BMT CTN #0901 Statistical Analysis Plan (SAP)

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Finalized after the team call on 5/11/15

Protocol:

BMTCTN #0901 Full vs. RIC in MDS/AML

Protocol Synopsis:

The BMT CTN protocol #0901 titled "A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Comparing Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia" is a Phase III, multicenter trial comparing outcomes after allogeneic hematopoietic stem cell transplantation (HCT) for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) between patients receiving myeloablative conditioning (MAC) versus reduced intensity conditioning (RIC) regimens. The primary objective is to compare 18-month overall survival (OS) rates between the two groups. Secondary objectives include comparisons of disease-free survival rates, rates of transplant-related mortality, incidence of relapse, hematologic recovery, kinetics of donor cell engraftment, incidence of graft failure, incidence and severity of acute and chronic graft-versus-host disease (GVHD), rates of infectious complications, rates of ≥ grade 3 toxicities, immune reconstitution and quality of life. Per the original study design, the target sample size is 356 patients with 178 on each arm and patients will be followed for up to 18 months post-transplantation on the study.

Study Status and Publication Plan:

The study opened to accrual in June 2011 and closed accrual in April 2014 per DSMB recommendation. By the time of accrual closure, 272 patients were enrolled to the study. All patients have completed 1-year follow up by May 1, 2015. It is expected that all except 30 patients would have completed 18-month follow up by June 2015. And it is expected that the last 30 patients would complete 18-month follow up per protocol by the end of October 2015. The Endpoint Review Committee (ERC) has reviewed the primary endpoint and some secondary endpoints including relapse/progression and GVHD for all the study patients with the available data and it is expected that ERC process including data QC will be completed by early June 2015. Data lock is planned on June 5, 2015 to generate the preliminary analysis report. Analysis report will be updated in October to include the result of the primary endpoint. The analysis report will be provided to the team within 2 weeks of the data lock. The writing team will prepare a late-breaking ASH abstract (submission deadline in October 2015) and also work on the manuscript for a simultaneous publication of ASH presentation and manuscript.

Primary Endpoint and Final Analysis:

The primary endpoint of BMT CTN 0901 is overall survival (OS) at 18 months from the time of randomization. The hypothesis to be tested is that reducing the intensity of the conditioning regimen will decrease treatment-related mortality without increasing relapse so that overall survival will be improved. Participants are considered a failure if they die post randomization and time to this event is the time from randomization to death or last follow-up, whichever comes first. The primary analysis is a pointwise comparison of the survival proportions between treatment arms.

Three interim analyses on the primary endpoint were conducted and reviewed by the BMT CTN Data and Safety Monitoring Board. It was approved by DSMB that the final analysis of the primary endpoint would be conducted when all patients have completed the 18-month follow up per the protocol, as expected to be October 2015. The final boundary to be used for the final analysis was recomputed from the original study design since the study did not reach the target sample size of 356 when the accrual was closed. The actual maximum information was less than the target maximum information and the re-computation is to ensure the cumulative type I error alpha as 0.05 at the end of the study after the previously conducted interim analyses. The secondary endpoints may have minor changes using the fully mature data in October from the June data but we do not expect major changes.

Patients to Include:

The study enrolled a total of 272 patients. Two hundred and sixty-five patients received a transplant per study. All the patients will be included for the primary endpoint using intent-to-treat principle. For some secondary endpoints, only transplanted patients will be included to evaluate the post-transplant outcomes, which will be specified below for each.

Additional data source and data analysis:

Also the long-term follow-up data (beyond 18 months, up to 2 or 3 years depending on data availability) will be retrieved from CIBTMR data system to evaluate the long-term survival between the two treatment arms in an exploratory analysis.

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DATA SUMMARY:

Brief summary for the report being provided. Descriptions for each exhibit are shown below in order.

EXHIBIT 0901-1: DEMOGRAPHICS AND BASELINE CHARACTERISTICS BY TREATMENT ARM

These will be described in a table as below. Frequencies and percents for categorical covariates, using Fisher's test for treatment comparison. Median and range for continuous covariates, using T test for treatment comparison.

