-transplant Cy has used bone marrow as the graft source. Use of PBSC instead of marrow may allow wider applicability of this approach but there is concern about higher risks of acute and chronic GVHD due to the 5-10-fold higher number of T-cells in the allograft. Recently, groups in Houston and Seattle/London reported small studies in which PBSC were substituted for bone marrow with post transplant Cy in the haploidentical donor setting.[65, 68] In both studies, the incidences of severe acute GVHD, chronic GVHD and non-relapse mortality at 1 year with PBSC were comparable to the rates seen with bone marrow.

Also, experience in HLA-matched siblings is being explored. Kasamon et al published on 10 patients receiving nonablative transplants for lymphoma[69] and Bolaños-Meade on 3 patients with sickle cell disease[66]. Kasamon's patients also received rituximab and Bolaños-Meade's received antithymocyte globulin. Rates of GVHD and transplant related mortality were very low. Therefore, the inclusion of post-transplant high dose Cy with MMF and tacrolimus as GVHD prophylaxis after a non-ablative conditioning regimen seems to be justified.

1.5. Benchmark Analysis and Composite Endpoint

In order to better evaluate the efficacy of novel approaches for GVHD prophylaxis, a benchmark analysis was performed using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) for patients who received a RIC HSCT.

The CIBMTR maintains an outcomes registry that prospectively collects data from all centers performing allogeneic HSCTs and almost all centers performing autologous HSCTs in the United States and about 100 non-US centers. Centers must report all consecutive patients and provide longitudinal follow-up on those patients according to set timelines that include a pretransplant report, a 100 day report, a 6 month report and an annual report through 6 years post transplant followed by a biannual report in perpetuity. Data are reported on two tracks: a "Transplant Essential Data" track and a "Comprehensive Report Form" track. Centers provide a pretransplant Transplant Essential Data form for all patients. Data from this form are used to select patients for the Comprehensive Report Form track using a weighted random selection that over selects patients with rare diseases or procedures or for the purposes of specific studies. For example, most patients on BMT CTN trials are selected for the Comprehensive Report Form track so that data collected by the CIBMTR can supplement clinical trial data collected through AdvantageEDC and can allow for long-term follow-up of trial patients for specific late effects of treatment. Longitudinal data are collected for patients on both the Transplant Essential Data and Comprehensive Report Form Track; the data differ in quantity and granularity. Data quality is ensured by computerized error checks and on-site audits.

The objective of the benchmark analysis was to select promising approaches to be further studied and to explore novel endpoints that could not only assess GVHD, but also the complex relationships between relapse and GVHD as well as prolonged use of immune suppression. The control population selected from the CIBMTR database was comprised of patients who received HSCT in a US center from 2006 to 2009 and who received tacrolimus and methotrexate as their sole GVHD prophylaxis. Data from single institution studies of the three agents to be tested in this protocol were also studied. Populations differed according to disease, donor, conditioning intensity, disease risk and patient age. Each institutional cohort was compared with the CIBMTR controls, adjusting for differences in baseline populations using multivariate regression techniques. Table 1.5a summarizes the results of both univariate and multivariate analyses.

Table 1.5a: UNIVARIATE AND MULTIVARIATE RESULTS FROM THE BENCHMARK ANALYSIS

Outcome		**Tac+MTX Control** (95%CI)	**Post Cy** (95%CI)	**Tac+MTX+ Bortezomib** (95%CI)	**Tac+MTX+ Maraviroc** (95%CI)
Grade III-IV Acute GVHD	HR	1.00	0.90 (0.58-1.4)	0.48 (0.22-1.01)	0.91 (0.4-2.05)
	Incidence at 6 mo (95%CI)	25% (23-26%)	23% (15-33%)	14% (6-25%)	13% (3-29%)
CGVHD	HR	1.00	0.24 (0.14-0.41)	0.73 0.49-1.1)	0.29 (0.12-0.69)
	Incidence at 12 mo (95%CI)	45% (43-46%)	13% (7-20%)	43% (28-58%)	19% (7-35%)
Overall Survival	HR	1.00	1.07 (0.82-1.4)	0.53 (0.34-0.83)	0.80 (0.46-1.4)
	Probability at 12 mo (95%CI)	60% (58-61%)	57% (47-66%)	79% (66-88%)	64% (47-77%)
Disease free survival	HR	1.00	1.21 (0.94-1.56)	0.67 (0.44-1.02)	1.20 (0.76-1.91)
	Probability at 12 mo (95%CI)	52% (51-53%)	46% (37-55%)	67% (51-78%)	46% (29-61%)

HR=Hazard Ratio, CI=Confidence Interval. The event for overall survival was death and the event for disease free survival was death or relapse. A hazard ratio (HR) greater than 1 implies that a specific group has more events at any time compared to the Tac+MTX Control reference group (indicated by a HR of 1.00).

We also were interested in evaluating a composite endpoint that would better reflect reductions in either or both acute and chronic GVHD as well as the sometimes opposite effects of reducing GVHD on transplant-related mortality and relapse. First the prognostic impact of acute GVHD was investigated as a time dependent covariate. Grades 3 and 4 but not grade 2 acute GVHD were significantly associated with survival (Table 1.5b)

Table 1.5b: IMPACT OF MAXIMUM GRADE OF ACUTE GVHD AS A TIME-DEPENDENT COVARIATE ON MORTALITY

Max Grade Acute GVHD	N	RR (95% CI)	p-value
0-1	1815	1.00	
2	863	1.02 (0.9-1.15)	0.779
3	609	1.34 (1.17-1.52)	<0.001
4	246	3.39 (2.88-3.99)	<0.001

RR=relative risk; CI=confidence interval

Using this information and considering the potential impact of these regimens on chronic GVHD (Table 1.5a), we computed the composite endpoint of Grade 3/4 acute GVHD-free, chronic GVHD-free, relapse-free survival (GVHD/relapse-free survival or GRFS). The GRFS endpoint was calculated for the patients in the CIBMTR Tac+MTX control group (see above) who received RIC HSCT from 2006 to 2009 and who fulfilled the eligibility for the planned BMT CTN 1203 trial (N=628). The one year probability of GRFS was 23% (95% CI, 20-26%). This rate was used as the baseline rate for power and sample size calculations for this clinical trial. We also investigated whether GRFS rates differed by disease, for the diseases allowed in the trial. Table 1.5c demonstrates one year GRFS rates by disease and the hazard ratio for the inverse of GRFS in each disease group compared to patients with AML, adjusting for other patient characteristics in multivariate analysis.

Table 1.5c: ONE YEAR GRFS BY DISEASE

Disease	**1 year GRFS**	**Hazard Ratio**	**p-value**
Acute Myelogenous Leukemia[a]	25%	1.00	--
Acute Lymphoblastic Leukemia[a]	24%	1.04 (0.69-1.56)	0.848
Chronic Myeloid Leukemia[b]	25%	1.11 (0.79-1.57)	0.537
Myelodysplastic Syndrome[c]	12%	1.55 (1.18-2.04)	0.002
Chronic Lymphocytic Leukemia[d]	16%	1.42 (1.11-1.82)	0.005
Non-Hodgkin Lymphoma[d]	30%	0.89 (0.70-1.12)	0.305

[a]In first or subsequent remission; [b]chronic or accelerated phase; [c]< 5% blasts; [d]chemosensitive

Patients transplanted for myelodysplastic syndrome and those transplanted for chronic lymphocytic leukemia had higher risks of treatment failure than patients transplanted for other diseases; however the reasons for treatment failure differed in these two groups. Rates of grade III-IV acute GVHD were higher in patients with chronic lymphocytic leukemia than in patients with other diseases; rates of disease relapse were higher in patients with myelodysplastic syndrome than in patients with other diseases. For analysis of this trial, disease will be categorized as low risk (acute leukemia, chronic myeloid leukemia, non-Hodgkin lymphoma) or high risk (chronic lymphocytic leukemia or myelodysplastic syndrome) and randomization will be stratified based on risk status.

1.6. Rationale

This multicenter Phase II clinical trial will evaluate three novel GVHD prophylaxis approaches for their efficacy in improving the proportion of patients who do not develop severe acute GVHD, chronic GVHD that requires systemic therapy and disease progression or relapse by one year post-transplant. All treatment arms will be compared to a contemporary control group from the CIBMTR database in which all patients received the most commonly used GVHD prophylaxis regimen, Tac+MTX. The results of this study will identify the most promising approach(es) to be tested in a Phase III trial. Selection of the most promising therapy(ies) will be made based on the magnitudes of difference in the primary endpoint between each intervention group and the control.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

This is a Phase II randomized, open label, multicenter trial to identify the most promising GVHD prophylaxis approach(es) for patients with malignant disease receiving an allogeneic PBSC transplant after a RIC regimen. Patients will be randomized to one of three new strategies: Tac/MTX/Bortezomib, Tac/MTX/Maraviroc or Tac/MMF/Cy. The primary endpoint of GVHD/relapse or progression-free survival post-transplant will be compared to a non-randomized contemporary Tac/MTX control group collected through the CIBMTR to identify which agents are promising relative to control. The control group of patients will not be individually matched to patients randomized to one of the treatment arms; rather they will be selected to satisfy similar eligibility requirements and multivariate regression analysis will be used to adjust for potential differences in the groups. Comparisons among the three randomized arms will also be used to guide selection of the most promising agent for further study.

2.2. Hypothesis and Specific Objectives

2.2.1. Hypothesis

At least one of the three treatment approaches will have promising GRFS compared to the control group, which is anticipated to have a rate of GRFS by 1 year of 23%.

2.2.2. Study Objectives

The primary objective of the randomized trial is to compare one year GVHD/relapse or progression-free survival (GRFS) after HSCT between each of three novel GVHD prophylaxis approaches and a contemporary control. An event for this time to event outcome is defined as grade III-IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse or progression, or death by any cause. Secondary objectives are to describe rates of grade II-IV and III-IV acute GVHD, visceral acute GVHD and chronic GVHD; immunosuppression-free survival rate at one year; neutrophil and platelet engraftment; donor cell engraftment, immune reconstitution, disease relapse or progression; transplant-related mortality; rates of Grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; incidence of infections; and overall survival.

2.3. Patient Eligibility

2.3.1. Inclusion Criteria

1. Age 18-75 years (patient is older than 18.0 and less than 76.0 years old)
2. Patients with acute leukemia, chronic myelogenous leukemia or myelodysplasia with no circulating blasts and with less than 5% blasts in the bone marrow.

3. Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular, marginal zone, diffuse large B-cell, Hodgkin's Lymphoma,or mantle cell lymphoma with chemosensitive disease at time of transplantation
4. Planned reduced intensity conditioning regimen (see eligible regimens in Table 2.4a)
5. **Patients must have a related or unrelated peripheral blood stem cell donor as follows:**
    a. Sibling donor must be a 6/6 match for HLA-A and -B at intermediate (or higher) resolution, and -DRB1 at high resolution using DNA-based typing, and must be willing to donate peripheral blood stem cells and meet institutional criteria for donation.
    b. Unrelated donor must be a 7/8 or 8/8 match at HLA-A, -B, -C and –DRB1 at high resolution using DNA-based typing. Unrelated donor must be willing to donate peripheral blood stem cells and be medically cleared to donate stem cells according to NMDP criteria.
6. Cardiac function: Ejection fraction at rest ≥ 45%
7. Estimated creatinine clearance greater than 50 mL/minute (using the Cockcroft-Gault formula and actual body weight)
8. Pulmonary function: DLCO ≥ 40% (adjusted for hemoglobin) and FEV1 ≥ 50%
9. Liver function: total bilirubin < 1.5 x the upper limit of normal and ALT/AST < 2.5x the upper normal limit. Patients who have been diagnosed with Gilbert's Disease are allowed to exceed the defined bilirubin value of 1.5x the upper limit of normal.
10. Female subjects (unless postmenopausal for at least 1 year before the screening visit, or surgically sterilized), agree to practice two (2) effective methods of contraception at the same time, or agree to completely abstain from heterosexual intercourse, from the time of signing the informed consent through 12 months post transplant (see Section 2.6.4 for definition of postmenopausal).
11. Male subjects (even if surgically sterilized), of partners of women of childbearing potential must agree to one of the following: practice effective barrier contraception (see Section 2.6.4 for list of barrier methods), or abstain from heterosexual intercourse from the time of signing the informed consent through 12 months post transplant.
12. Signed informed consent

2.3.2. Exclusion Criteria

1. Prior allogeneic transplant
2. Karnofsky Performance Score < 70%
3. Active CNS involvement by malignant cells
4. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment.

5. Presence of fluid collection (ascites, pleural or pericardial effusion) that interferes with methotrexate clearance or makes methotrexate use contraindicated
6. Patients with transformed lymphoma (e.g., Richters transformation arising in follicular lymphoma or chronic lymphocytic leukemia)
7. Patients seropositive for the human immunodeficiency virus (HIV)
8. Patient with active Hepatitis B or C determined by serology and/or NAAT
9. Patients with hypersensitivity to bortezomib, boron or mannitol
10. Patients with ≥ grade 2 sensory peripheral neuropathy
11. Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure (see Appendix D), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
12. Female patients who are lactating or pregnant
13. Patients with a serious medical or psychiatric illness likely to interfere with participation in this clinical study
14. Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the Protocol Officer or one of the Protocol Chairs.
15. Planned use of ATG or alemtuzumab in conditioning regimen.
16. Planned post-transplant therapy (including use of TKIs).
17. Inability to withhold agents that may interact with hepatic cytochrome P450 enzymes (CYP3A4), or glutathione S-transferases involved in bortezomib and/or busulfan metabolism during day -5 through day +7. It is acceptable to use alternative non-interacting medications during this period, and then resume prior medications.
18. Patients with secondary acute myeloid leukemia arising from myeloproliferative disease, including CMML, with evidence of active myeloproliferative features or myelofibrosis in the background.

2.3.3. Eligibility for the Control Arm

Patients in the control arm will be identified from patients prospectively reported to the CIBMTR from U.S centers not enrolling to the BMT CTN 1203 study and which agree to participate in this study. Control patients will not be individually matched to patients on one of the randomized treatment arms, but rather will satisfy similar eligibility requirements. Patients will need to fulfill the same inclusion criteria for the clinical trial according to Section 2.3.1, plus the following:

1. Receive Tac/MTX as the sole GVHD prophylaxis approach
2. Receive the same regimens as specified in Table 2.4a
3. Receive PBSC as the graft source

Exclusion criteria for the controls:

1. Karnofsky Performance Score < 70%
2. Active CNS involvement by malignant cells
3. Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and with progression or no clinical improvement) at time of enrollment
4. Patients seropositive for the human immunodeficiency virus (HIV)
5. Patient with active Hepatitis B or C determined by serology and/or NAAT

Data for all eligible patients in centers agreeing to participate as control centers will be used to constitute the control database for this study.

2.4. Treatment Plans

It is recommended that adjusted ideal body weight be used when calculating conditioning regimen chemotherapy doses..

Ideal Body Weight (IBW) Formulas:

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

Adjusted Ideal Body Weight Formula:

AIBW = IBW + [(0.25) x (ABW - IBW)]

2.4.1 Conditioning Regimens

Eligible patients will receive a reduced intensity or nonmyeloablative conditioning regimen according to Table 2.4a. Other regimens deemed to be RIC and not included in Table 2.4a, might be considered after review by the protocol chairs/officer.

TABLE 2.4a: CONDITIONING REGIMENS[1]

Reduced Intensity Conditioning	Nonmyeloablative Conditioning
Fludarabine/Busulfan (Flu/Bu) • Fludarabine (120-180 mg/m^2) • Busulfan (≤8 mg/kg PO or 6.4 mg/kg IV)	**Fludarabine/Cyclophosphamide (Flu/Cy)** • Fludarabine (90-120 mg/m^2) • Cyclophosphamide (120 mg/kg or 2250 mg/m^2)
Fludarabine/Melphalan (Flu/Mel) • Fludarabine (120-180 mg/m^2) • Melphalan (≤150 mg/m^2)	**Fludarabine /Total Body Irradiation (Flu/TBI)** • Fludarabine (90 mg/m^2) • TBI (200 cGy)
	Fludarabine/ Cyclophosphamide/TBI (Flu/Cy/TBI) • Fludarabine (150 mg/m^2) • TBI (200 cGy) • Cyclophosphamide (29 mg/kg)

[1]Addition of antithymocyte globulin or alemtuzumab is not allowed.

Fludarabine and busulfan (Flu/Bu)

The recommended Flu/Bu regimen is the following:

- Days -6 to -2: Flu (30 mg/m^2/day, total dose of 150 mg/m^2)

  Busulfan Options
  Busulfan without PK - Days -5 to -4: Busulfan (4 mg/kg/day PO or 3.2 mg/kg/day IV or 130 mg/m^2/day IV; total dose of 8 mg/kg or 6.4 mg/kg or 260 mg/m^2 respectively)

  OR
  Busulfan with PK – Days -6 to -3: Busulfan 100 mg/m^2/day IV daily for 4 days to target an AUC of 4000 µMol*min/day (course AUC of 16,000 µMol*min). A test dose may be administered prior to Day -6 per institutional standards.

  The sequence of fludarabine and busulfan administration will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above. For patients receiving busulfan doses according to pharmacokinetics, targeting doses to area under the curve of 4000µMol/min or less is allowed. For CNS seizure prophylaxis, the use of Keppra is allowed. Phenytoin and other potent CYP3A4 inducers are not allowed for seizure prophylaxis to avoid drug interactions..

Fludarabine and melphalan (Flu/Mel)

The recommended Flu/Mel regimen is the following:

- Days -5 to -2: Flu (30 mg/m^2/day, total dose of 120 mg/m^2)
- Day -1: Mel (140 mg/m^2)

The sequence of fludarabine and melphalan administration will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above. Dividing the dose of melphalan into two days is allowed.

Fludarabine and cyclophosphamide (Flu/Cy)

The recommended Flu/Cy regimen is the following:

- Days -5 to -3: Flu (30 mg/m^2/day, total dose of 90 mg/m^2)
- Days -4 to -2: Cyclophosphamide (750 mg/m^2/day, total dose of 2250 mg/m^2)

  Alternatively:
- Days -3 to -2: Cyclophosphamide (60 mg/kg/day, total dose of 120 mg/kg)

The sequence of fludarabine and cyclophosphamide administration will be done according to institutional standards as long as the prescribed doses are the same as the recommended regimen above. Addition of rituximab conditioning in patients with lymphoproliferative disease is allowed. Dose and intervals of rituximab conditioning can be determined according to institutional guidelines. However, rituximab use after stem cell infusion is not permitted.

