BMT CTN #1203 Statistical Analysis Plan (SAP)
Version 0.01
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Reviewed by DCC STAT Committee on:
Reviewed by the protocol team on:
Finalized on:

Protocol

BMT CTN #1203 A Multi-center Phase II Trial Randomizing Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

Protocol Synopsis

BMT CTN protocol #1203 is a Phase II, multi-center trial designed to compare the treatment effects in three arms of GVHD prophylaxis to contemporary controls. The three arms are: (1) Tacrolimus (Tac)/Methotrexate (Mtx) with bortezomib 1.3 mg/m^2 IV daily Days +1, +4 and +7 post HSCT, (2) Tac/Mtx with maraviroc 300 mg PO twice a day from Day -3 to 30 post HSCT, and (3) cyclophosphamide (Cy) 50 mg/kg Day +3 and +4, followed by Tac and mycophenolate mofetil (MMF).

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. Secondary objectives are to describe for each treatment arm the following:

- Incidence of grade II-IV and III-IV of acute GVHD up to 180 days
- Incidence of chronic GVHD up to 1 year
- Immunosuppression-free survival at 1 year
- Hematologic Recovery (neutrophil and platelet)
- Donor cell engraftment
- Disease relapse or progression
- Transplant-related mortality at days 100, 180, and 1 year
- Proportion of grade 3 or more toxicities according to the CTCAE

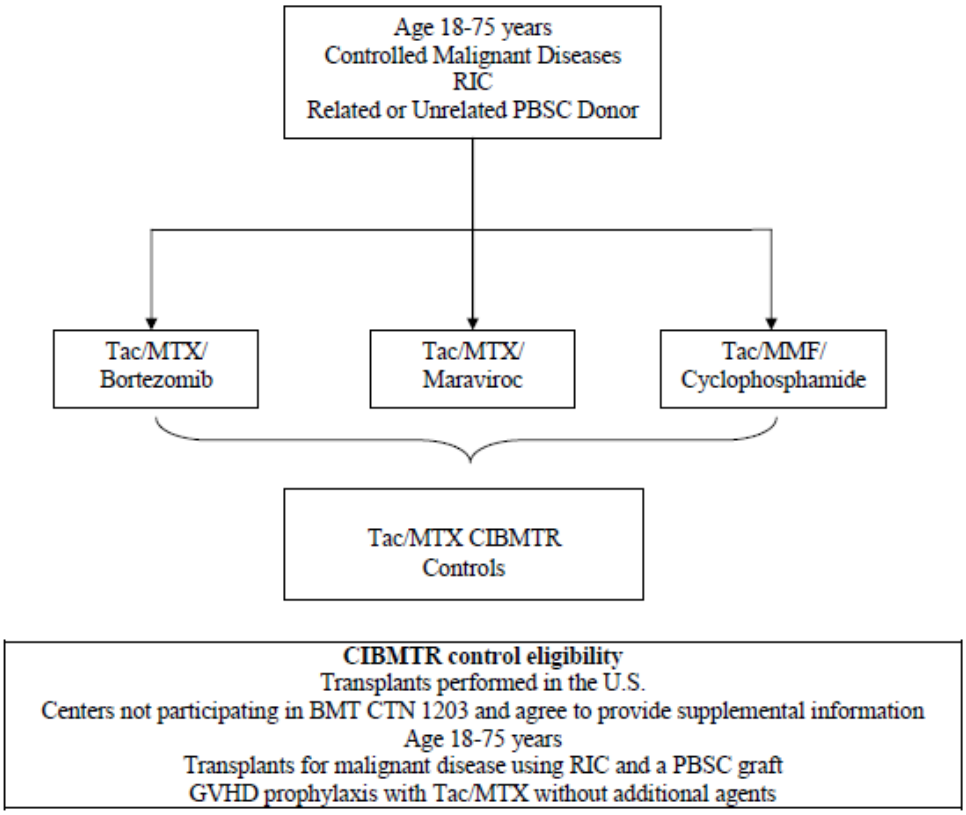
- Incidence of infections
- Disease-free survival
- GVHD-free survival
- Overall survival

The target enrollment is 540 patients. This includes 90 randomized patients to each of the 3 treatment arms and 270 non-randomized CIBMTR contemporary controls. Participants will be accrued over a 30 month period then followed for an additional year post HSCT.

Study Treatment

All patients will be randomized within 7 days prior to the initiation of conditioning therapy. Randomization will be stratified by donor type/HLA mismatching (Matched Sibling vs. Matched Unrelated vs. Mismatched Unrelated) and by disease risk. 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.

Outline of Treatment Plan



Inclusion and Exclusion Criteria

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

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.

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, plus the following:

1. Receive Tac/MTX as the sole GVHD prophylaxis approach
2. Receive the same regimens as specified in Table 2.4a of the protocol
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

Response Variables and Data Collection Time Points

Participants are evaluated for progression and disease status assessments at study entry at day 100, day 180 and day 365 post transplant. Disease relapse/progression is reported on event-driven forms. GVHD assessments are performed weekly from day 7 until day 63 post-transplant, and then at days 100, 120, 150, 180, 270, and 365 post-transplant.

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 of the protocol).

Time Line

The study opened for accrual in September 2014 and completed accrual in June 2016. There were no interim analyses planned for efficacy. An interim analysis for futility was planned based on the 6 month GRFS when 30 participants in each arm have 6 months of follow-up available. The interim analysis for futility was conducted and presented at the DSMB meeting in April 2016. The database for the study will be locked after completion of participants' 1-year follow up and data review by Endpoint Review Committee (ERC). The ERC is planning to begin adjudicating cases in Fall 2016.

General Statistical Considerations

Sample Size and Power Calculations

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 hazard ratio (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 II 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 1 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 1: 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

Missing Data

For time-to-event outcomes, participants who are lost to follow-up before completion of follow-up are censored at the time of loss to follow-up with definitions detailed in the description of each analysis.