Table 1

	Treatment Arm			
	MAC (N=) N (%)	**RIC (N=) N (%)**	**Total (N=) N (%)**	**P-value**
Total Transplanted				
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				
Not Answered				
Age, yrs				
Mean (Std. Dev.)				
Median (range)				
18-29				
30-39				
40-49				
50-65				

Table 1 (cont'd)

	Treatment Arm			
	MAC (N=) N (%)	**RIC (N=) N (%)**	**Total (N=) N (%)**	**P-value**
Total Transplanted				
Primary Diagnosis				
Myelodysplastic Syndrome (MDS)				
Acute Myelogenous Leukemia (AML)				
Conditioning Regimen				
Busulfan/Fludarabine (Flu/Bu)				
Busulfan/Cyclophosphamide (Bu/Cy)				
Cyclophosphamide/Total Body Irradiation (Cy/TBI)				
Fludarabine/Melphalan (Flu/Mel)				
Conditioning Regimen for AML/MDS				
MDS				
Busulfan/Fludarabine (Flu/Bu)				
Busulfan/Cyclophosphamide (Bu/Cy)				
Cyclophosphamide/Total Body Irradiation (Cy/TBI)				
Fludarabine/Melphalan (Flu/Mel)				
AML				
Busulfan/Fludarabine (Flu/Bu)				
Busulfan/Cyclophosphamide (Bu/Cy)				
Cyclophosphamide/Total Body Irradiation (Cy/TBI)				
Fludarabine/Melphalan (Flu/Mel)				

Table 1 (cont'd)

	Treatment Arm			
	MAC (N=) N (%)	**RIC (N=) N (%)**	**Total (N=) N (%)**	**P-value**
Total Transplanted				
MDS WHO Classification				
Refractory Anemia				
Refractory Anemia with Ringed Sideroblasts				
Refractory Cytopenia with Multilineage Dysplasia				
Refractory Cytopenia with Multilineage Dysplasia and Ringed Sideroblasts				
Refractory Anemia with Excess Blasts-1 (5-10% blasts)				
Refractory Anemia with Excess Blasts-2 (10-20% blasts)				
Myelodysplastic Syndrome, Unclassified				
MDS Associated with Isolated Del(5q)				
AML WHO Classification				
AML with recurrent genetic abnormalities				
AML with multilineage dysplasia				
AML and myelodysplastic syndromes, therapy related				
AML, not otherwise categorized				
Antithymocyte Globulin Used as Part of Conditioning Regimen				
Yes				
No				
GVHD prophylaxis				
Tacrolimus/Methotrexate				
Sirolimus/Tacrolimus				
Tacrolimus/MMF				
Cyclosporine/MMF				
Cyclosporine/Methotrexate				
Other				

Table 1 (cont'd)

	Treatment Arm			
	MAC (N=) N (%)	**RIC (N=) N (%)**	**Total (N=) N (%)**	**P-value**
Total Transplanted				
# Non-transplant				
# Treatment Crossover				
Donor Type and HLA Match				
Sibling Donor				
Related Donor 7/8				
Related Donoe 8/8				
Unrelated Donor 7/8				
Unrelated Donor 8/8				
Karnofsky Performance Score				
100				
90				
80				
70				
Donor Source				
Peripheral Blood				
Bone Marrow				
CMV Status				
Positive				
Negative				

Table 1 (cont'd)

	Treatment Arm			
	MAC (N=) N (%)	**RIC (N=) N (%)**	**Total (N=) N (%)**	**P-value**
Total Transplanted				
Risk Status				
Standard				
High				
Unknown				
Total				
AML Risk Status				
Standard				
High				
Unknown				
Total AML patients				
MDS Risk Status				
Standard				
High				
Total MDS patients				

Notes: Risk status data will be provided by CIBMTR, AML risk status evaluated based on cytogenetics tests. MDS risk status based on IPSS score. IPSS = International Prognostic Scoring System. High-risk MDS is defined as patients with intermediate-II or high IPSS.

Other baseline data including HCT-CI, time from diagnosis to transplant will also be provided for each treatment arm, and these data also need to be retrieved from CIBTMR data system.