Fludarabine and total body irradiation (Flu/TBI)

The recommended Flu/TBI regimen is the following:

- Days -5 to -3: Flu (30 mg/m^2/day, total dose of 90 mg/m^2)
- Day 0: TBI 200 cGY (pre-stem cell infusion)

Fludarabine, total body irradiation and cyclophosphamide (Flu/Cy/TBI)

The recommend Flu/Cy/TBI regimen is the following:

- Days -6 to -5: Cy (14.5 mg/kg/day, total dose of 29 mg/kg)
- Days -6 to -2: Flu (30 mg/m^2/day, total dose of 150 mg/m^2)
- Day -1: TBI 200 cGY

2.4.2 Hematopoietic Stem Cell Transplantation

Mobilized PBSC is the only allowed graft source for patients enrolled in this clinical trial.

Donors will undergo G-CSF mobilization according to local institutional and donor center practices. PBSC will be collected by apheresis according to local institutional guidelines. Plasma and red cell depletion are allowed for volume reduction or ABO incompatibility but any other form of graft manipulation (including ex-vivo T cell depletion) is not permitted.

The target stem cell dose is between 2 x 10^6/kg and 10 x 10^6/kg (actual body weight) $CD34^+$ cells. The maximum CD34+ cell dose is 10 x 10^6/kg.

Up to two leukapheresis procedures may be performed to obtain the minimum $CD34^+$ cell target. If, after two leukapheresis procedures, fewer than 2 x 10^6/kg $CD34^+$ cells have been collected, transplant centers will have the discretion to continue PBSC cell harvesting or to proceed to bone marrow harvesting to obtain sufficient cells. If bone marrow harvesting is needed in order to meet the desired cell dose, the transplant center needs to notify the Protocol Coordinator, Chairs or Officer.

If more than 10 x 10^6/kg $CD34^+$ stem cells are collected, the excess will either be discarded or cryopreserved for future use, but will not be administered to the patient.

PBSC will be administered on Day 0 to all patients according to individual institutional guidelines after appropriate processing and quantification has been performed by the local laboratory. Stem cells are administered through an indwelling central venous catheter. If infusion occurs over two days, Day 0 is the day the last infusion is completed. Sites should avoid infusion after 4pm because this complicates the administration of Bortezomib if dose modifications are required due to toxicity. If modifications are required, late infusion of the stem cell source could alter the calendar schedule and result in either a missed dose or a protocol violation.

2.4.3 Tacrolimus/Methotrexate/Bortezomib

Tacrolimus

Tacrolimus will be given per institutional practices, orally at a dose of 0.05 mg/kg or intravenously at a dose of 0.03 mg/kg starting Day -3. The dose of tacrolimus may be rounded to the nearest 0.5 mg for oral formulations. Subsequent dosing will be based on blood levels. The dose should be adjusted accordingly to maintain a suggested level of 5-15 ng/mL. If patients are on medications which alter the metabolism of tacrolimus (e.g. azoles), the initial starting dose and subsequent doses should be altered as per institutional practices. Tacrolimus taper can be initiated at a minimum of 90 days post HSCT if there is no evidence of active GVHD. The rate of tapering will be done according institutional practices but patients should be off tacrolimus by Day 180 post HSCT if there is no evidence of active GVHD.

Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Patients with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 3-8 ng/mL).

Methotrexate

Methotrexate will be administered, per institutional practices, at the doses of 15 mg/m^2 IV bolus on Day +1, and 10 mg/m^2 IV bolus on Days +3, +6 and +11 after hematopoietic stem cell infusion. The Day +1 dose of methotrexate will be given at least 24 hours after the hematopoietic stem cell infusion and at least 30 minutes after the first dose of bortezomib. Dose reduction of

MTX due to worsening creatinine clearance after initiation of conditioning regimen, high serum levels or development of oral mucositis is allowed according to institutional practices.

Bortezomib

Bortezomib will be administered at the dose of 1.3 mg/m^2 (based upon actual body weight) as an approximately 3-5 second IV push on Days +1, +4, and +7 after hematopoietic stem cell infusion. There must be at least 72 hours between each dose of bortezomib. Subcutaneous administration of bortezomib is not allowed on this protocol.

Bortezomib dose modifications:

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0

Neuropathic pain and peripheral sensory neuropathy are to be managed as described in Table 2.4b.

Table 2.4b: Management of Patients With VELCADE-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms[a]	**Modification of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or parasthesias) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities or Daily Living [ADL][b])	Reduce VELCADE to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m^2 (*missed dose days will not be made up*).
Grade 4 (life-threatening consequence; urgent intervention indicated)	Discontinue VELCADE

Source: VELCADE USPI issued January 2012.
Abbreviations: ADL = activities of daily living
a Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
b Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc
c Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Patients with mild hepatic impairment (bilirubin ≤ 1.5 × ULN) do not require dose adjustment. If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (**>** 1.5 -3.0 X ULN) after exposure to Bortezomib, the dose should be held until the toxicity returns to < Grade 2. Restarting Bortezomib must be done at the next lower dose level as below.

Once bortezomib is reduced for any toxicity, the dose may not be re-escalated.

If after bortezomib has been held, the toxicity does not resolve, then bortezomib must be discontinued.

If the toxicity resolves, as described above, bortezomib may be restarted at the same schedule the patient was on prior to holding therapy, and the dose must be reduced by approximately 25% as follows:

- If the patient was receiving 1.3 mg/m^2, reduce the dose to 1 mg/m^2.
- If the patient was receiving 1 mg/m^2, reduce the dose to 0.7 mg/m^2.

2.4.4 Tacrolimus/Methotrexate/Maraviroc

Tacrolimus

Tacrolimus will be given per institutional practices, orally at a dose of 0.05 mg/kg or intravenously at a dose of 0.03 mg/kg starting Day -3. The dose of tacrolimus may be rounded to the nearest 0.5 mg for oral formulations. Subsequent dosing will be based on blood levels. The dose should be adjusted accordingly to maintain a suggested level of 5-15 ng/mL. If patients are on medications which alter the metabolism of tacrolimus (e.g. azoles), the initial starting dose and subsequent doses should be altered as per institutional practices. Tacrolimus taper can be initiated at a minimum of 90 days post HSCT if there is no evidence of active GVHD. The rate of tapering will be done according to institutional practices but patients should be off tacrolimus by Day 180 post HSCT if there is no evidence of active GVHD.

Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Patients with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 3-8 ng/mL).

Methotrexate

Methotrexate will be administered, per institutional practices, at the doses of 15 mg/m^2 IV bolus on Day +1, and 10 mg/m^2 IV bolus on Days +3, +6 and +11 after hematopoietic stem cell infusion. The Day +1 dose of methotrexate will be given at least 24 hours after the hematopoietic stem cell infusion. Dose reduction of MTX due to worsening creatinine clearance after initiation of conditioning regimen, high serum levels or development of oral mucositis is allowed according to institutional practices.

Maraviroc

Maraviroc will be dosed at 300 mg orally twice a day and will start on Day -3 *prior* to hematopoietic stem cell infusion, and continue until Day 30 post HSCT. If the patient requires a two-day stem cell infusion, maraviroc treatment will end 30 days after the first infusion day (on day 29). There are no food restrictions.

Maraviroc dose modifications

The dose of maraviroc for patients who are not taking strong inhibitors or inducers of CYP 450 is 300 mg twice daily. The dose will be adjusted in patients who take specific concomitant medications based on Table 2.4c. In particular, the use of anti-seizure medications that induce CYP 450 is allowed (with maraviroc dose adjustment) only if patients are taking them chronically. The use of these medications (carbamazepine, phenobarbital, and phenytoin) as anti-seizure prophylaxis during conditioning is not allowed.

TABLE 2.4c: MARAVIROC DOSING REGIMEN WITH CONCOMITANT MEDICATIONSConcomitant Medications	**Dose of Maraviroc**
Potent CYP3A inhibitors (with or without a potent CYP3A inducer)[1]: ketoconazole, itraconazole, clarithromycin	150 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor): Rifampin, carbamazepine, phenobarbital, and phenytoin	600 mg twice daily

[1] Both voriconazole and posaconazole are moderate CYP3A inhibitors and do not require dose adjustment of maraviroc. Pharmacokinetic data on maraviroc and voriconazole combination demonstrated no need for dose reduction of maraviroc.

Renal dysfunction does not require a dose modification in patients who receive maraviroc 300 mg twice daily and the drug should not be held in severe renal dysfunction or in patients undergoing renal replacement therapy. In patients who receive maraviroc 600 mg twice daily or 150 mg twice daily due to concomitant medications, the drug should be held in severe renal failure (CrCl <30 mL/min), and restarted when the CrCl ≥ 30 at the same dose level due to lack of data for these dose levels and according to the approved prescribing information. Renal function will be calculated using the Cockcroft-Gault formula and actual body weight.

Maraviroc dose reduction of 50% will take place if the following requirement is met:

Symptoms of postural hypotension such as dizziness, syncope or loss of consciousness together **with** evidence for postural hypotension defined as a decrease in supine to standing blood pressure of at least 10 mmHg (diastolic) or 20 mmHg (systolic) or a standing systolic blood pressure lower than 90 mmHg. The drug must be held until symptomatic hypotension resolves prior to reducing the dose.

The following events will mandate holding maraviroc therapy:

- Grade 3 or higher liver toxicity not attributable to other causes such as infection, GVHD, toxicity from other drugs or sinusoid obstructive syndrome/veno-occlusive disease.
- Other non-hematologic grade 3 or higher toxicity, which is not attributable to other causes such as GVHD, infection, disease relapse and chemotherapy toxicity.
- Severe mucositis, nausea or other complications that precludes administration of an oral medication.
- Persistent symptomatic postural hypotension after reduction to 150 mg twice daily dose.

The drug should be restarted at the same dose after recovery of related toxicities to grade 2 or lower or identification of an alternative cause for these toxicities.

GVHD does not require holding maraviroc therapy unless other criteria are met (e.g., grade 3 liver toxicity).

2.4.5 Tacrolimus/Mycophenolate Mofetil/Cyclophosphamide

Tacrolimus

Tacrolimus will be given per institutional practices, orally at a dose of 0.05 mg/kg or intravenously at a dose of 0.03 mg/kg starting Day +5. Serum levels of tacrolimus will be measured at Day 7 and then should be checked weekly thereafter, and the dose adjusted accordingly to maintain a suggested level of 5-15 ng/mL. Tacrolimus taper can be initiated at a minimum of 90 days post HSCT if there is no evidence of active GVHD. The rate of tapering will be done according to institutional practices but patients should be off tacrolimus by Day 180 post HSCT if there is no evidence of active GVHD.

Dose reductions should be made if toxicity is present or whole blood levels are above the recommended range, in the absence of toxicity. Patients with severe intolerance of tacrolimus may be placed on cyclosporine (trough level of 200-400 ng/mL) or sirolimus (trough level of 3-8 ng/mL).

Mycophenolate mofetil (MMF)

MMF will be given at a dose of 15 mg/kg TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (1g TID, IV or PO). MMF prophylaxis will start Day 5 and discontinue after the last dose on Day 35, or may be continued if active GVHD is present.

Cyclophosphamide

Hydration prior to cyclophosphamide may be given according to institutional standards. A recommended approach is as follows: Patients are instructed to increase fluids overnight before cyclophosphamide administration. Hydration with normal saline at 3 ml/kg/hr IV will be started 2 hours prior to cyclophosphamide, then the rate will be reduced to 2 ml/kg/hr for 1 hour pre-cyclophosphamide and continued at 2 ml/kg/hr for 8 hours post-cyclophosphamide.

Mesna will be given in divided doses IV 30 min pre- and at 3, 6, and 8 hours post-cyclophosphamide or administered per institutional standards. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of Mesna is equal to 80% of the total daily dose of cyclophosphamide.

Cyclophosphamide [50 mg/kg IBW; if ABW < IBW, use ABW] will be given on Day 3 post-transplant (between 60 and 72 hours after the start of the PBSC infusion) and on Day 4 post-

transplant (approximately 24 hours after Day 3 cyclophosphamide). Cyclophosphamide will be given as an IV infusion over 1-2 hours (depending on volume).

It is crucial that no immunosuppressive agents are given prior to transplant, or until 24 hours after the completion of the post-transplant cyclophosphamide. This includes corticosteroids as anti-emetics.

2.5 Supportive Care

All supportive care will be given in keeping with the BMT CTN Manual of Procedures and local institutional practice. Supportive care will be administered in a similar fashion to subjects randomized to all three arms of the study.

2.5.1 Growth Factors

G-CSF may be given per institutional guidelines.

2.5.2 Blood Products

Transfusion thresholds for blood product support will be consistent with the BMT CTN MOP and standard institutional guidelines. All blood products will be irradiated.

2.5.3 Prophylaxis Against Infections

Patients will receive infection prophylaxis according to institutional guidelines. Infection prophylaxis will include, but is not limited to, agents or strategies (e.g., PCR screening and preemptive therapy) to reduce the risk of bacterial, herpes simplex, CMV, HHV-6, EBV, Pneumocystis jiroveci, and fungal infections:

- Antifungal therapy: Prophylaxis with fluconazole or other antifungal agents can be given as per local institutional guidelines.
    - **Fluconazole, voriconazole and other azoles** are expected to increase serum tacrolimus levels, therefore, dosages of tacrolimus should be adjusted accordingly. These drugs also interact with bortezomib and it is recommended to avoid using them from Day 0 to Day +7 among patients who are randomized to bortezomib.

- **CMV:** CMV monitoring will be done according to institutional guidelines. It is recommended that weekly assessment for CMV be done through Day 60 post-transplant. Any reactivation and/or CMV disease will be captured in this study. An Infection form must be submitted in AdvantageEDC.

2.5.4 Intravenous Immune Globulin (IVIG)

IVIG administration will be according to local institutional standard practice.

2.6 Participant Risks

2.6.1 Therapy Toxicities

All toxicities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

2.6.2 Tacrolimus

Tacrolimus side effects include:

- Cardiovascular: hypertension
- Neurologic: confusion, dizziness, insomnia, seizures, tremors, changes in how clearly one can think
- Gastrointestinal: nausea, vomiting
- Hematologic: microangiopathic hemolytic anemia, thrombocytopenia
- Endocrine and metabolic: hypomagnesemia, hypokalemia, hypocalcemia, hyperlipidemia
- Miscellaneous: unwanted hair growth, changes in vision, liver problems, reversible renal insufficiency, infections and post-transplant lymphoproliferative disorders

2.6.3 Methotrexate

The most frequently reported adverse reactions associated with methotrexate use as GVHD prophylaxis include:

- Neurologic: fever, dizziness, chills, undue fatigue
- Gastrointestinal: ulcerative stomatitis, nausea, abdominal distress, diarrhea
- Hematologic: leucopenia, anemia, and suppressed hematopoiesis (leading to infection)
- Miscellaneous: abnormal liver tests, kidney failure, and pulmonary complications after transplantation

2.6.4 Bortezomib

To date, more than 436,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib.

Prescribing physicians and health care practitioners are referred to their locally approved product label for bortezomib regarding Indications and Usage, Contraindications, Warnings, and Precautions.

The known anticipated risks of bortezomib therapy are presented in Appendix H. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent bortezomib dosed at 1.3 mg/m^2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

The most common Bortezomib side effects include:

- Hematologic: anemia, neutropenia, thrombocytopenia, leucopenia, lymphopenia
- Neurologic: asthenia, dizziness, anxiety, syncope, headache, insomnia, fever, rigors, chills, sensory peripheral neuropathy, and leukoencephalopathy, including reversible posterior leukoencephalopathy syndrome
- Pulmonary: cough, dyspnea, pleural effusion, pneumonitis, interstitial pneumonia, edema acute respiratory distress syndrome (ARDS)
- Cardiovascular: hypotension, tachycardia, atrial fibrillation, palpitation, congestive heart failure, bradycardia, atrial flutter, atrioventricular block, arrhythmia, cardiac failure, cardiac arrest, pericardial effusion, pericarditis
- Infectious: reactivations of herpes zoster, opportunistic infections
- Gastrointestinal: weight loss, decreased appetite, anorexia, constipation, dehydration, diarrhea, heartburn, dyspepsia, stomatitis, nausea, vomiting, ileus, GI perforation, acute pancreatitis
- Metabolic: hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia
- Renal: renal failure
- Neuromuscular and skeletal: arthralgias, back pain, bone pain, muscle cramp and myalgias
- Miscellaneous: rash, hemorrhage, blurred vision, deafness, hepatitis, hyperbilirubinemia

Other medical events of interest that are considered not causally related to bortezomib include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Genotoxicity testing has shown that bortezomib is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

Additional details on the potential risks of bortezomib may be found in the current Investigator's Brochure.

Bortezomib Precautions and Restrictions

It is not known what effects bortezomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit. *Postmenopausal is defined as the time after which a woman has experienced twelve (12) consecutive months without a menstrual period.*
- Surgically sterile
- If they are of childbearing potential (i.e., not postmenopausal or surgically sterile), agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 12 months post-transplant, or agree to completely abstain from heterosexual intercourse. It is strongly recommended that at least 1 of these 2 methods be 'highly effective' (see Table 2.6).

Table 2.6 Methods of Contraception

Highly Effective Methods	Other Effective Methods (barrier methods)
Intra-uterine devices (IUD)	Latex condom
Hormonal contraceptives (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide Cervical cap Sponge
If one of the highly effective methods cannot be used, using 2 effective methods at the same time is recommended.	

Male patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to one (1) of the following:

- Practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug,
- Completely abstain from heterosexual intercourse.

2.6.5 Maraviroc

Maraviroc side effects include:

- Neurologic: fever, dizziness (including postural dizziness), insomnia, anxiety, consciousness disturbances, depression, pain
- Dermatologic: rash, pruritus, folliculitis, skin neoplasms (benign), erythema, acne

- Pulmonary: upper respiratory tract infection, cough, bronchitis, sinusitis, breathing abnormality, respiratory tract/sinus disorder
- Cardiovascular: Vascular hypertensive disorder
- Endocrine and metabolic: lipodystrophy
- Gastrointestinal: Appetite disorders, constipation
- Genitourinary: Urinary tract/bladder symptoms, genital warts
- Hematologic: Neutropenia (grades 3/4)
- Hepatic: Transaminases increased (grades 3/4), bilirubin increased (grades 3/4)
- Neuromuscular and skeletal: Joint disorders, parasthesia, sensory abnormality, myalgia, peripheral neuropathy
- Ocular: Conjunctivitis, infection/inflammation
- Miscellaneous: Herpes infection, sweat gland disturbances, influenza

2.6.6 Mycophenolate mofetil (MMF)

MMF side effects include:

- Neurologic: headache, tremors, insomnia, dizziness, excessive fatigue, weakness
- Cardiovascular: tachycardia
- Pulmonary: dyspnea
- Gastrointestinal: nausea, vomiting, dyspepsia, abdominal pain, diarrhea, hematemesis and hematochezia
- Hematologic: Neutropenia, thrombocytopenia, unusual bruising, and anemia
- Endocrine and metabolic: hyperlipidemia
- Miscellaneous: rash, edema, change in vision, infection, second cancers, teratogenicity, miscarriage, limited effectiveness of birth control, and progressive multifocal leukoencephalopathy (PML).

