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

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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 ≥ 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 < 1.5x 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 ≥ 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.

***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.

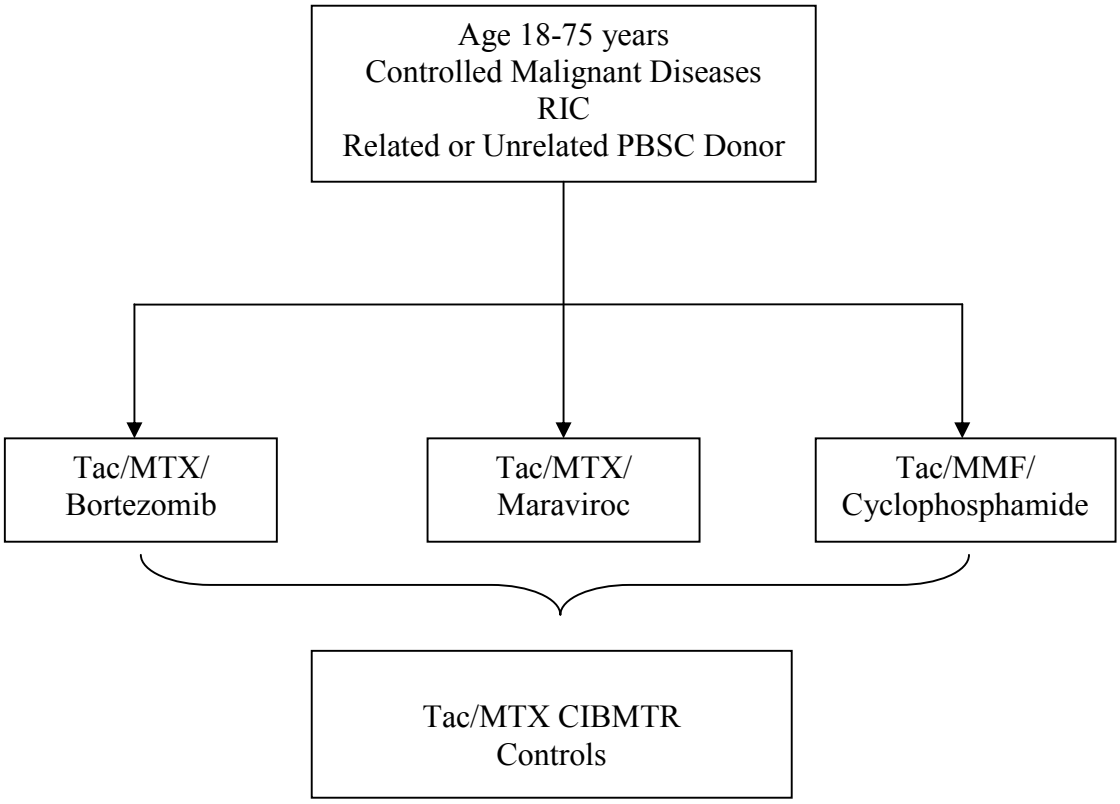
Primary endpoint:
- GVHD/relapse or progression-free survival (GRFS) by 1 year: this time to event outcome is defined as grade III-IV acute GVHD, chronic GVHD requiring systemic treatment, disease relapse or progression, or death by any cause.

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