EXHIBIT 0901-2: OVERALL SURVIVAL BY TREATMENT ARM

The primary objective is to compare 18-month overall survival (OS) rates between the two groups. Overall survival (OS) curve will be plotted by treatment arm. OS curve will show the Kaplan-Meier estimates of OS from the time of transplant to 18 months, where death from any cause are treated as events. Kaplan-Meier estimate at 18 months be provided with 95% confidence intervals. All patients will be included for the primary endpoint. The time to this event is the time from randomization to death, loss to follow up or end of study whichever comes first.

The test statistic is the standardized difference in the Kaplan Meier estimates of overall survival, and is written as

$$Z_{KM} = \frac{\hat{S}_{RIC}(18m) - \hat{S}_{MAC}(18m)}{\sqrt{\hat{V}(\hat{S}_{RIC}(18m)) + \hat{V}(\hat{S}_{MAC}(18m))}}$$

where $\hat{S}_{MAC}(18m)$ and $\hat{S}_{RIC}(18m)$ are the product limit estimates of the survival function for the MAC and the RIC at 18 months post randomization, respectively, while $\hat{V}(\hat{S}_{MAC}(18m))$ and $\hat{V}(\hat{S}_{RIC}(18m))$ are the variances (per Greenwood's formula) of the product limit estimates at 18 months. The critical values and type I error for the interim analyses are shown in below table.

Time of Interim Analysis for DSMB Review	Information Fraction	Critical Value	Test Statistic	Type I Error	Cumulative Type I Error
Nov 2013	0.19 (0.25)	5.010	-1.13	0.00000	0.00000
April 2014	0.45 (0.59)	3.144	−2.00	0.00167	0.00167
Nov 2014	0.71 (0.93)	2.430	−2.09	0.01396	0.01563

The final boundary was computed to be ±1.964 using group sequential boundaries after accounting for the change in maximum information of the study. The final analysis will compute the test statistic using all available final information based on the 18-months survival estimates. If the |test statistic| would exceed 1.964, significance of efficacy for the primary endpoint would be reached.

Results for the primary endpoint will be summarized in the below table, besides the OS curve.

Primary Endpoint	18 month OS (95% CI)	Test Statistic	Final boundary	P-value
	MAC: RIC:			

In a secondary analysis, the 18-month OS probabilities will be compared using the adjusted OS probabilities proposed by Zhang et al. The adjusted survival probabilities are estimated using the Cox proportional hazards model stratified by treatment. Disease risk, donor type and all demographic and baseline characteristic shown to be significantly different between treatment arms will be included in the Cox model to adjust for potential imbalances. The proportional hazards assumption will be checked for all covariates. If there are indications of differential effects over time, the final model will be stratified by factors with non-proportionality. Details will be described in the multivariate analysis part.

Note/Concern: Final p-value will not be available for regular ASH abstract due to the timeline so will submit a late-breaking abstract to ASH. . Multivariate analysis will be conducted after the ASH abstract for the presentation/manuscript.

EXHIBIT 0901-3: DISEASE-FREE SURVIVAL BY TREATMENT ARM

Disease-Free Survival (DFS) will be analyzed as a secondary endpoint. Patients are considered a failure of this endpoint if they die or suffer from disease relapse or initiate non-protocol AML or MDS therapy. Per protocol, the time to this event is the time from randomization to relapse, death, initiation of non-protocol AML or MDS therapy, loss to follow up or end of study whichever comes first. Disease-free survival curves will be estimated using Kaplan-Meier estimator and 95% confidence interval will be provided. Kaplan Meier estimates of DFS at 18 months will be compared between treatment arms using pointwise comparison. Relapse before transplant will also be counted as event for this endpoint.

Results for this endpoint will be summarized in the below table, besides the DFS curve.

Secondary Endpoint: DFS	**Treatment Arm**		**P-value**
	MAC	**RIC**	
18 month DFS (95% CI)			

A secondary analysis of DFS will be performed by comparing the adjusted DFS probabilities at 18 months. This will be described in the multivariate analysis part.