2.6.7 Cyclophosphamide

Cyclophosphamide side effects include:

- Gastrointestinal: nausea, vomiting, anorexia, mucositis, stomatitis, abdominal pain, diarrhea
- Cardiovascular: cardiomyopathy, fluid weight gain/edema
- Hematologic: myelosuppression, hemolytic anemia

- Miscellaneous: skin rash, alopecia, hemorrhagic cystitis, pulmonary toxicity, temporary lethargy, secondary cancers, gonadal function impairment, sterility, and damage to fetus if taking drug while pregnant

2.7 Study Drug Supply

2.7.1 Tacrolimus, Methotrexate, Cyclophosphamide and Mycophenolate Mofetil

Tacrolimus, methotrexate, cyclophosphamide and mycophenolate mofetil are commercially available agents and will be administered as described in Section 2.4.

2.7.2 Bortezomib and Maraviroc

Bortezomib will be provided by Millennium Pharmaceuticals, Inc. and distributed by the BMT CTN 1203 Central Pharmacy directly to transplant centers. Maraviroc will also be provided by the study and distributed by the BMT CTN 1203 Central Pharmacy directly to transplant centers.

BORTEZOMIB

Drug Supply, Preparation, Handling and Storage:
Bortezomib for Injection (supplied by Millennium Pharmaceuticals, Inc.) is a sterile lyophilized powder for reconstitution and is supplied in vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5mg of bortezomib contain 35mg of mannitol.

Vials containing lyophilized Bortezomib for Injection will be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

Bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling Bortezomib solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation will be disposed of according to standard practices. A log must be kept of all disposed materials.

Drug is available in sterile, single use vials containing 3.5 mg of Bortezomib. The vials are not patient specific. Each vial of Bortezomib for Injection will be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing. For intravenous infusions, reconstitution must be with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP with a concentration of 1 mg/mL. Prior to reconstitution the vials will remain in the cartons to

protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted Bortezomib will be administered promptly and in no case more than 8 hours after reconstitution.

Administration:
Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using institutional standards. **Any discrepancy between the <u>calculated</u> dose and dose administered and the reason for the discrepancy must be recorded in the source documents.**

The appropriate amount of Bortezomib will be drawn from the injection vial and administered as an intravenous (IV) push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

There must be at least 72 hours between each dose of bortezomib.

Drug Ordering:
Bortezomib will be supplied to participating centers from the BMT CTN 1203 Central Pharmacy. Refer to the BMT CTN 1203 Study Drug Guide for additional information regarding study drug supply and ordering, or contact the BMT CTN 1203 DCC Protocol Coordinator.

Drug Accountability:
Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and return to the BMT CTN 1203 Central Pharmacy or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates, and patient numbers.

Drug Destruction:
Investigational bortezomib (expired or end of study) will be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

<u>MARAVIROC</u>

Drug Supply, Preparation, Handling and Storage:
Maraviroc (Selzentry®) is manufactured by Pfizer, Inc.

Maraviroc will be supplied in 150 mg and 300 mg tablets and will be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF).

Administration:
Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

Maraviroc will be dispensed under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be per protocol Section 2.4.4.1 (Maraviroc) and Section 2.4.4.2 (Maraviroc Dose Modifications). Maraviroc can be taken with or without food. Tablets should be swallowed whole. However, if necessary they may be crushed and administered to the patient in a liquid or pudding.

Drug Ordering:
Maraviroc will be supplied to participating centers from the BMT CTN 1203 Central Pharmacy. Refer to the BMT CTN 1203 Study Drug Guide for additional information regarding study drug supply and ordering, or contact the BMT CTN 1203 DCC Protocol Coordinator.

Drug Accountability:
Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and return to the central pharmacy or disposal of the drug will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates, and patient numbers.

Drug Destruction:
Investigational maraviroc (expired or end of study) will be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is GVHD/relapse or progression-free survival (GRFS). All randomized patients and patients in the contemporary CIBMTR control will be analyzed for this endpoint. An event for this time to event outcome is defined as grade III-IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse or progression, or death by any cause. Patients will be followed up for at least one year for this endpoint.

Use of systemic immunosuppressive therapy for treatment of chronic GVHD is at the discretion of the treating physicians. The event of interest is the development of chronic GVHD severe enough to warrant any additional systemic treatment(s). Also, continuation of study-mandated GVHD prophylaxis beyond Day 180 in the presence of chronic GVHD will also be considered an event with time to event determined as date of chronic GVHD onset.

3.2. Secondary Endpoints

3.2.1. Acute GVHD

Cumulative incidences of grade II-IV and III-IV acute GVHD will be determined. Acute GVHD will be graded according to the BMT CTN MOP. The time of onset of acute grades II-IV and III-IV acute GVHD will be recorded, as well as the maximum grade achieved. This endpoint will be evaluated through 180 days post HSCT. Within the acute GVHD endpoint, the proportion of patients with visceral involvement (liver or gut) will be described.

3.2.2. Chronic GVHD

The cumulative incidence of chronic GVHD will be determined. Data will be collected directly from providers and chart review according to the recommendations of the NIH Consensus Conference. Eight organs will be scored on a 0-3 scale to reflect degree of chronic GVHD involvement. Liver and pulmonary function test results, and use of systemic therapy for treatment of chronic GVHD will also be recorded. These data will allow calculation of the NIH global severity scores of mild, moderate and severe chronic GVHD, which has been associated with transplant related mortality and overall survival. Assessment of chronic GVHD will occur up to one year post HSCT.

3.2.3. 1-year Immunosuppression-free Survival

Patients who are alive, relapse-free, and do not need ongoing immune suppression to control GVHD at one year post HSCT are considered successes for this endpoint. Immune suppression is defined as any systemic agents used to control or suppress GVHD. Corticosteroid doses of >10 mg present will be considered active systemic immune suppression treatment. Patients who

discontinued immune suppression ≤ 15 days prior to the 1-year time point will be considered to be on immune suppression for this endpoint.

3.2.4. Hematologic Recovery

Hematologic recovery will be assessed according to neutrophil and platelet counts recovery after HSCT. Neutrophil recovery is defined as achieving an absolute neutrophil count (ANC) ≥ 500/mm^3 for three consecutive measurements on three different days. The first of the three days will be designated the day of neutrophil recovery. The competing event is death without neutrophil recovery. For patients who never drop ANC below 500/mm^3, the date of neutrophil recovery will be Day +1 post HSCT.

Platelet recovery is defined by two different metrics: the first day of a sustained platelet count >20,000/mm^3 or >50,000/mm^3 with no platelet transfusion in the preceding seven days. The first day of sustained platelet count above these thresholds will be designated the day of platelet engraftment. For patients who never drop their platelet count below 20,000/mm^3 or 50,000/mm^3, the date of platelet recovery will be Day +1 post HSCT.

3.2.5. Donor Cell Engraftment

Donor cell engraftment will be assessed with donor/recipient chimerism studies. Chimerism may be evaluated in bone marrow, whole blood or blood cell fractions, including CD3 and CD33 or CD15 fraction. For the purpose of this protocol, mixed chimerism is defined as the presence of donor cells, as a proportion of total cells to be < 95% but > 5% in the bone marrow or peripheral blood. Full donor chimerism is defined as ≥ 95% of donor cells. Mixed and full chimerism will be evidence of donor cell engraftment. Donor cells of ≤ 5% will be considered as graft rejection. The proportion of patients with each level of chimerism described above will be described as part of this outcome. For sorted blood cell fractions, CD3+ donor cell chimerism will be used to define the donor/recipient chimerism status.

3.2.6. Disease Relapse or Progression

Relapse is defined by either morphological or cytogenetic evidence of acute leukemia or MDS consistent with pretransplant features, or radiologic evidence of lymphoma, documented or not by biopsy. Progression of disease applies to patients with lymphoproliferative diseases (lymphoma or chronic lymphocytic leukemia) not in remission prior to transplantation. The event is defined as increase in size of prior sites of disease or evidence of new sites of disease, documented or not by biopsy.

Acute leukemia and MDS – Relapse will be diagnosed when there is:

- Reappearance of leukemia blast cells in the peripheral blood; or,
- >5% blasts in the bone marrow, not attributable to another cause (e.g. bone marrow regeneration)

- The appearance of previous or new dysplastic changes (MDS specific) within the bone marrow with or without falling donor chimerism; or
- The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid or
- The reappearance of cytogenetic abnormalities present prior to transplantation

Lymphoproliferative Diseases – Relapse or progression will be diagnosed when there is:

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site will only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the sum of the product diameters of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

  Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

- In addition to the criteria above, patients with CLL 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.

Institution of any therapy to treat persistent, progressive or relapsed disease, including the withdrawal of immunosuppressive therapy or donor lymphocyte infusion, will be considered evidence of relapse/progression regardless of whether the criteria described above were met.

3.2.7. Transplant-related Mortality

The cumulative incidence of TRM will be estimated at Days 100, 180, and 1 year after HSCT. An event for this endpoint is death without evidence of disease progression or recurrence. Disease progression or recurrence will be considered competing events.

3.2.8. Toxicity

All grades ≥ 3 toxicities according to CTCAE, version 4 will be tabulated for each intervention arm. The proportion of patients developing grade ≥ 3 AE across intervention arms will be compared.

3.2.9. Infections

The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each intervention arm. The cumulative incidence of CMV reactivation in the first 100 days post HSCT will be described. All Grade 2 and 3 infections will be reported according to the BMT CTN MOP.

3.2.10. Disease-Free Survival

Disease free survival is the time from date of transplant to death or relapse/progression, whichever comes first. The event for this endpoint is relapse/progression or death. Patients alive and disease free will be censored at last follow-up.

3.2.11. GVHD-Free Survival

An event for this time to event outcome is defined as grade III-IV acute GVHD, chronic GVHD requiring systemic immunosuppressive treatment, or death by any cause. The time for this GVHD-free survival endpoint is the time from date of transplant to death or grade 3/4 acute GVHD or chronic GVHD requiring immunosuppressive treatment, whichever comes first. Patients alive without experiencing an event will be censored at last follow-up.

3.2.12. Overall Survival

Overall survival is defined as the time interval between date of transplant and death from any cause or for surviving patients, to last follow-up. The event for this endpoint is death from any cause.

CHAPTER 4

4. PATIENT ENROLLMENT AND EVALUATIONS

4.1. Approaching Patients, Eligibility Screening and Obtaining Consent

Subjects will be approached for this study after the decision to proceed with transplantation is made and a suitable HLA-matched PBSC donor is identified. Patients willing to participate in the trial will sign an Institutional Review Board approved consent form. Transplant physicians will evaluate the patient eligibility for randomization onto this study (see Section 2.2). Eligibility criteria will be verified and ineligible patients will proceed off study and no further follow-up will be obtained. Transplant center personnel will record the documentation of patient consent in EMMES AdvantageEDC^{SM} (Electronic Data Capture, an Internet-based data entry system) and patients will be registered through AdvantageEDC.

4.2. Transplant Protocol Registration

Before randomization occurs, the transplant center must state through AdvantageEDC which conditioning regimen will be used for the enrolled subject. Such a registration step will avoid potential biases that preferential use of a certain regimen on one treatment arm could confer to the study. At this stage, the transplant center will also verify that the patient is still a candidate for transplantation, and eligible for the trial.

4.3. Randomization

Once the subject is deemed eligible and has given written informed consent, and the transplant center has confirmed patient eligibility and registered the patient's conditioning regimen, randomization occurs. Patients should be randomized as close as possible to the initiation of the conditioning regimen, and preferably within 7 days of and not more than 14 days from the initiation of conditioning. If there is a delay in conditioning, certain pre-transplant evaluations will have to be repeated. Refer to section 4.6.1 Patient Assessments-pre-transplant evaluations.

4.4. Treatment Scheduling

Treatment should be initiated as soon as possible after randomization. This will prevent subject attrition prior to HSCT for reasons such as disease progression. Consequently, all treatments related to the transplant should be scheduled PRIOR to randomization. This includes planning an admission date and ensuring that the PBSC donor can be mobilized and undergo apheresis in a coordinated fashion with the planned transplant.

4.5. Patient Evaluation

The patient pre-transplant evaluation must be completed within three weeks (≤21 days) of randomization. If an unexplained delay in treatment occurs and the initiation of conditioning is greater than 14 days after randomization, some pre-transplant evaluations may need to be

repeated. See section 4.6.1 Patient Assessments-pre-transplant evaluations. This step is necessary because patient organ function, infection status and status of malignancy may vary over time. This evaluation will protect patients with a new contraindication to transplant from initiating transplant therapy at an unsafe time.

4.6. Study Monitoring

The follow-up schedule for scheduled study visits is outlined in Table 4.6a. A detailed description of each of the forms and the procedures required for forms completion and submission can be found in the Data Management Handbook and User's Guide.

TABLE 4.6a: FOLLOW-UP SCHEDULE

Study Visit	Target Day Post-Transplant
Baseline	≤ 42 days from conditioning
1 week	7 ± 2 days
2 week	14 ± 2 days
3 week	21 ± 2 days
4 week	28 ± 2 days
5 week	35 ± 2 days
6 week	42 ± 2 days
7 week	49 ± 2 days
8 week	56 ± 2 days
9 week	63 ± 2 days
100 day	100 ± 7 days
4 month	120 ± 7 days
5 month	150 ± 7 days
6 month	180 ± 14 days
9 month	270 ± 14 days
12 month	365 ± 14 days

4.6.1. Patient Assessments

Table 4.6b summarizes patient clinical assessments over the course of the study.

TABLE 4.6b: PATIENT CLINICAL ASSESSMENTS

Study Assessments/ Testing	Baseline	7	14	21	28	35	42	49	56	63	100	120	150	180	270	365
History, physical exam, weight and height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky performance status (see Appendix F)	X										X			X	X	X
HCT-Specific Comorbidity Index score (see Appendix G)	X															
HLA typing (donor and recipient)	X															
CBC[1], differential, platelet count, and blood chemistries[2]	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Estimated creatinine clearance[3]	X															
Infectious disease titers[4]	X															
EKG and LVEF	X															
DLCO and FEV1	X															X
Disease evaluation[5]	X										X			X		X
Chest x-ray or chest CT	X															
Pregnancy test[6]	X															
GVHD assessments[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity assessments[8]					X				X		X			X	X	X
Chimerism[9]	X				X						X					
Blood samples for future research (see Appendix C)[10]	X					X					X			X		X

[1]CBC with differential performed three times weekly from Day 0 until ANC > 500/mcL for three days and platelet count > 20,000/mcL after nadir, while hospitalized. CBC then performed weekly through Day 63 post-transplant and every other week through Day 100 post-transplant, then at Days 180, 270 and 365 post-transplant.

[2]Blood chemistries include: serum creatinine, bilirubin, alkaline phosphatase, AST and ALT. Blood chemistries performed twice weekly until hospital discharge. Blood chemistries performed weekly after hospital discharge until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant.

[3]Estimated creatinine clearance is calculated using the Cockcroft-Gault formula and actual body weight.

[4]Infectious disease titers include: CMV, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.

[5]Evaluation of the malignant disease: For acute leukemia, CML and MDS this includes a bone marrow aspirate and biopsy. For lymphomas this includes imaging studies, which will be done according to institutional practices, or the same as prior to transplant, for matter of comparison.

[6]Pregnancy test must be performed $\leq$ 30 days before the start of the transplant conditioning regimen. Pregnancy test is required for females of child-bearing potential and may be performed per institutional practices.

[7]GVHD assessments performed weekly from Day 7 until Day 63 post-transplant, and then at Days 100, 120, 150, 180, 270, and 365. The GVHD assessment will include a review of **all** abnormalities experienced **during the entire assessment period** and the **highest grade** for each abnormality (*whether attributed to GVHD or not*) during the assessment period will be recorded on the Acute GVHD form, the Follow-up GVHD form, and the Chronic GVHD Provider Survey in AdvantageEDC.

[8]The toxicity assessment will include a review of **all** toxicities experienced **during the entire assessment period** and the **highest grade** for each toxicity during the assessment period will be recorded on the Toxicity form in AdvantageEDC.

[9]Chimerism may be evaluated in bone marrow, whole blood or blood cell fractions, including CD3 and CD33 or CD15 fraction. The actual measurement dates may be within +/- 7 days of the recommended time points.

[10]The pre-transplant baseline sample must be collected prior to the initiation of the transplant conditioning regimen.

Pre-transplant evaluations

The following observations must be completed within three weeks (≤21 days) of patient randomization, and within (≤) 35 days of conditioning. If the initiation of conditioning is greater than 14 days from randomization then pre-transplant evaluations must be completed according to institutional practice, unless otherwise indicated.

- History, physical examination, height and weight.
- Karnofsky performance status and HCT-Specific Comorbidity Index score.
- CBC with differential and platelet count, serum creatinine, bilirubin, alkaline phosphatase, AST and ALT.
- Estimated creatinine clearance, using the Cockcroft-Gault formula and actual body weight.
- Infectious disease titers to include: CMV antibody, Hepatitis panel (HepA Ab, HepB SAb, HepB SAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.
- EKG and LVEF (may be performed ≤ 56 days prior to patient randomization).
- Pulmonary function tests, including DLCO and FEV1 (may be performed ≤ 56 days prior to patient randomization).Disease evaluation for patients with acute leukemia, CML or MDS includes a bone marrow aspirate and biopsy for pathology and cytogenetics. **A bone marrow biopsy must be performed ≤21 days prior to randomization and must be repeated if not within 35 days prior to the initiation of the transplant conditioning regimen.**
- Disease evaluation for patients with lymphomas includes imaging studies for matters of comparison post-transplant., the types of which may be determined according to the center's institutional practices. **Imaging studies must be done within (≤) 42 days prior to patient randomization, and if the initiation of conditioning is greater than 14 days from randomization (or ≥ 56 days from last imaging) then should be repeated according to the center's standard requirements.**
- Chest X-ray or chest CT.
- Pregnancy test per institutional practices for females of child-bearing potential. **NOTE: pregnancy test must be performed ≤ 30 days prior to enrollment and must be repeated if not within 30 days prior to the initiation of the transplant conditioning regimen.**
- Pre-transplant donor and recipient samples for post-transplant chimerism studies.
- Pre-transplant blood samples for future research (prior to initiation of conditioning).