Multiple Comparisons

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 for each treatment arm to the control group, based on a multivariate Cox regression model. If none of the treatments has GRFS better than the control, the overall (Familywise) type I error rate is approximately 11-13%.

Interim Analyses

No interim analyses for efficacy are planned for this study. However, an interim analysis for futility is planned for the primary outcome of GRFS. The interim analysis for futility is based on the 6 month GRFS when 30 participants 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 will be considered. This futility stopping rule is meant to be a guidance only, based on an expected 6 month GRFS of 45-50%. Formal statistical testing may be considered if the stopping rule is triggered.

Analysis Populations

The study will enroll a total of 540 participants and all transplanted participants will be included in the primary analysis according to the treatment arm and strata at time of randomization (modified intent-to-treat analysis).

Secondary analyses will examine the eligible population (EP),

Subgroup Analyses

Discuss with PIs.

Adjustment for Covariates

The primary analysis will consist of a comparison of GRFS for each treatment arm compared to the control, based on a multivariate Cox regression model adjusted for age, disease and donor type/HLA matching. The following baseline/demographic factors will also be considered to be included in the model: gender, race, ethnicity, conditioning regimen, primary diagnosis, age, Karnofsky performance score, HCT-specific comorbidity index score, disease status, donor/recipient CMV status, time to transplant, donor/recipient sex match, donor/recipient ABO

match. The choice of which baseline/demographic factors to include in the model will be determined using the stepwise variable selection procedure with a significance level of 10%.

GRFS is a composite outcome that is calculated using the onset date of acute GVHD, onset date chronic GVHD, use of immune suppression drugs date, relapse date, progression date and overall survival. If the GRFS comparison is significant (in a particular treatment arm) then these outcomes will also be compared between treatment arm and control using a multivariate Cox regression model that contains the same independent variables as in the primary analysis.

Changes to Planned Analyses

Table titles and layout are for example purposes only, and may not be the final layout or wording chosen for publications or presentations.

[Update as needed]

Analysis of Participant Demographic and Baseline Characteristics

Descriptive statistics for baseline characteristics will be presented by treatment group. Formal testing for treatment group differences of baseline characteristics will not be conducted.

Participant Compliance

A table listing significant protocol deviations will be provided by treatment group.

Software

All analyses of the main protocol will be conducted using SAS 9.4 or higher software, or R version 3.3.1 or higher.

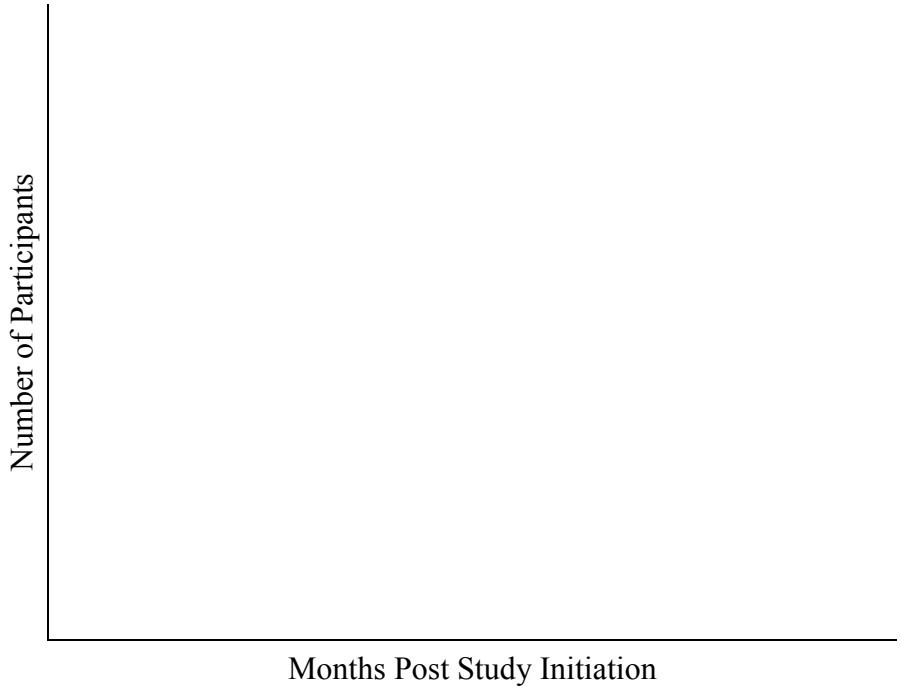
Study Operational Tables

Template tables are provided for the main analyses.

Exhibit 1203-1: Enrollment

A graph will be provided showing projected and actual accrual from study initiation to accrual closure.

Figure #. Accrual to 1203



An accrual table will provide the number and percentage of centers enrolling 0-10, 11-20, 21-40, and 40+ participants.

Table #. Accrual Information

Number of Participants Enrolled Per Center	Number of Enrolling Centers	% of Enrolling Centers
Total	XX	100.0%
1-10		
11-20		
21-40		
40+		

The number of centers which were activated but did not enroll participants will be noted separately.

Exhibit 1203-2: Participant Disposition and Follow-Up

A consort diagram will be provided showing the number of participants and compliance with each phase of the protocol. A table will be provided with descriptive statistics on length of follow-up by assigned treatment arm.

Exhibit 1203-3: Participant Baseline Characteristics

Baseline characteristics and demographics will be described by frequencies and percents for categorical covariates, and minimum, maximum, median, mean, and standard error for continuous covariates. The following covariates will be included:

- Treatment Group Assignment
- Strata (donor type/HLA matching, disease risk)
- Gender
- Ethnicity
- Race
- Patient Age
- Karnofsky performance score
- Planned RIC Regimen
- Primary Diagnosis
- Disease Status by Diagnosis
- Donor/Recipient CMV Status
- HCT-Specific Comorbidity Index Score
- Time to Transplant
- Donor/Recipient Sex Match
- Donor/Recipient ABO Match

Other baseline covariates will be summarized at the request of the investigators. P-values for treatment group comparisons will not be provided.