Post-transplant evaluations

The following observations will be made according to Table 4.6b:

- History and physical exam to assess GVHD and other morbidity weekly through Day 63 post-transplant, then at Days 100, 120, 150, 180, 270 and 365 post-transplant. GVHD will be monitored in accordance with BMT CTN guidelines as specified in the BMT CTN Manual of Procedures (BMT CTN MOP). GVHD assessments from Day 7 through Day 63 post-transplant, and then at Days 100, 120, 150, 180, 270, and 365 post-transplant.
- Assessment for toxicities at Days 28, 56, 100, 180, 270 and 365 post-transplant.
- CBC with differential performed at least three times a week from Day 0 until ANC > 500/μL for 3 days and platelet count > 20,000/μL for 3 days (while hospitalized only) after nadir is reached. Thereafter, CBC weekly until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant.
- Serum creatinine, bilirubin, alkaline phosphatase, ALT and AST, twice a week until hospital discharge and then weekly until Day 63 post-transplant, then every other week through Day 100 post-transplant, and then at Days 180, 270 and 365 post-transplant.
- Chimerism studies performed at Days 28 and 100 post-transplant. Chimerism may be evaluated in bone marrow, whole blood or blood cell fractions, including CD3 and CD33 or CD15 fraction. The actual measurement dates may be within +/- 7 days of the recommended time points.
- Disease evaluation of the malignant disease at Days 100, 180 and 365 post-transplant: For acute leukemia, CML and MDS this includes a bone marrow aspirate and biopsy for pathology and cytogenetics. For lymphomas this includes imaging studies, which will be done according to institutional practices and the same as prior to transplant, for matter of comparison.
- Pulmonary function tests, including DLCO and FEV1 at Day 365 post-transplant.
- Data on occurrence of infections and recorded as per the BMT CTN MOP.
- Blood samples for optional future research to be collected at Days 35, 100, 180 and 365 post-transplant (Appendix C).

4.6.2. Criteria for Forms Submission

Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. Forms that are not entered into AdvantageEDC within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into the AdvantageEDC and integrated into the Data and Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File, as detailed in the Data Management Handbook.

4.6.3. Reporting Patient Deaths

Recipient death information must be entered into AdvantageEDC within 24 hours of knowledge of the patient's death. If the cause of death is unknown at that time, it need not be recorded at that time. However, once the cause of death is determined, the form must be updated in AdvantageEDC.

4.7. Adverse Event Reporting Requirements

Reporting of adverse events on the BMT CTN 1203 trial has unique requirements due to the addition of bortezomib and maraviroc as part of this protocol. Adverse event reporting requirements are summarized below and further described in Appendix J.

4.7.1. Definitions

Adverse Event: An Adverse Event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.

Expectedness: An adverse event can be Expected or Unexpected

- **Expected adverse events** are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- **Unexpected adverse events** are those that vary in nature, intensity or frequency from information in the current adverse event list, the Investigator's Brochure, the package insert, or when it is not included in the informed consent document as a potential risk.

4.7.2. BMT CTN Adverse Event Reporting Guidelines

It is BMT CTN policy that AEs must be reported even if the investigator is unsure whether a relationship exists between the adverse event and the use of the study treatment. Reporting of AEs for BMT CTN 1203 will be consistent with the BMT CTN Manual of Procedures. Additional requirements specific to this protocol are outlined below and in Appendix J.

In BMT CTN studies, expected adverse events are reported via the web-based electronic data capture system, AdvantageEDC. Events are captured on calendar-driven case report forms (e.g., Toxicity and Hematology/Chemistry) or event-driven case report forms (e.g., Relapse/Progression, Secondary Graft Failure, and Death).

Unexpected, grades 3-5 AEs, irrespective of the attribution of the event to the study drug /procedure/treatment, will be reported through the expedited AE reporting system via AdvantageEDC, and will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The BMT CTN 1203 protocol has three distinct interventions to which patients are randomized. Determination of expectedness for events occurring on each treatment arm will be at the discretion of the investigator as described in

Appendix J, section J.3. **Unexpected, grades 4-5 AEs must be reported within 24 hours of knowledge of the event. Unexpected, grade 3 AEs must be reported within three business days of knowledge of the event.** The NHLBI Data and Safety Monitoring Board will receive summary reports of all adverse experiences at least twice yearly.

4.7.3. Additional Adverse Event Reporting Requirements for Patients Randomized to the Tacrolimus/Methotrexate/Bortezomib Arm

Millennium Pharmaceuticals, Inc. (MPI) is supplying bortezomib for this study and a description of additional adverse event reporting requirements for this study, detailed in **Appendix J** apply to any patient who is randomized to receive bortezomib as part of the GVHD prophylaxis regimen. The additional adverse event reporting period for bortezomib begins with the first dose (Day +1) and continues until 30 days after the last dose of bortezomib (Day +7 plus 30 days = Day +37). Along with the additional adverse event reporting requirements, any adverse event reported through the expedited AE reporting system will include the investigator's assessment of relationship to bortezomib (unrelated, unlikely, possible, probable, or definite).

4.7.4. Adverse Event Reporting for Patients Randomized to the Tacrolimus/Methotrexate/ Maraviroc Arm

Patients randomized to the maraviroc arm will have all unexpected grade 3-5 AEs reported throughout the course of the study, including the investigator's assessment of relationship to maraviroc (unrelated, unlikely, possible, probable, or definite).

4.7.5. Procedures for Reporting Exposure to Bortezomib or Maraviroc During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while taking bortezomib or maraviroc for this study, she must inform the Investigator immediately and permanently discontinue study drug. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported within 24 hours of the Investigator's knowledge of the pregnancy. The event must be reported through the expedited AE reporting system via AdvantageEDC (Adverse Event forms).

The Investigator will follow the subject until completion of the pregnancy, and must report the outcome of the pregnancy and neonatal status as a follow-up to the original expedited AE report in AdvantageEDC.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the Investigator must also immediately report the pregnancy as detailed above. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

4.8. CIBMTR Data Reporting

Centers participating in BMT CTN trials must register pre- and post-transplant outcomes on all consecutive hematopoietic stem cell transplants done at their institution during their time of participation to the Center for International Blood and Marrow Transplant Research (CIBMTR).

Registration is done using procedures and forms of the Stem Cell Transplant Outcomes Database (SCTOD). (Note: Federal legislation requires submission of these forms for all US allotransplant recipients.) Enrollment in BMT CTN 1203 must be indicated on the SCTOD pre-transplant registration form. Additionally, CIBMTR pre- and post- transplant Comprehensive Report Forms must also be submitted for all patients enrolled on this trial. CIBMTR forms will be submitted directly to the CIBMTR at the times specified on the Form Submission Schedule.

4.9. Registration of CIBMTR Controls

This clinical trial will compare outcomes from patients enrolled in the intervention arms to a contemporary control from the CIBMTR. Selection of the controls will start by the selection of transplant centers, which will not be the same centers participating in the enrollment of patients in the intervention arms.

4.9.1. Selection of Control Arm Participating Transplant Centers

CIBMTR research centers with experience in submitting comprehensive report forms to the CIBMTR will be eligible to participate in the study. Additionally, participating centers will need to agree to participate in this study and to submit all CIBMTR and supplemental report forms required for this study reported according to the pre-specified schedule.

4.9.2. Enrollment procedure for the control arm

Data reported on pre-transplant Transplant Essential Data forms to CIBMTR by participating centers will be monitored on a weekly basis to screen patients who fulfill the eligibility criteria. Control patients who fulfill eligibility criteria (Section 2.2.3) and who have signed a consent to allow their data to be used for research will be assigned to the CIBMTR comprehensive data reporting track (CRF–track) and centers will be notified. Forms due requirements for the CRF track will be implemented. Expected data reporting will be same as what routinely is collected by the CIBMTR from patients in the CRF-track, including basic recipient information, disease specific and infusion information, and follow-up at 100 days, 6 months and at 1 year. All required data for the primary end point analysis is included in the CIBMTR data reporting forms. Supplemental data collection related to immune suppression use will be collected along with the 1 year follow up form. CIBMTR data from control patients will be reviewed systematically for elements of the primary endpoint.

Timely data reporting will be a requirement for the control patients and reporting compliance will be monitored quarterly. A minimum of 270 controls will be targeted in order to ensure sufficient patients comparable to the randomized population for the comparison.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1 Study Design

The study is designed as a Phase II randomized, open label, multicenter trial to identify the most promising GVHD prophylaxis approach(es) for allogeneic transplant recipients with malignant disease using a reduced intensity conditioning regimen. Patients will be randomized to one of three promising new strategies: Tac/MTX/Bortezomib, Tac/MTX/Maraviroc or Tac/MMF/Cy. The primary endpoint of GRFS will be compared to a non-randomized concurrent Tac/MTX control group collected through the CIBMTR to identify which agents are promising on the basis of their efficacy relative to control. The control group of patients will not be individually matched to patients randomized to one of the treatment arms; rather, they will satisfy similar eligibility requirements and multivariate regression will be used to adjust for potential differences in the groups. Estimates of primary and secondary endpoints for the three randomized arms will also be used to guide selection of the most promising agent(s) for further study. The target enrollment is 540 patients (270 patients across the 3 treatment arms and 270 CIBMTR contemporary controls).

5.1.1. Accrual

It is estimated that 30 months of accrual will be necessary to enroll the targeted sample size. Both Core and Affiliate Centers will enroll patients on this study. Accrual will be reported by race, ethnicity, gender, and age.

5.1.2. Randomization

All patients will be randomized within 7 days prior to the initiation of conditioning therapy. Randomization will be performed in a 1:1:1 ratio using random block sizes for the three arms. Randomization will be stratified by donor type/HLA mismatching (Matched Sibling vs. Matched Unrelated vs. Mismatched Unrelated) and by disease risk (High vs Low, see Section 1.5).

5.1.3. Primary Endpoint

The primary endpoint is time to GRFS from the time of transplant. All transplanted patients will be followed for the primary endpoint for at least one year; however the primary endpoint will be analyzed as a time to event endpoint. The primary analysis will be performed using a modified intent-to-treat principle and will be performed among transplanted patients only.

5.1.4. Primary Hypothesis

The primary objective of the study is to determine which if any of the three GVHD prophylaxis strategies have promising GRFS compared to a non-randomized CIBMTR control group. To address this objective, the hazard ratio (HR) for GRFS will be estimated for each treatment arm

compared to the control group, after adjustment for patient characteristics as described in Section 5.5. The hypotheses of interest for each comparison to control are:

$$H0: HR=1 \text{ vs. } Ha: HR<1.$$

5.2. Sample Size and Power Considerations

Sample size and power considerations are based on the comparison of each treatment group (n=90 patients) to the concurrent nonrandomized CIBMTR control cohort (n=270 patients). A treatment is considered promising relative to the control if its HR relative to control, after adjustment for covariates, is significant at the one-sided significance level of 0.05. We are using one-sided testing since this is a phase 2 trial to identify whether one of these agents is promising relative to the control, and we are not interested in detecting treatments that are worse than control since they would not be pursued further. Control rates for GRFS are expected to be approximately 23% by one year, based on a recent analysis of CIBMTR data, although we considered control rates at one year as high as 35%. In addition to the final analysis, an interim analysis for futility will be conducted after 30 patients in each group have 6 months of follow-up, anticipated to be approximately 50% through the accrual period assuming uniform accrual over 30 months. If fewer than 14 patients are alive and GVHD/relapse free at 6 months, closure of the study arm for futility will be considered.

The operating characteristics of this study design, including the impact of the futility stopping rule, were determined in a simulation study. GRFS was assumed to follow an exponential distribution, and follow-up was censored at one year for all patients. The probability of GRFS by one year was assumed to be 23% or 35% for the control group, while probabilities of GRFS for the treatment groups were 5%, 10%, or 20% higher at one year, depending on the scenario. Probabilities of stopping for futility were calculated for each arm, along with the expected sample size (ExpN) assuming uniform accrual over 30 months. Final probabilities of identifying a treatment as promising relative to control were estimated, along with the probability of identifying at least one treatment as promising. This latter probability is the same as the Familywise Type I error rate when all the treatments have the same GRFS. Finally, we included the probabilities of selecting a particular treatment arm as the winner, among those identified as promising, based on having the lowest HR relative to control. However, this is for illustrative purposes only, since it is possible that multiple treatments may be identified as good candidates for further study in a follow on phase 3 trial. This probability is most interpretable when there is clear separation in outcomes between the best treatment and the other treatments. The simulation results are shown in Table 5.2 below. Adjustment for covariates was not incorporated into the simulation study, although it will be used in the final analysis.

This study design has 81-87% power to identify a treatment as promising when its GRFS at one year is 15% better than control. The probability of stopping an arm for futility is approximately 37% for treatment arms which are no better than control, when the control is correctly specified (23% at one year). If the control rates are higher, there is less impact of the futility boundary, with a 6% likelihood of stopping an arm for futility when it has the same outcome as the control. If none of the treatments has GRFS better than the control, the overall (Familywise) type I error rate is approximately 11-13%. When the best treatment has GRFS which is 15% better than the

other two arms, the probability of correct selection of the winner based on having the best observed outcomes is over 80%. This means that there is at least an 80% chance that the truly best treatment will have the best observed outcomes. When the GRFS for the best treatment is only 10% better than the other two treatments, there is a 75-81% chance of correctly selecting the winner.

TABLE 5.2: OPERATING CHARACTERISTICS OF STUDY DESIGN

GRFS at 1 Year				Probability of Stopping for Futility			Individual Power			Overall	Probability of Selection as Best			
Control	A	B	C	A	B	C	A	B	C	Power	A	B	C	ExpN
0.23	0.23	0.23	0.23	38.3%	37.0%	37.4%	4.1%	3.9%	4.2%	10.9%	3.8%	3.5%	3.7%	222.6
0.23	0.38	0.23	0.23	3.0%	38.0%	37.4%	86.9%	4.4%	4.0%	87.3%	86.5%	0.4%	0.4%	237.1
0.23	0.38	0.38	0.38	3.2%	3.2%	36.5%	86.0%	86.2%	4.0%	97.0%	48.6%	48.3%	0.1%	252.0
0.23	0.38	0.38	0.23	3.1%	3.2%	3.3%	86.8%	86.0%	86.9%	99.2%	33.4%	32.4%	33.4%	266.0
0.23	0.38	0.33	0.33	3.2%	8.8%	8.6%	86.0%	58.8%	58.3%	95.2%	61.7%	17.2%	16.3%	261.3
0.23	0.38	0.28	0.28	3.1%	19.3%	18.9%	86.1%	24.5%	24.6%	89.8%	80.7%	4.5%	4.6%	252.7
0.35	0.35	0.35	0.35	5.8%	6.0%	6.0%	4.4%	4.9%	4.7%	12.6%	4.0%	4.4%	4.3%	262.5
0.35	0.50	0.35	0.35	0.2%	5.5%	5.6%	81.3%	4.6%	4.5%	82.0%	80.8%	0.6%	0.6%	265.3
0.35	0.50	0.50	0.35	0.2%	0.2%	5.9%	81.4%	80.8%	4.2%	94.4%	46.9%	47.3%	0.2%	267.4
0.35	0.50	0.50	0.50	0.2%	0.1%	0.2%	81.5%	81.7%	81.0%	98.0%	33.2%	33.2%	31.6%	269.8
0.35	0.50	0.45	0.45	0.1%	0.5%	0.6%	82.5%	52.4%	52.6%	92.8%	59.7%	16.5%	16.6%	269.5
0.35	0.50	0.40	0.40	0.1%	2.0%	2.2%	81.0%	20.6%	20.9%	85.1%	75.2%	5.1%	4.8%	268.2

5.3. Interim Analysis and Stopping Guidelines

5.3.1. Interim Analysis for Efficacy

There will be no interim analyses for efficacy.

5.3.2. Interim Analysis for Futility

An interim analysis for futility will be conducted based on the 6 month GRFS when 30 patients in each arm have 6 months of follow-up available. If fewer than 14 are alive and GVHD/relapse free among the first 30 patients on an arm, closure of the study arm for futility will be considered. This futility stopping rule is meant to be a guidance only, based on an anticipated 6 month GRFS in the control group of 45-50%; the DSMB may also consider other factors, such as the risk characteristics of these patients, when deciding whether to follow the futility stopping rule. A futility stopping rule which incorporates a direct comparison to the concurrent CIBMTR controls along with risk adjustment is not feasible because of the different sources for data collection. However, if a futility rule is triggered so that the DSMB is considering dropping an arm for futility, a comparison with CIBMTR controls may be considered before a final decision to drop an arm is made.

5.3.3. Guidelines for Safety Monitoring

Monitoring of a key safety endpoint will be conducted monthly, and if rates significantly exceed pre-set thresholds, the NHLBI will be notified in order that the DSMB can be advised. Policies and composition of the DSMB are described in the BMT CTN's Manual of Procedures. The stopping guideline serves as trigger for consultation with the DSMB for additional review.

The key safety endpoint for this study is mortality. The rate of mortality will be monitored up to 100 days post-randomization separately in each of the three treatment arms. At least three events must be observed in order to trigger review. The expected probability of 100 day mortality after a reduced intensity conditioning transplant is 10-15%, based on CIBMTR data. Each month, the null hypothesis that the 100-day mortality rate is less than or equal to 15% is tested. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be used for monitoring, as described in greater detail below and in Appendix E.

This sequential testing procedure conserves type I error at 5% across all of the monthly examinations for a treatment arm. The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of endpoints (e.g., patients experiencing death). The continuation region of the SPRT is defined by two parallel lines. Only the lower boundary will be used for monitoring to protect against excessive 100-day mortality. If the graph falls below the lower boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment reaches the maximum of 90 patients.

This procedure assumes a censored exponential distribution for the time until death during the first 100 days, and censors follow-up time after 100 days. Only deaths that occur on or before

the patient has been followed for 100 days are counted. Total time on study is computed as time from registration to death, or to 100 days, whichever comes first, summed for all patients on study.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRT:

- A SPRT contrasting 15% versus 30% 100-day rate of mortality results in decision boundaries with a common slope of 13.310 and a lower intercept of –42.278, with nominal type I and II errors of 7% and 15%, respectively.

The actual operating characteristics of the truncated test, shown in Table 5.3, were determined in a simulation study that assumed uniform accrual of 90 individuals over a 30 month time period, and exponential time to failure after randomization.

TABLE 5.3: OPERATING CHARACTERISTICS OF SEQUENTIAL TESTING PROCEDURE FROM A SIMULATION STUDY WITH 10,000 REPLICATIONS

Day 100 MORTALITY

True 100-Day Rate	15%	25%	30%
Probability Reject Null	0.046	0.650	0.917
Mean Month Stopped	32.3	21.3	14.4
Mean # Endpoints in 100 Days	13.1	14.4	11.6
Mean # Patients Enrolled	87.6	60.5	42.5

For example, the testing procedure rejects the null hypothesis in favor of the alternative 5% of the time when the true 100-day mortality rate is 15%, and 92% of the time when the rate is 30%. This corresponds to a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.08$. When the true 100-day mortality rate is 30%, on average, the DSMB will be consulted 14 months after opening, when 12 events have been observed in 42 patients.

5.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all patients. Characteristics to be examined are: age, gender, race/ethnicity, performance status, primary disease, disease specific risk categories, hematopoietic cell transplant comorbidity index (HCT CI), donor type and HLA matching, donor/recipient CMV status, donor/recipient sex match, donor/recipient ABO match, and conditioning regimen. Between group comparisons will be performed for continuous variables via a Kruskal-Wallis test and for categorical variables, via the chi-square test.

5.5. Analysis of Primary Endpoint

Kaplan-Meier curves along with 90% confidence intervals will be constructed to estimate GRFS probabilities for each treatment group as well as the control. The primary analysis will consist of a comparison of GRFS among transplanted patients for each treatment arm to the control group, based on a multivariate Cox regression model. The following factors will be included in the regression model: age, disease, donor type/HLA matching. In addition, a stepwise model building strategy with a significance level of 0.1 will be used to consider additional factors from the list of demographic/baseline characteristics. A significance level of 0.05 (one-sided) will be used for the hazard ratio of each treatment arm relative to the control to determine whether a treatment should be considered promising for further study. Confidence intervals for the hazard ratio using a 90% confidence level will also be constructed for each hazard ratio. The familywise type I error rate over all the comparisons to the control is expected to be approximately 10-11% based on simulations in Section 5.2. This familywise type I error rate can be interpreted as the probability of incorrectly identifying at least one of the treatments as promising when they all have identical GRFS compared to the control. Direct statistical comparison of GRFS among the randomized treatment arms will not be conducted, since the study is not powered for these comparisons.

5.6. Analysis of Secondary Endpoints

Since this is a Phase II trial, most of the analysis of secondary endpoints will involve estimation with 90% confidence intervals rather than formal statistical comparisons. All secondary endpoints will be described from the time of transplantation; however, the number of patients randomized but dropping out prior to transplantation will also be described by treatment arm. No direct statistical comparisons among the randomized treatment arms will be conducted, since the study is not powered for these comparisons. For a select set of endpoints (acute and chronic GVHD, TRM, relapse, DFS, and survival) which are components of the composite primary endpoint, an analysis comparing each treatment arm to the control group will be conducted. To alleviate concerns about multiple testing, these secondary analyses for a particular treatment group will only be performed if the primary endpoint is significantly different between that treatment group and the control group. Details of the analyses of secondary endpoints are given below.

5.6.1. Acute GVHD

Incidence of acute GVHD grade II-IV and grade III-IV up to 180 days will be estimated with 90% confidence intervals for each treatment group as well as the control using the cumulative incidence estimate, treating death prior to aGVHD as a competing event. A multivariate Cox regression model for the cause-specific hazard of aGVHD will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

5.6.2. Chronic GVHD

Incidence of chronic GVHD up to 1 year will be estimated with 90% confidence intervals for each treatment group as well as the control using the cumulative incidence estimate, treating death prior to chronic GVHD as a competing event. A multivariate Cox regression model for the cause-specific hazard of chronic GVHD will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

5.6.3. Immunosuppression-Free Survival at One Year

Proportions of patients alive, relapse free, and off immune suppression at one year will be described for each treatment group and for the control, along with 90% confidence intervals. If there is censoring prior to one year, multistate models will be constructed to estimate these probabilities. Agreement between this endpoint and the primary endpoint of GRFS will be described using cross-tabulation frequencies and assessed using the Kappa statistic.

5.6.4. Hematologic Recovery

Probabilities of neutrophil recovery by Day 28 and Day 100 will be described with 90% confidence intervals for each treatment group using the cumulative incidence estimate, treating death as a competing event. Similarly, probabilities of platelet recovery by Day 60 and Day 100 will be described with 90% confidence intervals for each treatment group using the cumulative incidence estimate, treating death as a competing event.

5.6.5. Donor Cell Engraftment

Donor chimerism at Day 28 and Day 100 after transplantation in each of the randomized treatment arms will be described numerically as median and range for those evaluable as well as according to proportions with full (>95%), mixed (5-95% donor cells), graft rejection (<5%), or death prior to assessment of donor chimerism. Incidence of secondary graft failure (chimerism <5% after initial donor cell engraftment) will be described for each arm using frequencies.

5.6.6. Disease Relapse or Progression

Incidence of disease relapse or progression up to 1 year will be estimated with 90% confidence intervals for each treatment group as well as the control using the cumulative incidence estimate, treating death prior to disease relapse as a competing event. A multivariate Cox regression model for the cause-specific hazard of relapse or progression will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

5.6.7. Transplant-related Mortality

Incidence of transplant-related mortality (TRM) up to 1 year will be estimated for each treatment group as well as the control using the cumulative incidence estimate, treating disease relapse or progression as a competing event. A multivariate Cox regression model for the cause-specific

hazard of TRM will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

5.6.8. Toxicity

All Grade ≥ 3 toxicities will be tabulated by grade for each randomized treatment arm, by type of toxicity as well as the peak grade overall. Toxicity frequencies will be described for each time interval as well as cumulative over time.

5.6.9. Infections

The number of infections and the number of patients experiencing infections will be tabulated for each randomized treatment arm by type of infection, severity, and time period after transplant.

5.6.10. Disease-free Survival

Kaplan-Meier curves will be constructed to estimate disease free survival probabilities for each treatment group as well as the control. A multivariate Cox regression model for the risk of death or relapse/progression will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

5.6.11. GVHD-Free Survival

Kaplan-Meier curves will be constructed to estimate GVHD free survival probabilities for each treatment group as well as the control. A multivariate Cox regression model for the risk of death or GVHD will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

5.6.12. Overall Survival

Kaplan-Meier curves will be constructed to estimate overall survival probabilities for each treatment group as well as the control. A multivariate Cox regression model for the risk of death will be used to compare the treatment groups with the control group, after adjustment for baseline characteristics as described for the primary endpoint.

5.7. Safety Analysis

All reported serious adverse events potentially associated with study drugs will be carefully examined with respect to the severity and relationship to the study drugs. Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0.

5.8. Selection of Promising Approaches

The objective of the Phase II trial is to identify promising agents to be tested on a Phase III setting. Determination of whether a treatment is promising relative to control is based on identifying a significant effect relative to control on the primary endpoint using a 5% one-sided

significance level, and not on secondary analyses. Among those identified as promising relative to control using this criterion, the actual selection of promising agents for future study may also consider toxicities, secondary endpoints, and the magnitude of effect on the primary end point compared to the control cohort. Note that more than one approach might be identified as promising relative to control on the primary endpoint and be selected for further study.

APPENDIX A

HUMAN SUBJECTS

APPENDIX A

HUMAN SUBJECTS

1. Subject Consent

Candidates for the study will be identified as described in Chapter 4 of the protocol. The Principal Investigator or his/her designee at each transplant center will contact the candidates, provide them with information about the purpose of the study and obtain consent. The BMT CTN will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local Internal Review Board (IRB). The DCC will verify the adequacy of the consent forms prior to submission to the IRB. Each center must provide evidence of IRB approval.

2. Confidentiality

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code relaying the patient's identity with the ID code will be kept separately at the center. The ID code will be transmitted to the network.

3. Participation of Women and Minorities

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of leukemia and lymphoma in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment reports.

APPENDIX B

CONSENT FORMS

PATIENT INFORMED CONSENT

Informed Consent to Participate in Research

Your Name: _____

Study Title: A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

Protocol: BMT CTN 1203

Principal Investigator: *Insert local PI information*

Sponsor: The National Institutes of Health (NIH) is sponsoring this study by providing financial support through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

1. Introduction

We invite you to join this clinical trial, also known as a research study. We are doing this study because we want to compare three new combinations of medications to see which is better at preventing Graft-versus-Host Disease (GVHD). You are being asked to join this study because:

1. You have a disease that can be treated by a peripheral blood stem cell transplant; and
2. Your doctor plans on using a reduced-intensity conditioning regimen for your transplant.

This study will take at least two (2) years and will include 270 participants – 90 participants in each of three (3) treatment groups.

This Consent Form will tell you about the purpose of the study, the possible risks and benefits, other options available to you, and your rights as a participant in the study.

Everyone who takes part in research at [*insert facility name*] should know that:

- Being in any research study is voluntary.
- You may or may not benefit from being in the study. Knowledge we gain from this study may benefit others.

- If you join the study, you can quit the study at any time.
- If you decide to quit the study, it will not affect your care at [insert name of facility or institution].
- Please ask the study staff questions about anything that you do not understand, or if you would like to have more information.
- You can ask questions now or any time during the study.
- Please take the time you need to talk about the study with your doctor, study staff, and your family and friends. It is your decision to be in the study. If you decide to join, please sign and date the end of the Consent Form.

You and your doctor will discuss other treatment choices if you do not want to participate in this study.

2. Study Background

The National Institutes of Health (NIH), through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), are providing staff support and money for this research study. The BMT CTN and the NIH will make decisions about how to manage the study.

A stem cell transplant is a standard therapy for blood cancers such as acute and chronic leukemias, lymphoma and myelodysplastic disorders. A common problem that may occur after a stem cell transplant is a condition known as GVHD. The word "graft" refers to the donor blood cells that you will receive during your transplant. The word "host" refers to the person (in this case, you) receiving the cells. GVHD is a complication where the donor graft attacks and damages some of your (the transplant recipient's) tissues.

- GVHD can cause skin rash, intestinal problems such as nausea, vomiting, or diarrhea,
- It may also damage your liver and cause hepatitis or jaundice.
- GVHD may also increase your risks of infection.

3. Study Purpose

We are inviting you to take part in this study because you have a cancer of the blood or lymph glands and a stem cell transplant is a treatment option.

The purpose of this study is to compare three combinations of medications to see whether one or more of them are better than the current standard of care (Tacrolimus/Methotrexate) to prevent GVHD. These combinations of medication in this study are:

Treatment Group A: Tacrolimus, methotrexate and bortezomib

Treatment Group B: Tacrolimus, methotrexate and maraviroc

Treatment Group C: Tacrolimus, mycophenolate mofetil and cyclophosphamide

Doctors want to know which combination (A, B or C) is better, or if they give the same results. The current standard of care for preventing GVHD is Tacrolimus/Methotrexate. This combination is not available on this study. The study will help doctors make choices about medications to prevent GVHD for future transplant patients.

4. Right to Ask Questions and/or Withdraw

You have the right to ask questions about the study at any time. If you have questions about your rights as a participant or you want to leave the study, please contact:

[*insert contact info*]

Being in this study is voluntary. You can choose not to be in this study or leave this study at any time. If you choose not to take part or leave this study, it will not affect your regular medical care in any way.

Your study doctor and study staff will be available to answer any questions that you may have about taking part in or leaving this study.

5. Study Treatment and Tests

We will check your health before you start treatment, while you receive treatment, and for one year after transplant.

Before You Begin the Study

Before you begin the study, you will need to have several exams, tests or procedures to find out if you can be in the study. All patients participating in this study need to have a matched donor. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These include:

- Medical history
- Physical examination, including height and weight
- Blood and urine tests
- Heart function tests, including EKG and ejection fraction
- Lung (pulmonary) function tests
- Tests to evaluate your cancer, including a bone marrow aspirate/biopsy if you have acute leukemia, chronic myelogenous leukemia or myelodysplastic syndrome, and imaging studies if you have lymphoma.
- Chest X-ray or chest CT
- A pregnancy test if you are a woman able to have children. If you are pregnant, you will not be able to take part in this study.

- *Optional* blood samples for future research (see Section 19: Blood Samples for Future Research).

Study Participation

If you decide to join the study, your participation will last for **1 year** after your transplant. We will ask you to sign this Consent Form and you will get a copy of the signed form to keep.

Before the Transplant

Before your transplant, your doctor will choose from one of several conditioning regimens. The conditioning regimen prepares your body for transplant. It uses treatments such as chemotherapy and radiation to destroy the cancer cells and the cells that make up your immune system. Your doctor will decide which conditioning regimen you will receive before you are assigned to one of the three (3) treatment groups.

Randomization

We will use a computer to randomly assign you to 1 of 3 treatment groups. You will have an equal chance of being placed in 1 of the 3 groups. Neither you nor your doctor or study investigator will have any control over which treatment group you will be assigned.

During Your Transplant

The treatments that are used to prevent GVHD either start before or after the infusion of stem cells. These treatments are a combination of immune suppressing drugs and a standard component of the transplant.

The 3 treatment groups being included in this study are outlined below:

Treatment Group A: Tacrolimus, methotrexate and bortezomib

- Tacrolimus will be given daily per institutional standards, as a pill by mouth or by intravenous infusion (through your vein), beginning three (3) days before your transplant. The amount of drug given will slowly be decreased over time and eventually stopped. This process occurs over several months.
- Methotrexate will be given by intravenous infusion (through your vein) on four (4) different days (1, 3, 6 and 11) after your transplant.
- Bortezomib will be given by intravenous push (3-5 second shot in your vein) on three (3) different days (1, 4 and 7) after your transplant.

Treatment Group B: Tacrolimus, methotrexate and maraviroc group

- Tacrolimus will be given daily per institutional standards, as a pill by mouth or by intravenous infusion (through your vein), beginning three (3) days before your transplant. The amount of drug given will slowly be decreased over time and eventually stopped. This process occurs over several months.
- Methotrexate will be given by intravenous infusion (through your vein) on four (4) different days (1, 3, 6 and 11) after your transplant.

- Maraviroc will be given as a pill by mouth twice a day, beginning three (3) days before your transplant and will continue for 30 days after your transplant.

Treatment Group C: Tacrolimus, mycophenolate mofetil and cyclophosphamide group

- Tacrolimus will be given daily per institutional standards, as a pill by mouth or by intravenous infusion (through your vein), beginning on day five (5) after your transplant. The amount of drug given will slowly be decreased over time and eventually stopped. This process occurs over several months.
- Mycophenolate mofetil will be given daily by intravenous infusion (through your vein) or as a pill by mouth three times a day, beginning on Day 5 after your transplant, and will continue for 30 days. Your doctor may decide to continue this drug if active GVHD is present.
- Cyclophosphamide will be given by intravenous infusion (through your vein), over 1-2 hours, on Day 3 and Day 4 after your transplant.

Peripheral Blood Stem Cell Transplant
On your transplant day, the stem cells will be given to you through your catheter, like a blood transfusion. The cells will travel to your bone marrow where they will start to make healthy, new blood cells after several weeks.

Health Evaluations After the Transplant
We will test (evaluate) your health during the study. These tests and how often they are scheduled are standard care for patients receiving an allogeneic transplant. They would be done even if you were not part of this study. You will be watched closely for any signs and symptoms of GVHD.

- Physical exam to assess toxicities, and infections weekly until Day 63 and then at Days 100, 120, 150, 180, 270 and 365.
- Physical exam to assess GVHD weekly starting Day 7 until Day 63 and then at Days 100, 120, 150, 180, 270 and 365.
- Routine blood tests (cell counts, liver and kidney function) weekly until Day 63 and then at Days 100, 180, 270 and 365.
- Blood or bone marrow tests to find the amount of donor cells in your body on Days 28 and 100. This is also called *chimerism.*
- Disease evaluation tests to see how much cancer you have after treatment on Days 100, 180 and 365.
- Lung (pulmonary) function tests on Day 365.
- *Optional* blood samples for future research on Days 35, 100, 180 and 365 (see Section 19: Blood Samples for Future Research).

6. Risks and Discomforts

You will have side effects while on the study. Side effects can range from mild to serious.

The risks and discomforts of participating in this study will be similar to what you may have with stem cell transplant if you do not participate in this study, but you might do better or worse than on standard transplant treatment. Your health care team may give you medicines to help lessen side effects such as feeling sick to your stomach (nausea). In some cases, side effects can be long lasting or may never go away.

Risks and Toxicities Related to Medications

All immune suppressive drugs, except for bortezomib and maraviroc, are commonly used in allogeneic hematopoietic cell transplantation.

Table 1- Risks and Side Effects

Likely	What it means: This type of side effect is expected to occur in more than 20% of patients. This means that 21 or more patients out of 100 might get this side effect.
Less Likely	What it means: This type of side effect is expected to occur in 20% of patients or fewer. This means that 20 patients or fewer out of 100 might get this side effect.
Rare, but Serious	What it means: This type of side effect does not occur very often – in fewer than 2% of patients – but is serious when it occurs. This means that 1 or 2 patients (or fewer) out of 100 might get this side effect.