The following baseline and demographic characteristics will also be reported for the control population.

- Gender
- Ethnicity
- Race
- Age
- Karnofsky Performance Score
- HCT-Specific Comorbidity Index Score
- RIC Conditioning Regimen
- Primary Diagnosis
- Disease Status by Diagnosis
- Donor/Recipient CMV status
- Time to Transplant

- Donor Type/HLA matching
- Primary Diagnosis
- Donor/Recipient Sex Match
- Donor/Recipient ABO Match

Table #. Baseline Characteristics and Demographics of Participants (N = ###)

	Non-Randomized Control Arm	**Randomized Treatment Arms**			
	CIBMTR Controls (N=) N (%)	**Tac/MTX/ Bortezomib (N=) N (%)**	**Tac/MTX/ Maraviroc (N=) N (%)**	**Tac/MMF/Cy (N=) N (%)**	**Total* (N=) N (%)**
Gender					
Female					
Male					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Unknown					
Not Answered					
Race					
American Indian/Alaskan Native					
Asian					
Hawaiian/Pacific Islander					
Black or African American					
White					
More than One Race					
Other, Specify					
Unknown					

	Non-Randomized Control Arm	Randomized Treatment Arms			
	CIBMTR Controls (N=) N (%)	Tac/MTX/ Bortezomib (N=) N (%)	Tac/MTX/ Maraviroc (N=) N (%)	Tac/MMF/Cy (N=) N (%)	Total* (N=) N (%)
Not Answered					
Age, years					
Mean					
Std. Dev.					
Median (Range)					
Karnofsky Performance Score					
100					
90					
80					
70					
HCT-Comorbidity Index Score					
0					
1-2					
3 or greater					
Donor Type					
Related Donor					
Unrelated Donor					
HLA Match and Donor Type					

	Non-Randomized Control Arm	Randomized Treatment Arms			
	CIBMTR Controls (N=) N (%)	Tac/MTX/ Bortezomib (N=) N (%)	Tac/MTX/ Maraviroc (N=) N (%)	Tac/MMF/Cy (N=) N (%)	Total* (N=) N (%)
Matched Sibling					
Matched Unrelated					
Mismatched Unrelated					
Donor/Recipient CMV Status					
Pos/Pos					
Pos/Neg					
Neg/Pos					
Neg/Neg					
Donor/Recipient Sex Match					
Male/Male					
Male/Female					
Female/Male					
Female/Female					
Donor/Recipient ABO Match					
Matched					
Minor Mismatched					
Major Mismatched					
Planned RIC Regimen					

	Non-Randomized Control Arm	Randomized Treatment Arms			
	CIBMTR Controls (N=) N (%)	Tac/MTX/ Bortezomib (N=) N (%)	Tac/MTX/ Maraviroc (N=) N (%)	Tac/MMF/Cy (N=) N (%)	Total* (N=) N (%)
Fludarabine/Busulfan					
Fudarabine/Melphalan					
Fludarabine/Cyclophosphamide					
Fludarabine/TBI					
Fludarabine/Cyclophosphamide/ TBI					
Total Transplanted					
Time to Transplant from Dx, Months					
Mean					
Std. Dev.					
Median (Range)					
Primary Diagnosis					
Acute Lymphoblastic Leukemia (ALL)					
Acute Myelogeneous Leukemia (AML)					
Chronic Myelogenous Leukemia (CML)					

	Non-Randomized Control Arm	Randomized Treatment Arms			
	CIBMTR Controls (N=) N (%)	**Tac/MTX/ Bortezomib (N=) N (%)**	**Tac/MTX/ Maraviroc (N=) N (%)**	**Tac/MMF/Cy (N=) N (%)**	**Total* (N=) N (%)**
Chronic Lymphocytic Leukemia (CLL)					
Myelodysplastic Syndrome (MDS)					
Follicular Lymphoma					
Diffuse Large B-Cell Lymphoma					
Mantle Cell Lymphoma					
Hodgkin's Lymphoma					
Disease Status for Acute Leukemia Patients					
Primary Induction Failure					
First Complete Remission					
Second/Subsequent Complete Remission					
First Relapse					
Missing					
Disease Status for CML Patients					
First Chronic Phase					

	Non-Randomized Control Arm	Randomized Treatment Arms			
	CIBMTR Controls (N=) N (%)	Tac/MTX/ Bortezomib (N=) N (%)	Tac/MTX/ Maraviroc (N=) N (%)	Tac/MMF/Cy (N=) N (%)	Total* (N=) N (%)
Hematologic Complete Remission					
Accelerated Phase					
Blast Crisis					
Missing					
Disease Status for CLL Patients					
Nodular Partial Remission					
Partial Remission					
No Response/Stable Disease					
Disease Status for MDS Patients					
Complete Remission					
Hematologic Improvement					
No Response/Stable Disease					
Progression from Hematologic Improvement					
Missing					
Disease Status for Lymphoma Patients					
Partial Remission					

	Non-Randomized Control Arm	Randomized Treatment Arms			
	CIBMTR Controls (N=) N (%)	**Tac/MTX/ Bortezomib (N=) N (%)**	**Tac/MTX/ Maraviroc (N=) N (%)**	**Tac/MMF/Cy (N=) N (%)**	**Total* (N=) N (%)**
First Complete Remission					
Second/Subsequent Remission					
First Relapse					
Second/Subsequent Relapse					
Missing					

Analysis of Endpoints

EXHIBIT 1203-4: GVHD/Relapse or Progression-Free Survival by Treatment Arm

The time to this event is the time from HSCT to grade III-IV acute GVHD onset, chronic GVHD requiring systemic immunosuppressive treatment, disease relapse or progression, death by any cause, loss to follow-up or end of 1 year, whichever comes first. The treatment arms will be compared using a multivariate Cox regression model adjust for covariates chosen using a model building strategy (see adjustment for covariates section). There will be no overall type III chi-squared test used to test for differences. Rather, differences between the treatment arms and controls will be directly tested using a one-sided significance level of 0.05 (unadjusted for multiple comparisons). Kaplan-Meier curves along with 90% confidence intervals will also be constructed to estimate GRFS probabilities for each treatment arm as well as the controls.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #. Multivariate Cox PH Regression Model for GRFS (N = ###)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	Overall					#.###
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy	##	##.###	#.##		
Age (years)						
Primary Diagnosis	Overall					
	AML			1.00		
	ALL					
	CML					
	MS					
	CLL					
	NHL					
Donor type/HLA Matching	Overall					
	Matched Sibling			1.00		
	Matched Unrelated					
	Mismatched Unrelated					

Table #. One-year Kaplan-Meier Estimates (N = ###)

Group	Kaplan-Meier 1-year Estimate	90% Conf. Int.
Controls	##.#	(##.## - ##.##)
Tac/MTX/Bortezomib	##.#	(##.## - ##.##)
Tac/MTX/Maraviroc	##.#	(##.## - ##.##)
Tac/MMF/Cy	##.#	(##.## - ##.##)

Figure #. Comparison of Adjusted KM Curves for GRFS by Non-Randomized CIBMTR Controls with Randomized Treatment Groups

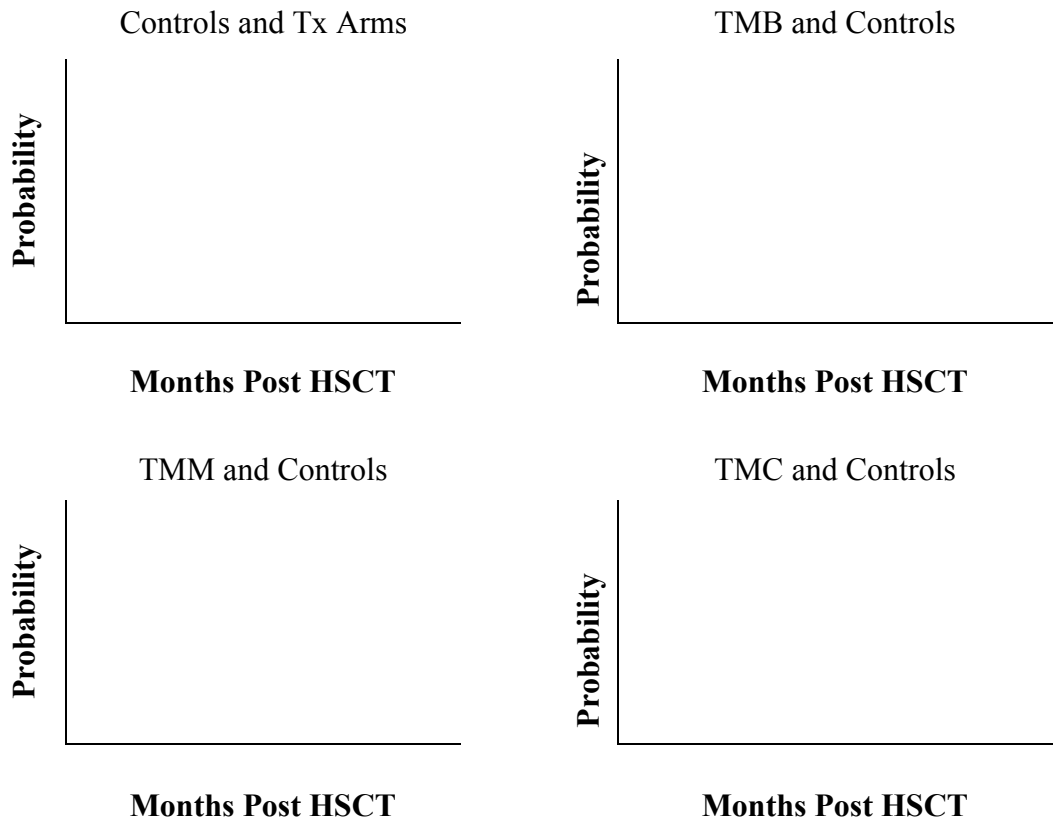


EXHIBIT 1203-5: Cumulative Incidence of Acute GVHD through Day 180 by Treatment Arm

The cumulative incidence of grade III-IV acute GVHD will only be compared to controls if a particular treatment arm compared to controls is significantly better. If there is a significant comparison then the acute GVHD comparison will be made using the same Cox regression model covariates as in the GRFS analysis. 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 as well as the controls using the cumulative incidence estimate, treating death prior to aGVHD as a competing risk.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #. Cumulative Incidence of Acute GVHD through Day 180 by Treatment Arm (N=)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	Overall					**#.###**
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy	##	##.###	#.##		#.###

Table #. Incidence of Acute GVHD by Grade and Treatment Arm (N=)

Group	Acute GVHD Cumulative Incidence Grade II-IV at 180 days	Acute GVHD Cumulative Incidence Grade III-IV at 180 days	90% Confidence Interval
Controls			
Tac/MTX/Bortezomib			
Tac/MTX/Maraviroc			
Tac/MMF/Cy			