Bortezomib (Velcade®)

Likely	Less Likely	Rare, but Serious
▪ Anemia ▪ Decreased platelet count with increased risk of bleeding ▪ Feeling weak, tired and generally uncomfortable ▪ Fever, with shaking chills ▪ Anorexia – loss of appetite ▪ Constipation ▪ Diarrhea ▪ Nausea ▪ Vomiting ▪ Abdominal pain	• Decreased white blood cell count with risk of infection • Difficulty sleeping • Skin rash with itching and redness • Low blood pressure • Changes in heart beat that can cause you to feel light-headed, dizzy, faint, short of breath, or have chest pain • Heartburn, dyspepsia • Bleeding (GI, pulmonary/upper respiratory) • Blood in the urine	• Coughing up blood • Syndrome associated with high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings • Hepatitis and liver failure • Inflammation of the intestines, stomach, or pancreas • Inflammation and fluid build-up in and around the lungs

Likely	Less Likely	Rare, but Serious
▪ Painful feelings or numbness and tingling in hands and feet	• Pneumonia and bronchitis • Confusion • Anxiety • Painful sores of the mouth and/or throat • Changes in the way things taste • Abnormal liver tests • Blurred vision • Inflammation of the eye • Aches and pains in muscles, joints and the bone in the arms and legs • Muscle weakness • Cough • Shortness of breath • Headache • Nose bleeds • Changes in blood sugar • Lowered amount of potassium and sodium in your blood • Increase in the amount of calcium in your blood • Flu-like symptoms such as chills, sore throat, runny nose and sinus and throat infections • Swelling or fluid build-up in the arms and legs, feeling dizzy and weight gain • Herpes virus such as shingles • New or worsening heart failure • Infections of the bladder, sinuses, throat, stomach and intestines and skin • Fungal infections in the mouth and throat • Life-threatening infections in the blood	• Inflammation of the layers surrounding your heart or collection of fluid around the heart • Loss of hearing • Bleeding in the brain • Loss of some to all vision in one or both eyes • Encephalopathy or brain dysfunction that can lead to death • Allergic reactions that may include skin swelling and/or swelling of the face or throat and could be severe or life-threatening • Severe, life-threatening or deadly rash with skin peeling and mouth sores • Pain, redness, swelling and infection in the area of the skin where bortezomib is injected • Pain in the mouth and throat when swallowing • Intestinal obstruction • Fast death of cancer cells that may let toxin into the blood and injure organs, such as the kidneys • Severe muscle weakness and paralysis

Cyclophosphamide (Cytoxan®)

Likely	Less Likely	Rare, but Serious
▪ Decreased white blood cell count with increased risk of infection ▪ Temporary hair loss ▪ Nausea ▪ Vomiting ▪ Loss of appetite ▪ Sores in mouth or on lips ▪ Diarrhea ▪ Stopping of menstrual periods in women ▪ Decreased sperm production in men ▪ Decreased platelet count (mild) with increased risk of bleeding	▪ Anemia ▪ Temporary tiredness ▪ Damage to the fetus if you become pregnant while taking drug ▪ Abdominal pain ▪ Skin rash ▪ Bleeding in the bladder	▪ Scarring of lung tissue, with cough and shortness of breath ▪ Severe heart muscle injury and death at very high doses ▪ New (secondary) cancers

Maraviroc (Selzentry®)

Likely	Less Likely	Rare, but Serious
▪ Fever, cough and flu-like symptoms ▪ Rash and redness of the skin ▪ Upper respiratory infections	▪ Fever ▪ Dizziness ▪ Insomnia ▪ Anxiety ▪ Depression ▪ Itching ▪ Benign skin tumors ▪ High blood pressure ▪ Decrease appetite ▪ Constipation ▪ Low white blood counts with increase risk of infections ▪ Joint pain ▪ Excessive sweating ▪ Nerve damage causing numbness, tingling, burning ▪ Muscle pain ▪ Bladder irritation ▪ Acne ▪ Abnormal liver tests ▪ Herpes infections ▪ Eye infections/inflammation ▪ Breathing abnormalities ▪ Genital warts ▪ Abnormal growth or change of fat in the body	▪ Loss of consciousness (fainting) ▪ Rash affecting the whole body ▪ Allergic reactions associated with liver damage and jaundice

Methotrexate

Likely	Less Likely	Rare, but Serious
▪ Decreased white blood cell count with increased risk of infection. ▪ Fatigue ▪ Infections	▪ Nausea/Vomiting ▪ Irritation or sores in the lining of the throat or mouth ▪ Diarrhea ▪ Abdominal discomfort ▪ Fever ▪ Chills ▪ Anemia ▪ Abnormal liver tests ▪ Kidney failure	▪ Dizziness ▪ Scarring of the lungs

Mycophenolate Mofetil (MMF, Cellcept®)

Likely	Less Likely	Rare, but Serious
▪ Miscarriage ▪ Birth defects ▪ Diarrhea ▪ Damage to unborn baby ▪ Limited effectiveness of birth control ▪ Stomach pain ▪ Upset stomach ▪ Nausea/Vomiting ▪ Headache ▪ Tremors ▪ Low white blood cell count with increased risk of infection ▪ Increased blood cholesterols ▪ Decreased platelet count with increased risk of bleeding ▪ Swelling of the hands, feet, ankles, or lower legs	▪ Anemia ▪ Rash ▪ Difficulty falling asleep or staying asleep ▪ Dizziness	▪ Difficulty breathing ▪ Unusual bruising ▪ Fast heartbeat ▪ Excessive tiredness ▪ Weakness ▪ Blood in stool ▪ Bloody vomit ▪ Change in vision ▪ Encephalopathy or brain dysfunction that can lead to death ▪ New (secondary) cancers

Tacrolimus (FK506, Prograf®)

Likely	Less Likely	Rare, but Serious
▪ Kidney problems ▪ Loss of magnesium, calcium, potassium ▪ High blood pressure ▪ Tremors ▪ Increases in cholesterol and triglyceride ▪ Decreased platelet count with increased risk of bleeding ▪ Infections	▪ Nausea ▪ Vomiting ▪ Liver problems ▪ Changes in how clearly one can think ▪ Insomnia ▪ Unwanted hair growth ▪ Confusion	▪ Seizures ▪ Changes in vision ▪ Dizziness ▪ Red blood cell destruction

It is very important that you do not eat grapefruit or drink grapefruit juice while taking Tacrolimus. Grapefruit has an ingredient called bergamottin, which can affect some of the treatment drugs used in this study. Common soft drinks that have bergamottin are *Fresca*, *Squirt*, and *Sunny Delight*.

Risks and Toxicities Related to Transplant

The following problems may occur as a result of stem cell transplantation. These risks may occur whether a transplant was done as part of the study or not:

Slow recovery of blood counts. The red blood cells, white blood cells, and platelets can be slow to recover after blood or marrow transplant. Until your blood counts recover, you will need blood and platelet transfusions, and will be at risk for bleeding and infections. To speed the recovery of the white cells as much as possible you may receive Filgrastim.

Graft failure. The stem cells (the "graft") may fail to grow inside your body. Past experience suggests that there can be up to a 10-15% chance of graft failure. If graft failure occurs, this may result in low blood counts for a long period of time. If your counts do not recover, you may need to receive a second transplant. Graft failure can be fatal.

Graft-Versus-Host Disease (GVHD). GVHD results from cells in the graft recognizing your body as foreign and attacking it. In most cases, GVHD can be successfully treated. Sometimes GVHD is severe or difficult to treat and may lead to death. You will be watched closely for this complication and given drugs to prevent and/or treat it.

Acute GVHD may produce skin rash, nausea, vomiting, diarrhea, abdominal pain, abnormalities of liver function, and an increased risk of infection. Chronic GVHD may produce skin rashes, hair loss, thickened dry skin, dry eyes, dry mouth, liver disease, weight loss, diarrhea, and an increased risk of infection. To confirm the diagnosis of acute or chronic GVHD, you may be asked to have a biopsy (a small sample of your tissue to look at under the microscope) of your skin, gut, or, rarely, your liver.

Other complications. Other complications may include:

a. Damage to the vital organs in your body. The transplant could cause problems in any body organ such as the heart, lungs, liver, gut, kidneys and bladder, or brain. The kidneys and the liver are most likely to be damaged. Some patients will experience serious lung problems from infections or the chemotherapy and radiation.

b. Serious infections. Full and complete recovery of your immune system may take many months. During this time, there is an increased risk of infections. You will be prescribed certain drugs to reduce the chance of those infections. However, these treatments do not always work. If you have an infection, you may have to stay in the hospital longer or be re-hospitalized after transplant. Although most infections can be successfully treated, some infections may result in death.

c. Relapse of disease or a new blood cancer. Your leukemia or lymphoma may come back even if the transplant is initially successful. In rare cases, a new blood cancer may develop from the donor cells. Cyclophosphamide can cause damage to blood cells, which may result in a blood cancer such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The blood cancer usually develops 2-10 years after treatment, or 6 years on average. The risk of developing a new blood cancer after allogeneic blood or marrow transplant is probably less than 2%. If cancer develops in your donor's blood cells, you may require additional treatment with chemotherapy or another blood or marrow transplant.

d. Risk to the unborn. The treatments in this study have <u>not</u> been proven to be safe at any stage of pregnancy. Therefore, if you are pregnant or nursing, you are not eligible for this study. Women who can become pregnant must use effective birth control while receiving chemotherapy, TBI, and drugs to prevent GVHD, and for 1 year after transplant. Effective birth control is defined as the following:

1. Refraining from all acts of vaginal sex (abstinence)
2. Consistent use of birth control pills
3. Injectable birth control methods (Depo-Provera, Norplant)
4. Tubal sterilization or male partner who has undergone a vasectomy
5. Placement of an IUD (intrauterine device)
6. Use of a diaphragm with contraceptive jelly and/or condoms with contraceptive foam every time you have sex.

Reproductive Risks

The drugs used in this research study may damage your reproductive organs, affect your ability to have children or possibly cause birth defects if you take them while you are pregnant. It is important that a woman is not pregnant or breast-feeding and does not become pregnant during the course of the study.

It is important that both women who can become pregnant and their male partners use birth control for
1 year after transplantation while on this study.

If you are a woman and can become pregnant, you will need to take a pregnancy test before you start the study. You should discuss ways to prevent pregnancy while you are in the study. Women who have gone through puberty may find that their menstrual cycle becomes irregular or stops permanently. This does not mean that you cannot become pregnant. You must still use an effective method of birth control during your transplant and continue until you are finished with your GVHD prevention treatment.

If you are a man, your body may not be able to produce sperm (become sterile). You should talk with your doctor about banking your sperm before having a transplant.

Please check with your doctor to understand more about these risks.

Additional Information about Bortezomib (Velcade®)

- The effect of Velcade® on reproduction and its safety in pregnancy are unknown. If you are a woman capable of becoming pregnant [anyone who has not undergone a hysterectomy (removal of the womb), has not had both ovaries removed or has not been post-menopausal (stopped menstrual periods) for more than 24 months in a row], you must have a negative pregnancy test before beginning treatment. In addition, you must not be breastfeeding a baby during this study.
- If you think that you have become pregnant or may have fathered a child while taking part in this study you must tell the study doctor immediately. The study doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. You should also notify the doctor managing your pregnancy that the mother/father received a study drug called Velcade®.
- If you are a woman and you become pregnant during your participation in this study, your treatment with Velcade® will be stopped and you may be withdrawn from some of the study procedures but not from follow-up by your study doctor. The study doctor will ask for your permission to stay in contact with you throughout the length of the pregnancy.
- If you are a man and your partner becomes pregnant, the study doctor will ask for your partner's permission to collect information about her pregnancy and the health of the baby.
- Laboratory tests show that Velcade® may damage DNA. Based on this information, it is possible that Velcade® may cause infertility in men and women.

Additional Information about MMF

- MMF could be damaging to an unborn baby if you are pregnant or become pregnant while receiving the drug.
- MMF can make birth control pills less effective and increase your chances of becoming pregnant while you are taking it.
- If you could become pregnant, you must use 2 effective forms of birth control for 4 weeks before starting MMF, during treatment, and for one year after transplantation.

If you think you might be pregnant or could be become pregnant prior to enrollment, you should not join this study.

Unforeseen Risks

New risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. We will promptly tell you about new information that may affect your decision to take part in the study. We may learn new things about reduced-intensity transplants that might make you want to stop being in the study. We will let you know if this happens and you can decide if you want to continue in the study.

Other Treatments or Medications

Some medicines react with each other, and it is important that you tell the study doctor or staff about any other drugs, treatments, or medicines you are taking. This includes non-prescription medications, vitamins and herbal treatments.

It is also important that you tell the study staff about any changes to these medications during your participation in the study.

For more information about risks and side effects, ask your study doctor.

7. Alternative Treatments

Participation in this study is optional. If you choose not to take part, you may still receive an allogeneic transplant to treat your disease. The treatment and evaluations you would receive could be very similar to what would receive if you join this study.

Your study doctor will talk with you about your options. If you decide not to participate in this study, your medical care will not be affected in any way.

Your other choices may include:

- Treatment with other drugs, radiation, or a combination of drugs and radiation without a transplant.
- An allogeneic blood or marrow transplant that is not part of the study, or another type of transplant
- Participation in another clinical trial, if available (check with your doctor)

- No treatment for your blood cancer at this time
- Comfort care

Every treatment option has benefits and risks. Talk with your doctor about your treatment choices before you decide if you will take part in this study.

8. Possible Benefits

Taking part in this study may or may not make your health better. The information from this study will help doctors learn more about medications used to prevent GVHD.

9. New Information Available During the Study

During this research study, the study doctors may learn about new information about the study drugs or the risks and benefits of the study. If this happens, they will tell you about the new information. The new information may mean that you can no longer participate in the study, or that you may not want to continue in the study.

If this happens, the study doctor will stop your participation in the study and will offer you all available care to suit your needs and medical conditions.

10. Privacy, Confidentiality and Use of Information

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. All your medical and demographic (such as race and ethnicity, gender and household income) information will be kept private and confidential. *(Name of Transplant Center)* and the organizations listed below will not disclose your participation by any means of communication to any person or organization, except by your written request, or permission, or unless required by federal, state or local laws, or regulatory agencies.

Individuals authorized by the organizations below will have access to your research and medical information. They may use this information for inspections or audits to study the outcomes of your treatment, or for required reporting to regulatory authorities (such as to the FDA for serious adverse events). In agreeing to participate, you consent to such inspections and to the copying of parts of your records, if required by these organizations.

- The National Institutes of Health (NIH), which include the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI)
- The Center for International Blood and Marrow Transplant Research (CIBMTR)
- The National Marrow Donor Program (NMDP)

- The Food and Drug Administration (FDA)
- Data and Coordinating Center of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC)
- Millennium Pharmaceuticals, Inc., supplier of bortezomib

We will not identify you by name in any publications or reports that come from these organizations or groups.

Information that does not include personally identifiable information about this clinical trial has been or will be submitted, at the appropriate and required time, to the government-operated clinical trial registry data bank, which contains registration, results, and other information about registered clinical trials.

This data bank can be accessed by you and the general public at www.ClinicalTrials.gov. Federal law requires clinical trial information for certain clinical trials to be submitted to the data bank.

11. Ending Your Participation

Being in this study is voluntary. You can choose to not be in this study, or leave this study at any time. If you choose not to take part or leave this study, your regular medical care will not be affected in any way. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

The study doctor or the study sponsor may stop the study at any time, and we may ask you to leave the study. We may ask you to leave the study if you do not follow directions or if you suffer from side effects of the treatment. If we ask you to leave the study, the reasons will be discussed with you. Possible reasons to end your participation in this study include:

- You do not meet the study requirements.
- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You are having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

If you decide to leave this study after taking the study treatment, or are asked to leave by your doctor for medical reason, you will need to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

12. Physical Injury as a Result of Participation

It is important that you tell your doctor, _____ *[investigator's name(s)]* or study staff if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

13. Compensation or Payment

You will not be paid for your participation in the research study. You will not get compensation or reimbursement for any extra expenses (travel, meals, etc.) you may have through your participation on this trial. Your participation in this research study may contribute to the development of commercial products from which Millennium Pharmaceuticals, Inc. (manufacturer of bortezomib) or others, may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

14. Costs and Reimbursements

Most of the visits for this research study are standard medical care for patients undergoing allogeneic transplants and will be billed to your insurance company. You and/or your health plan/insurance company will need to pay for some or all of the costs of standard treatment in this study

The drug bortezomib is being provided by the manufacturer (Millennium Pharmaceuticals, Inc.), free of charge. The drug maraviroc is being provided by the study, free of charge.

You or your insurance will not be charged for optional blood samples for research on this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

15. Ethical Review

The ethical aspects of this research study have been reviewed and approved by [name of IRB].

16. For More Information

If you need more information about this study, or if you have problems while you are participating in this study, you can contact the study doctor or his/her staff. They can be reached at the telephone numbers listed here:
[*Insert name and contact details*]

17. Contact Someone about Your Rights

If you wish to speak to someone not directly involved in the study, or if you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

[*Insert appropriate contact details*]

For questions about your rights while taking part in this study, call the _____*[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

18. Blood Samples for Research (*Optional*)

This section of the informed consent form is about future research studies that will be done using blood samples from people who are taking part in the main study described above. You may give small blood samples for these future research studies if you want to. You can still be a part of the main study even if you say "no" to giving blood samples for future research studies. You can say "yes" or "no" to giving blood samples for future research studies. Please mark your choice at the end of this section.

We would like to have five (5) small blood samples for future research. If you agree, these samples will be drawn before you begin the conditioning regimen for your transplant (3 teaspoons or 16 mL), and at 4 different times after your transplant: on Days 35, 100, 180 and 365 (10 teaspoons or 40 mL each). These samples will be kept and may be used in research to learn more about immune reconstitution, GVHD, cancer and other diseases. Usually the blood can be drawn from a vein in your arm at the same time as other blood collections. When the samples are given to investigators for research, no information about your name, address, phone number or other information that will let the researcher know who you are will be provided.

The samples collected for research purposes will be sent to the BMT CTN Repository. The samples will be labeled with unique codes that do not contain information that could identify you. A link to this code does exist. The link is stored at the Data and Coordinating Center for the Blood and Marrow Transplant Clinical Trials Network (BMT CTN DCC). The staff at the Repository where your sample is being stored does not have a link to this code. Your research samples will continue to be stored at the BMT CTN Repository until they are used up for approved research.

Genome-Wide Association Studies:
DNA from your stored blood samples might be used in genome-wide association (GWA) studies for a future project either done or supported by the National Institutes of Health (NIH). Genome-wide association studies are a way for scientists to find genes that have a role in human disease or treatment. Each study can look at hundreds of thousands of genetic changes at the same time.

If your coded samples are used in such a study, the researcher is required to add your test results and sample information into a public research database. This public database is called the NIH Genotype and Phenotype Database and it is managed by the National Center for Biotechnology Information (NCBI). The NCBI will never have any information that would identify you, or link you to your information or research samples, although the results of genetic studies could theoretically include identifying information about you.

Genetic Information Nondiscrimination Act:
A new federal law (2009), called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Things to Think About:

- The choice to let us have blood samples for future research is up to you. No matter what you decide to do, it will not affect your care.

- If you decide now that your blood can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your blood sample. Then any blood that remains will no longer be used for research.

- In the future, people who do research on these blood samples may need to know more about your health. While the study doctor or others involved in running this study may give the researchers reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

- Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

- Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

- Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Benefits:
The research that may be done with your blood is not designed specifically to help you. The benefits of research using blood include learning more about what causes GVHD, cancer and other diseases, how to prevent them, and how to treat them.

Risks:
There is a small risk of an infection or fainting from the blood draw.

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice:
Please read each sentence below and think about your choice. After reading each sentence, please indicate your choice below. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

No matter what you decide to do, it will not affect your care.

Statement of Consent

The purpose of storing blood samples for future research, the procedures involved, and the risks and benefits have been explained to me. I have asked all the questions I have at this time and I have been told whom to contact if I have more questions. I have been told that I will be given a signed copy of this consent form to keep.

I understand that I do not have to allow the use of my blood for research. If I decide to not let you store research samples now or in the future, it will not affect my medical care in any way.

I voluntarily agree that blood samples may be collected and that my blood and related information can be stored indefinitely by the BMT CTN Repository for research to learn about, prevent, or treat GVHD, cancer, or other health problems. I also understand that my DNA and health information may or may not be used in genome-wide association studies.

- ❑ I <u>do</u> agree to give blood samples for future research.
- ❑ I <u>do not</u> agree to give blood samples for future research.

____ ____________
Signature Date

♦ ♦

Health Insurance Portability and Accountability Act 1 (HIPAA1) Authorization to use and disclose individual health information for research purposes

A. **Purpose**:
As a research participant, I authorize the Principal Investigators and the researcher's staff to use and disclose my individual health information for the purpose of conducting the research study:

A Multi-Center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

B. **Individual Health Information to be Used or Disclosed**:
My individual health information that may be used or disclosed to do this research includes:

- Demographic information (for example: date of birth, sex, weight)
- Medical history (for example: diagnosis, complications with prior treatment)
- Findings from physical exams
- Laboratory test results obtained at the time of work up and after transplant (for example: blood tests, biopsy results)

C. **Parties Who May Disclose My Individual Health Information**:
The researcher and the researcher's staff may collect my individual health information from:
[*List hospitals, clinics or providers from which health care information can be requested*]

D. **Parties Who May Receive or Use My Individual Health Information**:
The individual health information disclosed by parties listed in item c and information disclosed by me during the course of the research may be received and used by the following parties:

<u>Principal Investigators and the researchers' staff</u>

Dr. Javier Bolaños-Meade, Co-Principal Investigator

Dr. John Koreth, Co-Principal Investigator

Dr. Ran Reshef, Co-Principal Investigator

<u>Study Sponsors</u>

- National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI), both of the National Institutes of Health (NIH),
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN), Data and Coordinating Center

[1] HIPAA is the Health Insurance Portability and Accountability Act of 1996, a federal law related to privacy of health information

Other organizations

- U.S. government agencies that are responsible for overseeing research such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state and local health departments.
- Millennium Pharmaceuticals, Inc., supplier of bortezomib

E. **Right to Refuse to Sign this Authorization**:
I do not have to sign this Authorization. If I decide not to sign the Authorization, I will not be allowed to participate in this study or receive any treatment related to research that is provided through the study.