Figure #. Cumulative Incidence of Grade II-IV Acute GVHD through Day 180

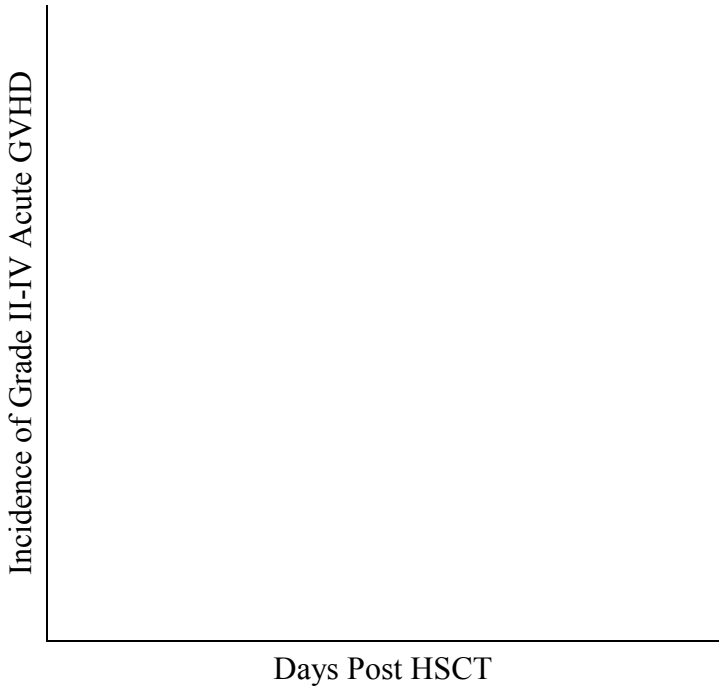


Figure #. Cumulative Incidence of Grade III-IV Acute GVHD through Day 180

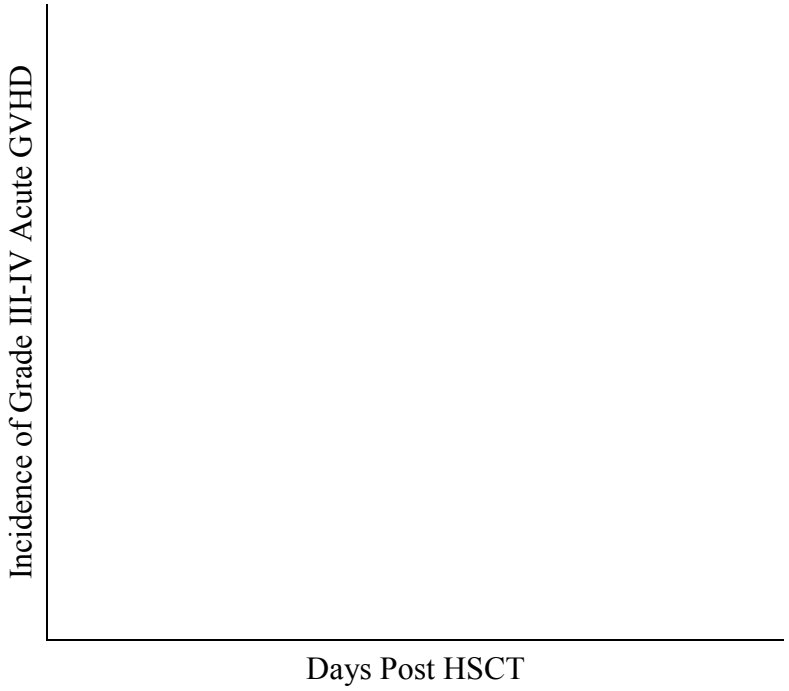


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EXHIBIT 1203-6: Cumulative Incidence of Chronic GVHD up to 1 year by Treatment Arm

The cumulative incidence of chronic GVHD will only be compared to controls if a particular treatment arm compared to controls is significantly better. If there is a significant comparison then the chronic GVHD comparison will be made using the same Cox regression model covariates as in the GRFS analysis. Incidence of chronic GVHD up to 1 year will be estimated with 90% confidence intervals for each treatment as well as the controls using the cumulative incidence estimate, treating death prior to cGVHD as a competing risk.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #. Cumulative Incidence of Chronic GVHD by Treatment Arm (N=)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	**Overall**					**#.###**
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy					

Table #. Cumulative Incidence of Chronic GVHD at 1 year by Treatment Arm (N=)

Group	Chronic GVHD Cumulative Incidence at 1 year	90% Confidence Interval
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Figure #. Cumulative Incidence of chronic GVHD

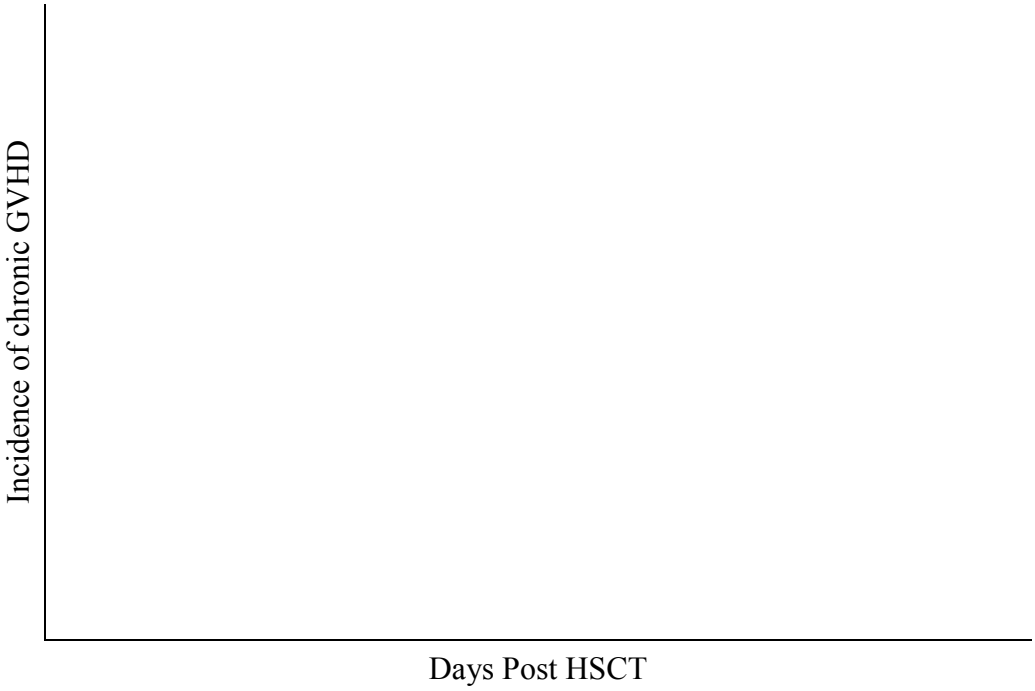


EXHIBIT 1203-7: Cumulative Incidence of Chronic GVHD Requiring Systemic Immunosuppression by Treatment Arm

TBD

EXHIBIT 1203-8: 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.