My decision not to sign this authorization will not affect any other treatment, payment, or enrollment in health plans or eligibility for benefits.

F. **Right to Revoke**:
I can change my mind and withdraw this authorization at any time by sending a written notice to the Principal Investigator to inform the researcher of my decision.

If I withdraw this authorization, the researcher may only use and disclose the protected health information already collected for this research study. No further health information about me will be collected by or disclosed to the researcher for this study.

G. **Potential for Re-disclosure**:
My individual health information disclosed under this authorization may be subject to re-disclosure outside the research study and no longer protected.

Examples include potential disclosures for law enforcement purposes, mandated reporting or abuse or neglect, judicial proceedings, health oversight activities and public health measures.

H. **This authorization does not have an expiration date.**

I have read and understood this Consent Form. The nature and purpose of the research study has been explained to me.

- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I understand that I may not directly benefit from taking part in the study.
- I understand that, while information gained during the study may be published, I will not be identified and my personal results will stay confidential.
- I have had the chance to discuss my participation in this research study with a family member or friend.
- I understand that I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
- I understand that I will be given a copy of this signed consent form.

_____

Participant Name Date

_____

Signature Date

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

_____

Name of Counseling Physician Date

_____

Signature of Counseling Physician Date

APPENDIX C

LABORATORY PROCEDURES

APPENDIX C

LABORATORY PROCEDURES

OPTIONAL RESEARCH SPECIMENS

Patients consenting to the optional future research will have samples collected for future research supporting the protocol, including assessment of immune reconstitution. All research sample aliquots will be given unique bar code designations that cannot be linked back to the participant's name or other identifying information. Laboratory test results, clinical information, etc., associated with the coded samples are provided to the Investigator only after completion of the protocol. Samples sent to researchers cannot be linked with any remaining samples at the repository.

Patient samples will be collected both prior to the initiation of treatment and at Days 35, 100, 180 and 365 post-treatment time points as specified in the table on the next page. All research samples will be collected and shipped same-day to the BMT CTN Repository for processing and sample aliquot storage. Sample collection and shipping procedures are detailed in the BMT CTN 1203 Laboratory Sample Guide.

Optional Research Samples							
Subjects	**Research Sample Type**	**Time Points [Total Blood Volume]**	**Sample Quantity**	**Stored Material**	**Sample Processing & Storage Site**	**Aliquots Stored**	**Purpose**
270 Patients **Patients encouraged to co-enroll on BMT CTN 1202 Biomarkers Study**	Peripheral Blood	**<u>Pre-Transplant</u>** (prior to initiation of conditioning regimen) 16 mL	6 mL EDTA	Whole Blood	BMT CTN Repository	Maximum 6 aliquots 1.0 mL whole blood aliquots; stored at -80º C	Undefined Future Research **(Genomic DNA Isolation)**
			10 mL Serum Clot Tube	Serum	BMT CTN Repository	Maximum **10 aliquots** ~ 0.5 mL aliquots; stored at -80º C	Undefined Future Research (**Proteomic**)
		<u>Post-Transplant</u> Days 35, 100, 180, and 365 **40 mL**	10 mL Serum Clot Tube	Serum	BMT CTN Repository	Maximum **10 aliquots** ~ 0.5 mL aliquots; stored at -80º C	Undefined Future Research (**Proteomic**)
			30 mL Heparin	Viable PBMC	BMT CTN Repository	Maximum **6 aliquots** 1.0 mL aliquots containing ~ 2.5-5.0 x 10^6 PBMC; controlled-rate frozen and stored in LN2	Undefined Future Research (**Cell-Functional & Gene Expression**)

Windows for Submitting Optional Research Samples				
Day 0 (Prior to Initiation of Conditioning)	**Day 35 (±2)**	**Day 100 (±7)**	**Day 180 (±14)**	**Day 365 (±14)**

APPENDIX D

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC DISEASE

APPENDIX D

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF CARDIAC DISEASE

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX E

DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

APPENDIX E

DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

Background – The Sequential Probability Ratio Test

Let $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0 : \theta = \theta_o$ versus $H_1 : \theta = \theta_1$ decides in favor of H_1 or H_0 if $L_n > c_\alpha$ or $L_n < c_\alpha$, respectively, where $L_n = \prod_i^n f(x_i;\theta_1) / f(x_i;\theta_0)$ is the likelihood ratio, and c_α is determined to have the size α. When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B < L_n < A$ for some constant $B < 1 < A$, stops sampling and decides in favor of H_1 as soon as $L_n > A$, and stops sampling and decides in favor of H_0 as soon as $L_n < B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$, and of accepting H_0 when $\theta = \theta_1$, respectively, and the expected sample size $E(N \mid \theta_j) \equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject } H_0) \le \alpha$ and $\Pr_1(\text{reject } H_0) \le \beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1, x2, ...$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1 (> \theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities α and β, the SPRT boundaries are given approximately by $A = (1-\beta)/\alpha$ and $B = \beta/(1-\alpha)$. The operating characteristics of the SPRT are given by $O(\theta,\alpha,\beta,\theta_0,\theta_1) = (A^{h(\theta)} - 1)/(A^{h(\theta)} - B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int (f(x;\theta_1)/f(x,\theta_2))^{h(\theta)} f(x;\theta)dx = 1$.

The formula $E(N;\theta) = [[(1-O(\theta)]\log A + O(\theta)\log B] / E(z;\theta)$ provides the average sample number for an arbitrary θ. The sample size distribution is very highly skewed, $Var(N) \approx [E(N)]^2$. Thus we will consider a truncated test with maximum sample size of N_0 and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Uncensored Exponential Survival Times

For example, we wish to construct a sequential test for the composite null hypothesis that the rate of TRM at 180 days is less than or equal to 5% versus the alternative hypothesis that it is greater than or equal to 5%. For the derivation of the uncensored SPRT, we will require that the type I error of the test be less than 10%, and that the test provide 90% power to reject the null hypothesis under a specified alternative that the true rate is 10%. A maximum sample size of 250 patients will be permitted.

Let us assume that the survival times, $T_1, T_2, ..., T_n$, are completely observed (uncensored) and are i.i.d. with exponential density function $f(T,\theta) = \theta e^{-\theta T}$. These assumptions will be relaxed to incompletely observed data subsequently. In the exponential parameterization, a 180-day survival rate of 95% translates into a mean survival of 9.747 years ($\theta_0 = .1026$), and 90% translates into a mean survival of 4.746 years ($\theta_1 = .2107$).

The SPRT is derived with reference to a simple null and alternative hypothesis, in this case, $H_0 : \theta = \theta_o = .1026$ versus $H_1 : \theta = \theta_1 = .2107$. However, since the log-likelihood ratio for the exponential, $\log \prod_i^n f(x_i;\theta_1) - \log \prod_i^n f(x_i,\theta_0) = n(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, is a monotone function of $\sum_i^n T_i$, the power of the test is non-decreasing in θ. Thus the SPRT is a one-sided level .10 test of a composite null ($H_0 : \theta \le \theta_o = .1026$) versus a composite alternative ($H_1 : \theta \ge \theta_o = .2107$), with power of $1-\beta = .90$ at the selected alternative $\theta = \theta_1 = .2107$.

The SPRT can be represented graphically. The continuation region is bounded by two parallel lines with common slope $(\theta_1 - \theta_0)/(\log\theta_1 - \log\theta_0) = 0.150$, and intercepts $\log A/(\log\theta_1 - \log\theta_0) =$ 3.05 and $\log B/(\log\theta_1 - \log\theta_0) =$ -3.05 for the lower and upper bounds, respectively. As each individual unit is put on trial and observed to fail, the current sample size, *n*, is plotted against the cumulative sum of failure times. When this graph crosses the upper boundary, the null hypothesis is rejected.

The maximum sample size of 250 patients requires that the SPRT be truncated. We choose to truncate the SPRT by declaring that if the test has failed to terminate after 250 patients, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at a sample size of 250 is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity.

Derivation of a Modified SPRT for Censored Exponential Data

The assumption of uncensored exponential survival times is flawed. However, we consider it reasonable to assume the hazard for TRM is constant over the first 180 days post-transplant, and

we will restrict our attention to this time interval. Furthermore, it is not practical to conduct a clinical study by putting each individual on trial, and waiting until that individual is observed to fail. We relax our assumptions as follows. Firstly, each individual's time on study will be computed as time from transplant to failure, or to the 180 day time point, whichever comes first. Secondly, we will put individuals on trial as soon as they become available, without waiting for the previous individual to fail.

Let us consider the impact of relaxing these assumptions one at a time. In a fixed sample size trial with uncensored exponential failure times, mean survival time is estimated by the sample mean of the failure times, or total time on study divided by the number of individuals enrolled. When censoring is introduced, the estimate becomes the total time on study divided by the number of observed (non-censored) failures. This suggests that in an exponential SPRT test modified to incorporate censoring, we replace the observed failure times, $T_1, T_2, ..., T_n$, with censored failures times, $x_1, x_2, ..., x_n$, and the current sample size, n, with the number of observed failures, d.

Now we relax the second assumption, and put individuals on trial as soon as they become available, without waiting for the previous individual to fail. Assume that three years are required for accrual of 250 patients to the study, and that the final analysis takes place 180 days after the last patient is entered. Putting all of this together, we propose a modified truncated SPRT, where at any interim time point, s, ranging from 0 to 3 years 180 days, the number of observed failures, *d(s)*, is plotted against the sum of observed time on study, $\sum_i^n X_i(s)$. In practice, monitoring will be scheduled monthly after the start of enrollment to the study. A further modification to the SPRT was to only use the upper boundary for stopping since the primary focus of the monitoring is to protect against unacceptable 180-day TRM rates.

Operating Characteristics of the Modified SPRT Test for Censored Exponential Data

Recall that the uncensored SPRT targeted a drop in TRM-free survival at Day 180 from 95% to 90%, with type I and II errors of 10% and 10%. Since only the upper boundary is used for monitoring, the continuation region of the test was bounded above by a line with a slope of 0.150 and intercept of 3.05. In our example, the sample size is large enough that the reduction in power due to truncation of the test is negligible compared to the increase in power because the modified SPRT, lacking a lower boundary, cannot stop early to "accept" the null hypothesis. In order to maintain type I error, we raise the upper boundary to make it harder to cross. Under the further assumption of uniform accrual over a three year period, and monthly interim analyses over the course of the study, the operating characteristics of the modified SPRT were obtained from a simulation study. These simulation show that an intercept of 4.02, corresponding to setting parameters α and β to 10% and 10%, result in empirical type I and II error rates of 10% and 10%.

Table E-1 Operating Characteristics of Sequential Testing Procedures from a Simulation Study with 100,000 Replications

True 180-Day Rate	**5%**	**10%**
Probability Reject Null	0.095	0.903
Mean Month Stopped	41.0	20.2
Mean # Endpoints in 180 days	11.8	11.6
Mean # Patients Enrolled	240.8	135.4

While the motivation for this testing procedure is largely heuristic rather than theoretical, the simulation results validate the approach. When the true rate of TRM on or before Day 180 was 5%, the test crossed the lower boundary in 9484 of 100,000 replications, for an estimated type I error rate of 9.5%. When the true rate of TRM on or before Day 180 was 10%, the test failed to cross the boundary in the in 9742 of 100,000 replications, for an estimated type II error rate of 9.7%. In this setting, on average, the boundary will be crossed at 20.2 months.

It is interesting to note that the SPRT derived above for exponential failure times with censoring at 180 days, has operating characteristics which are similar to those of a more traditional SPRT, derived for binomial variates with success probability equal to the 180 day failure rate. Using time to failure rather than a simple binary indicator of failure, leads to little improvement in power when failure times are censored relatively soon after entry on study. We speculate that if the constant hazard rate over the first 180 days were high, the exponential test would reject faster than the binomial test, but have not conducted simulation studies to demonstrate this.

APPENDIX F

KARNOFSKY PERFORMANCE STATUS SCALE

APPENDIX F

KARNOFSKY PERFORMANCE STATUS SCALE

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity; no special care needed.
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	Care for self, unable to carry on normal activity or to do work.	Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed.
60	Requires occasional assistance from others but able to care for most needs.	
50	Requires considerable assistance from others and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, but death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund	
0	Dead	

APPENDIX G

HCT-SPECIFIC COMORBIDITY INDEX SCORE

APPENDIX G

HCT-SPECIFIC COMORBIDITY INDEX SCORE

Comorbidities	Definition	Score
Migraine/headache		**0**
Osteoporosis		**0**
Osteoarthritis		**0**
Hypertension		**0**
Gastrointestinal	Including inflammatory bowel disease	**0**
Mild pulmonary	DLCo and/or FEV_1 >80% or Dyspnea on moderate activity	**0**
Mild renal	Serum creatinine 1.2-2 mg/dl	**0**
Endocrine		**0**
Bleeding		**0**
Coagulopathy	Deep venous thrombosis or pulmonary embolism	**0**
Asthma		**0**
Arrhythmia		**1**
Myocardial	Coronary artery disease, congestive HF, history of medically documented MI, EF≤50%	**1**
Mild hepatic	Chronic hepatitis, Bilirubin >ULN- 1.5 X ULN, or AST/ALT >ULN-2.5XULN	**1**
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular accident	**1**
Morbid obesity		**1**
Diabetes	Requiring treatment	**1**
Depression/anxiety		**1**
Infection	Requiring continuation of treatment after Day 0	**1**
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	**2**
Moderate pulmonary	DLCo and/or FEV_1 66-80% or Dyspnea on slight activity	**2**
Peptic ulcer	Patients who have required treatment	**2**
Moderate-severe renal	Serum creatinine >2 mg/dl, on dialysis, or prior renal transplantation	**2**
Valvular heart disease	Except mitral valve prolapse	**3**
Prior solid tumor	Requiring treatment with chemotherapy	**3**
Moderate-severe hepatic	Liver cirrhosis, Bilirubin >1.5 X ULN, or AST/ALT >2.5XULN	**3**
Severe pulmonary	DLCo and/or FEV_1 ≤65% or Dyspnea at rest or requiring oxygen	**3**

Total score is the sum of all comorbidities present at time of transplantation.

APPENDIX H

KNOWN ANTICIPATED RISKS OF BORTEZOMIB

APPENDIX H

KNOWN ANTICIPATED RISKS OF BORTEZOMIB

Table 1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term	
System Organ Class Observed Incidence	**Preferred Term**
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhoea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*, lower gastrointestinal haemorrhage*± rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication

Table 1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term	
System Organ Class **Observed Incidence**	**Preferred Term**
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bactaeremia*, cellulitis*, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache

Table 1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term	
System Organ Class Observed Incidence	**Preferred Term**
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome ϕ
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 16.
Most common = ≥ 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%.
* Fatal outcomes have been reported.
± Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.
ϕ Effective MedDRA update to version 14.0, the term 'reversible posterior leukoencephalopathy syndrome' updated to 'posterior reversible encephalopathy syndrome (PRES)'.

Table 2 Reports of Adverse Reactions From Postmarketing Experience	
System Organ Class Preferred Term	**Observed Incidence[a]**
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete	Rare
Cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes	Rare
Optic neuropathy	Rare
Blindness	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic shock	Rare
Progressive multifocal leukoencephalopathy	Very rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Autonomic neuropathy	Rare
Dysautonomia	Unknown
Encephalopathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease[b]	Rare
Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare

Table 2 Reports of Adverse Reactions From Postmarketing Experience	
System Organ Class Preferred Term	**Observed Incidence[a]**
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 16.

a Incidence is assigned using the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000, including isolated reports).

b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

APPENDIX I

PRODUCT COMPLAINTS FOR BORTEZOMIB

APPENDIX I

PRODUCT COMPLAINTS FOR BORTEZOMIB

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact MedComm Solutions (see below) and report the event.

For Product Complaints or Medication Errors,
call MedComm Solutions at
1-866-835-2233 (US and International)

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an Unexpected, Grade 3-5 Adverse Event, then the appropriate forms in AdvantageEDC should be completed (refer to Section 4.7 Adverse Event Reporting).

APPENDIX J

ADVERSE EVENT REPORTING REQUIREMENTS

APPENDIX J

ADVERSE EVENT REPORTING

J.1 Adverse Event Reporting

Adverse events (AEs) will be collected on calendar-driven forms and event-driven forms in AdvantageEDC.

The calendar-driven forms are those that appear in the AdvantageEDC Forms Grid for each enrolled patient at designated time points (e.g., Day 28 post transplant) throughout the course of the study. Completion of a calendar-driven form is expected by the Target Date for the given assessment period.

Calendar-driven forms for the BMT CTN 1203 study are as follows:

- **Toxicity Form**: this form documents all expected toxicities for the BMT CTN 1203 study; each toxicity is also assigned a grade, based on the NCI CTCAE Version 4.0.
- **Hematology/Chemistry Form**: this form documents selected hematology (CBC/differential) and blood chemistry results.
- **Follow-Up Status Form**: this form documents the status of each patient at various intervals on the study.

Event-driven forms must be completed when a certain event triggers the appearance of the form in the AdvantageEDC Forms Grid. Most often the event-driven form is triggered by information entered on the Follow-up Status Form. Event-driven forms for the BMT CTN 1203 study are as follows:

- **Re-Admission/Hospitalization Form**: this form documents all hospital admissions, *including* the admission for transplant for this study.
- **Infection Form**: this form documents infections from the Day 0 (date of transplant) through the 1-year post-transplant follow-up period.
- **Secondary Graft Failure Form**: this form captures the details associated with secondary graft failure. DO NOT report secondary graft failure as an Unexpected, Grade 3-5 Adverse Event.
- **Progression/Relapse Form**: the form captures detailed information associated with progression or relapse of the primary disease. DO NOT report progression or relapse as an Unexpected, Grade 3-5 Adverse Event.
- **Death Form**: this form documents the death of a patient from the time of study enrollment and randomization through the 1-year post-transplant follow-up period.
- **Bortezomib SAE Screening Form**: this form captures basic information on all SAEs only for patients randomized to the bortezomib arm from the first dose of bortezomib through 30 days after the last dose.