Table #. I Proportion Immunosuppression-free Survival at One Year (N=)

Group	Proportion Immunosuppression-free at 1 year	90% Confidence Interval
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Table #. Measuring Agreement between the Proportions of Patients Alive, Relapse-Free, and off Immune Suppression at One Year by GRFS Event (N=)

	Alive, relapse-free, and IS free at 1 yr		
GRFS event	**Yes**	**No**	**Kappa statistic**
No			
Yes			

EXHIBIT 1203-9: Cumulative Incidence of Relapse/Progression by Treatment Arm

The cumulative incidence of disease relapse or progression will only be compared to controls if a particular treatment arm compared to controls is significantly better. If there is a significant comparison then the disease relapse or progression comparison will be made using the same Cox regression model covariates as in the GRFS analysis. Incidence of disease relapse or progression up to 1 year will be estimated with 90% confidence intervals for each treatment as well as the controls using the cumulative incidence estimate, treating death prior to disease relapse or progression as a competing risk.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #. Cumulative Incidence of Relapse/Progression by Treatment Arm (N=)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	**Overall**					**#.###**
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy					

Table #. Cumulative Incidence at 1 year of Relapse/Progression by Treatment Arm (N=)

Group	Relapse/Progression Cumulative Incidence at 1 year	90% Confidence Interval
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Figure #. Cumulative Incidence Relapse/Progression

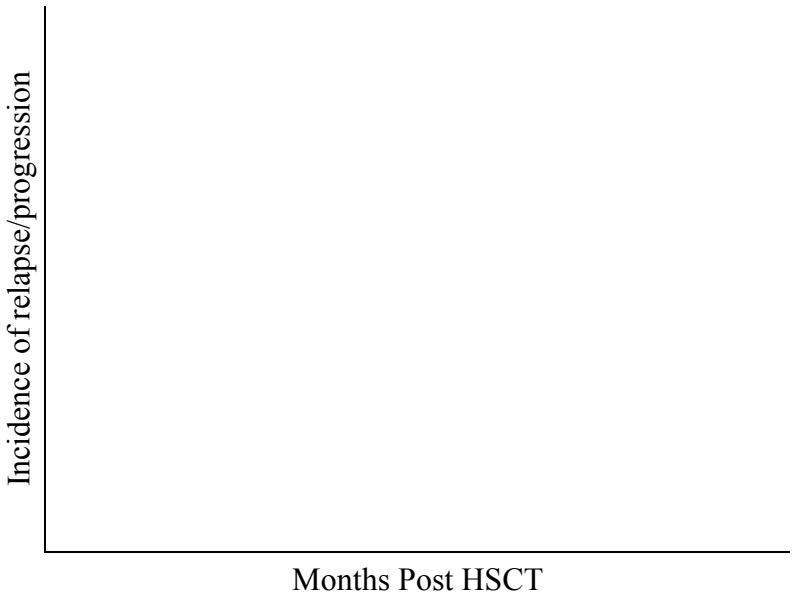


EXHIBIT 1203-10: Cumulative Incidence of Treatment-related Mortality by Treatment Arm

The cumulative incidence of treatment-related mortality will only be compared to controls if a particular treatment arm compared to controls is significantly better. If there is a significant comparison then the treatment-related mortality comparison will be made using the same Cox regression model covariates as in the GRFS analysis. Incidence of treatment-related mortality up to 1 year will be estimated with 90% confidence intervals for each treatment as well as the controls using the cumulative incidence estimate, treating disease relapse or progression as a competing risk.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #. Cumulative Incidence of Treatment-related Mortality by Treatment Arm (N=)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	**Overall**					**#.###**
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy					

Table #. Cumulative Incidence at Days 100, 180 and at 1 Year of Treatment-related Mortality by Treatment Arm (N=)

Group	Treatment-related Mortality Cumulative Incidence at day 100 [90% CI]	Treatment-related Mortality Cumulative Incidence at day 180 [90% CI]	Treatment-related Mortality Cumulative Incidence at 1 year [90% CI]
Controls			
Tac/MTX/Bortezomib			
Tac/MTX/Maraviroc			
Tac/MMF/Cy			

Figure #. Cumulative Incidence Treatment-related Mortality

EXHIBIT 1203-11: Disease-free Survival by Treatment Arm

Disease-free survival will only be compared to controls if a particular treatment arm compared to controls is significantly better. If there is a significant comparison then the disease-free survival comparison will be made using the same Cox regression model covariates as in the GRFS analysis. The model will be for the risk of death or relapse/progression. Kaplan-Meier curves will be constructed to estimate disease-free survival probabilities for each treatment arm as well as the controls.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #. Disease-free Survival by Treatment Arm (N=)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	**Overall**					**#.###**
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy					

Table #. Disease-free Survival at 1 year (N=)

Group	Kaplan-Meier Estimate of Disease-free Survival at 1 year	90% Confidence Interval
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Figure #. Disease-free Survival by Treatment Arm

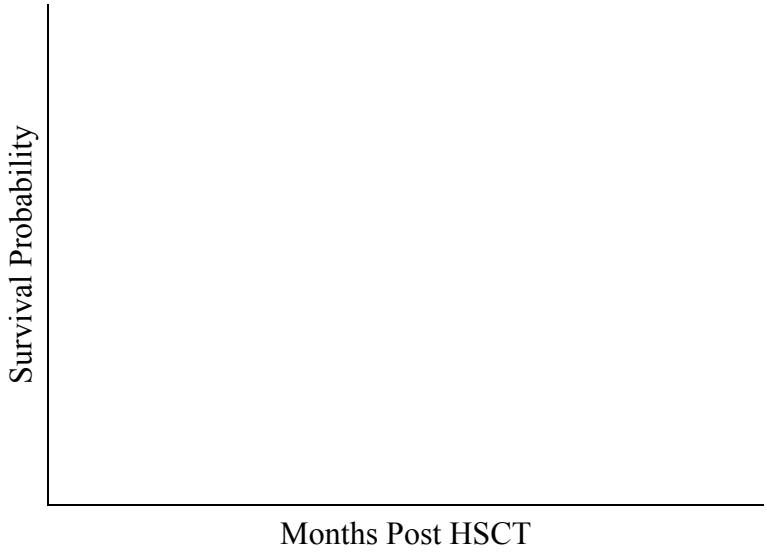


EXHIBIT 1203-12: GVHD-free Survival by Treatment Arm

GVHD-free survival will only be compared to controls if a particular treatment arm compared to controls is significantly better. If there is a significant comparison then the GVHD-free survival comparison will be made using the same Cox regression model covariates as in the GRFS analysis. The model will be for the risk of death, grade III-IV acute GVHD or chronic GVHD requiring immunosuppressive treatment. Kaplan-Meier curves will be constructed to estimate GVHD-free survival probabilities for each treatment arm as well as the controls.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #. GVHD-free Survival by Treatment Arm (N=)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	**Overall**					**#.###**
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy					

Table #. GVHD-free Survival at 1 year (N=)

Group	Kaplan-Meier Estimate of GVHD-free Survival at 1 year	90% Confidence Interval
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Figure #. GVHD-free Survival by Treatment Arm

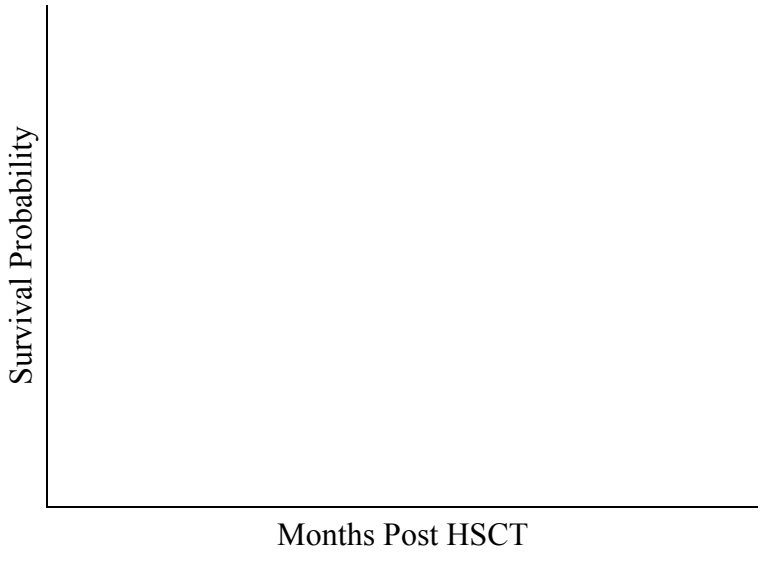


EXHIBIT 1203-13: Hematologic Recovery

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.

Table #. Probability of Neutrophil Recovery at Day 28 and 100 (N=)

Group	Probability of Neutrophil Recovery at Day 28 [90% CI]	Probability of Neutrophil Recovery at Day 100 [90% CI]
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Table #. Cumulative Incidence of Platelet Recovery at Day 60 and 100 (N=)

Group	Cumulative Incidence of Platelet Recovery at Day 60 [90% CI]	Cumulative Incidence of Platelet Recovery at Day 100 [90% CI]
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Figure #. Cumulative Incidence Neutrophil Recovery

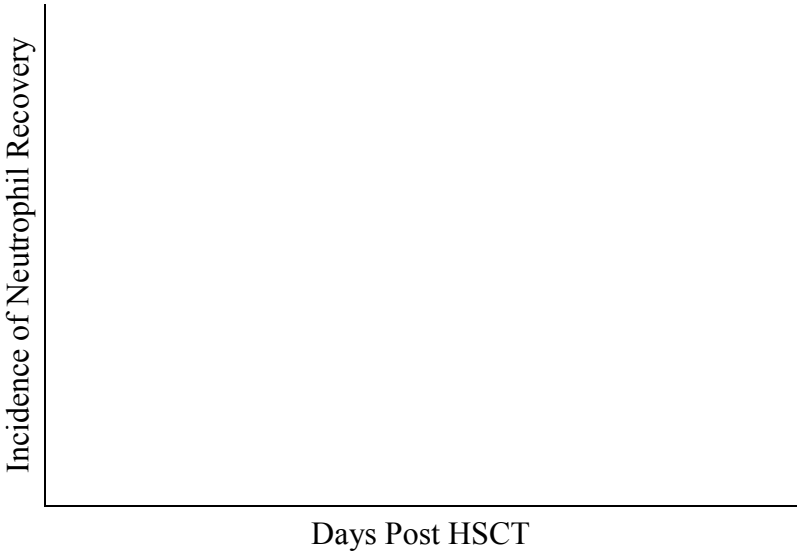


Figure #. Cumulative Incidence of Platelet Recovery

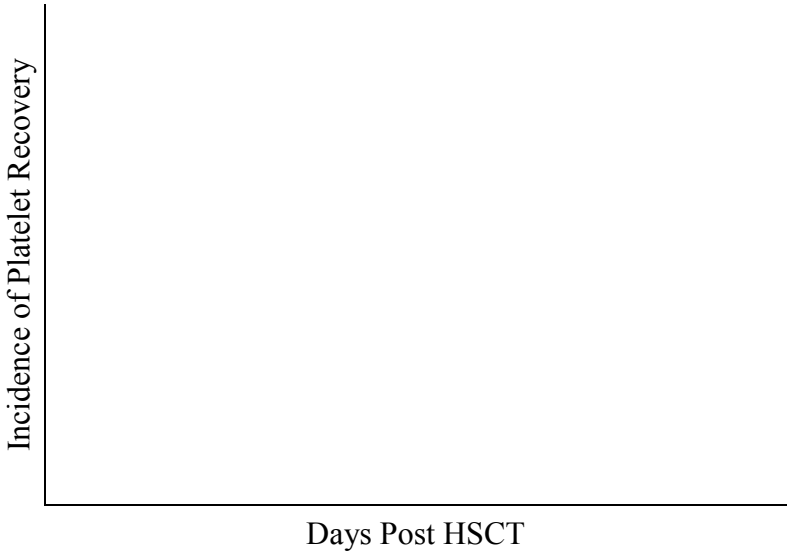


EXHIBIT 1203-14: Donor Cell Engraftment

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.