- **Adverse Event Forms**: this series of forms captures details on adverse events that are *both* unexpected and grades 3-5, based on the NCI CTCAE Version 4.0, regardless of attribution to any of the study interventions. These forms are also used to collect information on any SAE event required by the additional adverse event reporting requirements. These events will be reviewed by the Medical Monitor at the BMT CTN Data and Coordinating Center (DCC) within 2 business days of receiving the summary of the adverse event from the transplant center. If the Medical Monitor requires additional information to make his/her assessment, the transplant center will have 4 business days to respond to the request for additional information.

J.2 Reporting Expected Toxicities

Expected toxicities for all patients enrolled on BMT CTN 1302 will be collected on the BMT CTN 1203 Calendar-Driven Toxicity Form.

J.3 Reporting Unexpected, Grade 3-5 Adverse Events

All Unexpected, Grade 3-5 Adverse Events should be reported for every patient enrolled on the study from the time of enrollment until 1 years post transplant. Additional Adverse Event reporting applies to patients dependent on the treatment received on the study. Determination of the expectedness of adverse events should be differentiated between the arms at the discretion of the investigator. For example, sweat gland disturbances would be an expected risk associated with maraviroc, but the investigator should assess the expectedness for a patient experiencing sweat gland disturbances randomized to the bortezomib arm.

J.4 Additional Reporting Requirements for Patients Randomized to the Tacrolimus/ Methotrexate/Bortezomib from the 1st dose of Bortezomib through 30 Days After the Last Dose.

This section outlines the adverse event reporting requirements for all patients randomized to the Tacrolimus/Methotrexate/Bortezomib from the first dose

Millennium Pharmaceuticals, Inc. (MPI) is supplying bortezomib for all patients who are randomized to receive tacrolimus/methotrexate/bortezomib as GVHD prophylaxis on this study. MPI has adverse event reporting requirements **for all patients who receive study bortezomib.**

In addition to the standard BMT CTN guidelines for reporting adverse events (see Chapter 4, Section 4.7), MPI is requiring the reporting of **all** Serious Adverse Events (SAEs) that occur **after the initial dose** of study bortezomib (Day +1), **during treatment**, and **within 30 days of the last dose** of study bortezomib (Day +7 plus 30 days). This includes events meeting the definition of a Serious Adverse Event, per 21 CFR 312.32, as follows:

Serious Adverse Event: A serious adverse event (SAE) is any adverse event that results in one of the following outcomes, regardless of causality and expectedness:

- **Results in death**
- **Is life-threatening**. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- **Requires or prolongs inpatient hospitalization** (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- **Results in persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly or birth defect**; or
- **Is an important medical event** when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. 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.

Medical and scientific judgment should be exercised in deciding whether expected reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above (eg, suspected transmission of an infectious agent by a medicinal product is considered a Serious Adverse Event). Any event is considered a Serious Adverse Event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

J.4.1 Reporting Timelines for Events Occuring During Bortezomib Reporting Period

- **Fatal and Life-Threatening** events must be reported in AdvantageEDC within 24 hours, of the investigator's observation or awareness of the event.
- **All Other Serious** events (non-fatal/non-life-threatening) must be reported in AdvantageEDC within 3 calendar days of the investigator's observation or awareness of the event.

J.4.2 How to Report Serious Adverse Events During Bortezomib Reporting Period

All SAEs from the first dose of bortezomib through 30 days after the last dose will be reported in AdvantageEDC by completing theBortezomib SAE Screening Form. . All SAEs also require completion of the Adverse Event Forms (AE1-AE6), unless any of the following SAEs are determined to be unrelated or unlikely related to the bortezomib, then the Adverse Event Forms are not required:

- ***Neutropenia***
- ***Thrombocytopenia***
- ***Anemia***
- ***Minor bleeding episodes (i.e. epistaxis)***
- ***Graft-versus-host disease (GVHD)***
- ***Graft failure***
- ***Hepatic veno-occlusive disease (VOD)***
- ***Thrombotic microangiopathy (TMA)***

Accurate completion of the Bortezomib SAE and/or Adverse Event forms will allow the DCC to provide MPI with the details they require to fully understand each event, so it is *critical* that all fields are filled in and comprehensive supporting source documents for the event (PHI redacted) are uploaded to the appropriate forms.

If an adverse event does not meet the criteria of an SAE, it will require reporting on the Adverse Event form if it is both unexpected and grade 3-5 based on the BMT CTN standard reporting guidelines.

J.4.3 Frequently Asked Questions

Below are some examples of anticipated questions with regard to the reporting requirements detailed above. These questions do not cover all possible scenarios, therefore it is important to contact the BMT CTN Adverse Event or 1203 Protocol Coordinator should there be any questions or concerns regarding the reporting of an event and whether the event meets the MPI reporting requirements.

- **Since hospitalization is considered an SAE, should the patient's admission for transplant be reported as an SAE?** *NO. Admissions that are scheduled to occur during the study period, bu planned prior to study entry are not considered SAEs given the disease existed before the person was enrolled in the trial and provided that it did not deteriorate in an unexpected manner during the trial. The SAE reporting requirements also begin with the first dose of study drug (bortezomib on Day +1), so the admission for transplant will occur before this reporting begins. Among patients who undergo the transplant procedure as outpatients and have scheduled hospitalization at time they become neutropenic in the absence of fever, an SAE report is not required, unless the neutropenia prolongs the scheduled hospitalization.*
- **Is neutropenia and/or thrombocytopenia associated with the preparative regimen and experienced during the transplant admission considered a life-threatening event?** *NO. Pancytopenias associated with transplant are not considered life-threatening events for the purposes of these reporting requirements. If patients are discharged after the transplant, followed as outpatients, and then re-hospitalized for neutropenic fever prior to day 37, SAE reporting will be required.*
- **During the transplant admission a patient becomes critically ill (e.g., pneumonia requiring intubation). Does this event need to be reported as an SAE?** *YES. Even though the patient is already hospitalized, this is a life-threatening event that required intervention and likely prolonged hospitalization.*

- **A patient is discharged from the hospital post-transplant on Day +32, and is then re-admitted 2 days later for diarrhea and nausea. Should this re-admission be reported as an SAE?** *Possibly. Even though the subsequent hospitalization falls within the reporting period (Day +7 plus 30 days) the reason for admission is likely GVHD. If the GVHD is determined to be unrelated or unlikely related to the bortezomib, only the Bortezomib SAE screening form is required. If the GVHD is determined to be possibly, probably or definitely related to bortezomib, then an SAE should be reported on both the Bortezomib SAE screening form and the Adverse Event forms. If the work up is negative for GVHD of the gastrointestinal tract, then an SAE should be reported.*
- **A patient is discharged from the hospital post-transplant, and is then re-admitted for nausea, vomiting and diarrhea on Day +40. Should this hospitalization be reported as an SAE?** *It is not **required** that this event be reported as an SAE since the admission occurred outside of the reporting period (Day +7 plus 30 days). However, if the investigator has a reason to believe that the event is life-threatening and there is no evidence of GVHD, the event may be reported at the discretion of the investigator.*

J.5 Reporting Requirements for Patients Randomized to Tacrolimus/ Methotrexate/Bortezomib Beginning 30 days After the Last Dose of Bortezomib

This section outlines the adverse event reporting requirements for all patients beginning 30 days after the final dose of bortezomib until 1 year post transplant.

Table J-1 lists adverse events and toxicities for this study, as well as the form in AdvantageEDC that is used to document the event.

TABLE J-1: ADVERSE EVENTS FOR BMT CTN 1203 BEGINNING 30 DAYS AFTER THE LAST DOSE OF BORTEZOMIB BY ORGAN SYSTEM

Adverse Event	Collection Type	Collection Form[1]
AUDITORY DISORDERS		
Hearing loss	Calendar-Driven	Toxicity
BLOOD AND LYMPHATIC DISORDERS		
Anemia	Calendar-Driven	Toxicity
Neutropenia	Calendar-Driven	Toxicity
Thrombocytopenia	Calendar-Driven	Toxicity
Thrombotic thrombocytopenic purpura/ Thrombotic microangiopathy	Calendar-Driven	Toxicity
CARDIAC DISORDERS		
Cardiac arrhythmia	Calendar-Driven	Toxicity
Hypertension	Calendar-Driven	Toxicity
Hypotension	Calendar-Driven	Toxicity
Left ventricular systolic dysfunction	Calendar-Driven	Toxicity
Myocardial infarction	Calendar-Driven	Toxicity
New or worsening heart failure	Calendar-Driven	Toxicity
Pericardial effusion	Calendar-Driven	Toxicity

Adverse Event	Collection Type	Collection Form[1]
Pericarditis	**Event-Driven**	**Adverse Event Form**
Peripheral edema	**Calendar-Driven**	**Toxicity**
Restrictive cardiomyopathy	**Calendar-Driven**	**Toxicity**
GASTROINTESTINAL DISORDERS		
Abdominal pain	**Calendar-Driven**	**Toxicity**
Anorexia	**Calendar-Driven**	**Toxicity**
Constipation	**Calendar-Driven**	**Toxicity**
Diarrhea	**Calendar-Driven**	**Toxicity**
Dysgeusia (taste alteration)	**Calendar-Driven**	**Toxicity**
Dyspepsia (heartburn)	**Calendar-Driven**	**Toxicity**
Gastroenteritis	**Calendar-Driven**	**Toxicity**
Intestinal obstruction	**Event-Driven**	**Adverse Event Form**
Nausea	**Calendar-Driven**	**Toxicity**
Oral mucositis	**Calendar-Driven**	**Toxicity**
Vomiting	**Calendar-Driven**	**Toxicity**
GENERAL DISORDERS		
Fatigue	**Calendar-Driven**	**Toxicity**
Fever	**Calendar-Driven**	**Toxicity**
HEPATOBILIARY/PANCREAS DISORDERS		
Abnormal liver function tests	**Calendar-Driven**	**Toxicity**
Hepatitis	**Event-Driven**	**Adverse Event Form**
Liver failure	**Event-Driven**	**Adverse Event Form**
Pancreatitis	**Calendar-Driven**	**Toxicity**
HEMORRHAGIC DISORDERS		
Intracranial	**Event-Driven**	**Adverse Event Form**
Gastrointestinal	**Calendar-Driven**	**Toxicity**
Genitourinary	**Calendar-Driven**	**Toxicity**
Pulmonary/Upper respiratory	**Calendar-Driven**	**Toxicity**
IMMUNE SYSTEM DISORDERS		
Allergic reaction	**Event-Driven**	**Adverse Event Form**
Anaphylaxis (swelling of the skin and/or swelling of the face or throat)	**Event-Driven**	**Adverse Event Form**
INFECTIONS		
Fungal infections of the mouth and throat	**Event-Driven**	**Infection**
Herpes virus/shingles	**Event-Driven**	**Infection**
Infections of the bladder, sinuses, throat, stomach and intestines, and skin	**Event-Driven**	**Infection**
Sepsis	**Event-Driven**	**Infection**
METABOLISM AND NUTRITION DISORDERS		
Hypercalcemia	**Calendar-Driven**	**Toxicity**
Hyperglycemia	**Calendar-Driven**	**Toxicity**

Adverse Event	Collection Type	Collection Form[1]
Hypoglycemia	**Calendar-Driven**	**Toxicity**
Hypokalemia	**Calendar-Driven**	**Toxicity**
Hyponatremia	**Calendar-Driven**	**Toxicity**
Tumor lysis syndrome	**Event-Driven**	**Adverse Event Form**
MUSCULOSKELETAL AND TISSUE DISORDERS		
Arthralgia	**Calendar-Driven**	**Toxicity**
Myalgia	**Calendar-Driven**	**Toxicity**
Muscle weakness (generalized or specific area)	**Calendar-Driven**	**Toxicity**
NERVOUS SYSTEM DISORDERS		
Anxiety	**Calendar-Driven**	**Toxicity**
Confusion	**Calendar-Driven**	**Toxicity**
Depression	**Calendar-Driven**	**Toxicity**
Dizziness	**Calendar-Driven**	**Toxicity**
Encephalopathy	**Event-Driven**	**Adverse Event Form**
Headache	**Calendar-Driven**	**Toxicity**
Insomnia	**Calendar-Driven**	**Toxicity**
Neuropathy	**Calendar-Driven**	**Toxicity**
Reversible posterior leukoencephalopathy syndrome (PRES)	**Calendar-Driven**	**Toxicity**
Seizure	**Calendar-Driven**	**Toxicity**
Severe muscle weakness/paralysis	**Event-Driven**	**Adverse Event Form**
Somnolence	**Calendar-Driven**	**Toxicity**
Syncope (fainting)	**Calendar-Driven**	**Toxicity**
OCULAR/VISUAL DISORDERS		
Blurred vision	**Calendar-Driven**	**Toxicity**
Conjunctivitis	**Calendar-Driven**	**Toxicity**
Sudden loss of vision	**Event-Driven**	**Adverse Event Form**
RENAL DISORDERS		
Cystitis Non-infective	**Calendar-Driven**	**Toxicity**
Acute kidney injury	**Calendar-Driven**	**Toxicity**
Chronic kidney disease	**Calendar-Driven**	**Toxicity**
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Bronchitis	**Calendar-Driven**	**Infection**
Cough	**Calendar-Driven**	**Toxicity**
Dyspnea	**Calendar-Driven**	**Toxicity**
Hypoxia	**Calendar-Driven**	**Toxicity**
Pleural effusion	**Calendar-Driven**	**Toxicity**
Pneumonia	**Calendar-Driven**	**Infection**
Sinusitis	**Calendar-Driven**	**Toxicity**
Sore throat	**Calendar-Driven**	**Toxicity**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		

Adverse Event	Collection Type	Collection Form[1]
Pruritis	**Calendar-Driven**	**Toxicity**
Rash	**Calendar-Driven**	**Toxicity**
Hyperhidrosis (excessive sweating)	**Calendar-Driven**	**Toxicity**
VASCULAR DISORDERS		
Capillary leak syndrome	**Calendar-Driven**	**Toxicity**
Thromboembolic event	**Calendar-Driven**	**Toxicity**
OTHER		
Pregnancy	**Event-Driven**	**Adverse Event Form**
Other unexpected grade 3-5 AE	**Event-Driven**	**Adverse Event Form**

[1]Events determined to be at least possibly related to bortezomib that occur more than 30 days from the last dose may be reported via the Bortezomib SAE Screening Form and Adverse Event Form at the discretion of the investigator.

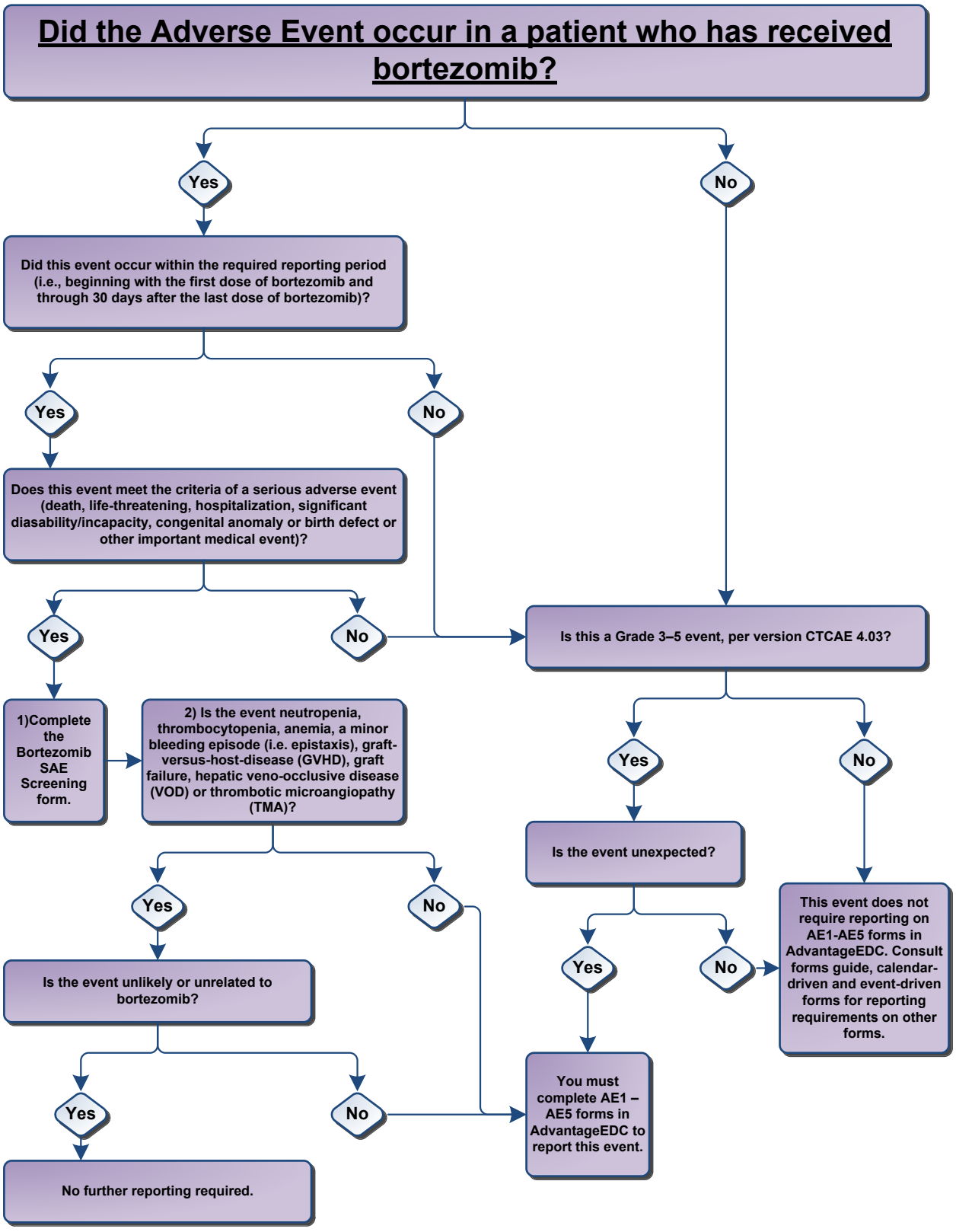
J.6 Reporting Requirements for All BMT CTN 1203 Participants

This section outlines the reporting requirements for all participants enrolled on BMT CTN 1203 from enrollment through 1 year post transplant..

For patients randomized to Tacrolimus/Methotrexate/Bortezomib and Tacrolimus/MMF/Maraviroc, an assessment of relationship to Bortezomib and Maraviroc is required in addition to an assessment of relationship to transplant.

Figure J-2 provides a decision tree for any adverse event that occurs on a patient randomized to any of the 3 treatment arms.

FIGURE J-2: DECISION TREE FOR ADVERSE EVENTS FOR BMT CTN 1203



APPENDIX K

REFERENCES

APPENDIX K

REFERENCES

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