Table #. Donor Cell Engraftment (N=)

	Treatment Arm			
	Tac/MTX/Bortezomib (N=) N (%)	**Tac/MTX/Maraviroc (N=) N (%)**	**Tac/MMF/Cy (N=) N (%)**	**Total* (N=) N (%)**
Chimerism	Median (range)	Median (range)	Median (range)	Median (range)
Full (>95% Donor Cells)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Mixed (5-95% Donor Cells)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Graft Rejection (<5% Donor Cells)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Death Prior To Assessment	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Incidence of Secondary Graft Failure	**N (%)**	**N (%)**	**N (%)**	**N (%)**

EXHIBIT 1203-15: 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.

EXHIBIT 1203-16: Infection

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.

Table #. Summary of Infections by Treatment Arm (N=)

	Treatment Arm				Total
	Tac/MTX/ Bortezomib	Tac/MTX/ Maraviroc	Tac/MMF/ Cyclophosphamide	CIBMTR Controls	
	N %	N %	N %	N %	
# Patients Transplanted					
# Patients with Infections (Grade 2-3)					
# Patients with Infection Reports =1 =2 =3 =4 =5 >=6					
Total Infection Events					
Maximum Severity by Patient					

	Treatment Arm				Total
	Tac/MTX/ Bortezomib	**Tac/MTX/ Maraviroc**	**Tac/MMF/ Cyclophosphamide**	**CIBMTR Controls**	
None					
Grade 2					
Grade 3					
Infection by Type (# of patients)					
Bacterial					
Viral					
Fungal					
Protozoal					
Other					
Non-microbiologically defined Infections (# of patients)					

EXHIBIT 1203-17: Overall Survival

Overall survival will only be compared to controls if a particular treatment arm compared to controls is significantly better. If there is a significant comparison then the overall survival comparison will be made using the same Cox regression model covariates as in the GRFS analysis. The model will be for the risk of death. Kaplan-Meier curves will be constructed to estimate overall survival probabilities for each treatment arm as well as the controls. Causes of death will also be summarized by treatment arm using a frequency table.

Participants who are lost to follow-up or withdraw before the follow-up is complete will be censored at the last date available.

Table #A. Overall Survival by Treatment Arm (N=)

Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	**Overall**					**#.###**
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy					

Table #B. Overall Survival by Treatment Arm (N=)

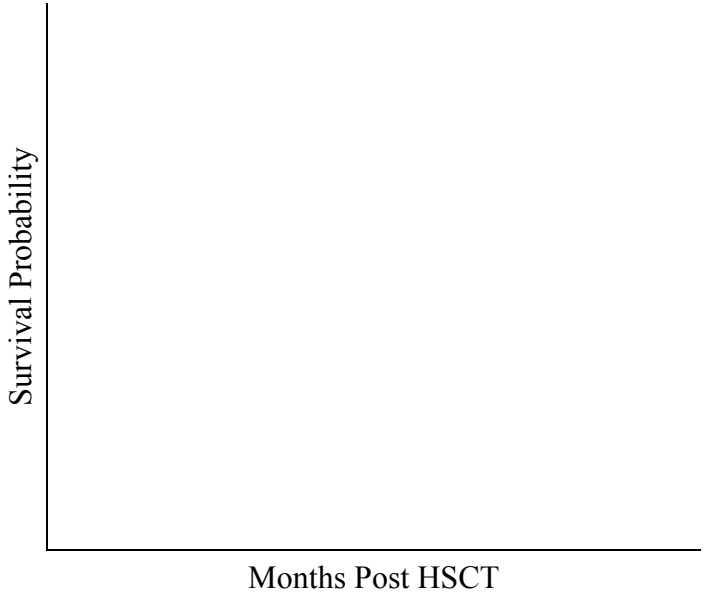
Covariates	Level	N	Coef.	HR	90% Conf. Int.	P-value
Treatment	Overall					#.###
	Controls	##	##.###	1.00	(##.## - ##.##)	#.###
	Tac/MTX/Bortezomib	##	##.###	#.##		#.###
	Tac/MTX/Maraviroc	##	##.###	#.##		#.###
	Tac/MMF/Cy	##	##.###	#.##		
Age (years)						
Primary Diagnosis	Overall					

	AML			1.00		
	ALL					
	CML					
	MS					
	CLL					
	NHL					
Donor type/HLA Matching	Overall					
	Matched Sibling			1.00		
	Matched Unrelated					
	Mismatched Unrelated					

Table #. Overall Survival At One Year (N=)

Group	Overall Survival At One Year	90% Confidence Interval
Controls		
Tac/MTX/Bortezomib		
Tac/MTX/Maraviroc		
Tac/MMF/Cy		

Figure #. Overall Survival by Treatment Arm



	Treatment Arm						Total	
	Tac/MTX/ Bortezomib		Tac/MTX/ Maraviroc		Tac/MMF/ Cyclophosphamide			
	N	(%)	N	(%)	N	(%)	N	(%)
Recurrence/Persistence								
Chronic GVHD								
Infection								
Bacterial								
Other								
Organism Not Identified								
Organ Failure								
Cardiac (Cardiomyopathy)								
Pulmonary								
Hemorrhage								
Intracranial								
Interstitial Pneumonia								
Adult Respiratory Distress Syndrome								
Other								
Total								
Total Accrual								
Total Deaths								