EXHIBIT 0901-4: RELAPSE/PROGRESSION BY TREATMENT ARM

Incidence of relapse will be estimated using cumulative incidence function, treating death as a competing risk. Incidence of relapse will be compared between the treatment arms using Gray's test. 18-month incidence rate will be provided with the 95% confidence interval for each treatment arm. Per protocol, the time to this event is the time from randomization to relapse, loss to follow up or end of study whichever comes first.

Results for this endpoint will be summarized in the below table, besides the cumulative incidence curve.

Secondary Endpoint: Relapse	Treatment Arm		P-value
	MAC	RIC	
12 month Incidence Rate (95% CI)			
18 month Incidence Rate (95% CI)			

In a secondary analysis, relapse will be compared between arms using a Cox proportional hazards model with treatment as the main effect. This will be described in the multivariate analysis part.

EXHIBIT 0901-5: TREATMENT-RELATED MORTALITY BY TREATMENT ARM

The event is death occurring from causes other than relapse. Incidence of Treatment-related Mortality (TRM) will be estimated using cumulative incidence function, treating relapse as a competing risk. Incidence of TRM will be compared between the treatment arms using Gray's test. To be consistent with the primary endpoint, the time to this event is the time from randomization to death without relapse, loss to follow up or end of study whichever comes first.

Results for this endpoint will be summarized in the below table, besides the cumulative incidence curve.

Secondary Endpoint: TRM	Treatment Arm		P-value
	MAC	RIC	
12 month Incidence Rate (95% CI)			
18 month Incidence Rate (95% CI)			

In a secondary analysis, TRM will be compared between arms using a Cox proportional hazards model with treatment as the main effect. This will be described in the multivariate analysis part.

EXHIBIT 0901-6: PRIMARY CAUSE OF DEATH BY TREATMENT ARM

Table listing the primary causes of death (COD) by treatment arm. The ERC adjudicated COD will be used instead of the center-reported COD. Results will be shown as below:

	Treatment Arm				Total	
	MAC		RIC			
	N	(%)	N	(%)	N	(%)
Relapse/Progression						
Graft Failure						
GVHD						
Infection						
Organ Failure						
Secondary Malignancy						
Hemorrhage						
Adult Respiratory Distress Syndrome						
Accidental Death						
Other						
Total						
Total Accrual						
Total Death (Percentage %)						

EXHIBIT 0901-7: NEUTROPHIL RECOVERY BY TREATMENT ARM

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) > 500 µL for three consecutive measurements on different days. The first of the three days will be designated the day of neutrophil engraftment.

Incidence of neutrophil recovery will be estimated using cumulative incidence function, treating death as a competing risk. Incidence of neutrophil recovery will be compared between the treatment arms using Gray's test. Incidence rate will be provided with the 95% confidence interval for each treatment arm.

Results for this endpoint will be summarized in the below table, besides the cumulative incidence curve.

Secondary Endpoint: Neutrophil Recovery	Treatment Arm		P-value
	MAC	RIC	
Day 28 incidence rate (95% CI)			
Day 42 incidence rate (95% CI)			
Median time to Neutrophil Recovery			

EXHIBIT 0901-8: PLATELET RECOVERY BY TREATMENT ARM

Platelet engraftment is defined as a platelet count > 20,000/μL for three consecutive measurements over three or more days without requiring platelet transfusions. The first of the three days will be designated the day of platelet engraftment. Subjects must not have had platelet transfusions during the preceding 7 days. The time to a platelet count > 50,000/μL will be collected as well. This endpoint will be evaluated through 100 days.

Incidence of platelet recovery will be estimated using cumulative incidence function, treating death as a competing risk. Incidence of platelet recovery will be compared between the treatment arms using Gray's test. Incidence rate will be provided with the 95% confidence interval for each treatment arm. Curve for cumulative incidence of platelet recovery will be displayed for both >20K in panel (A) and >50k in panel (B)

Results for this endpoint will be summarized in the below table, besides the cumulative incidence curve.

Secondary Endpoint: Platelet Recovery	Treatment Arm		P-value
	MAC	RIC	
Platelet Recovery to >20k			

Day 60 incidence rate (95% CI)			
Day 100 incidence rate (95% CI)			
Median time to Platelet Recovery			
Platelet Recovery to >50k			
Day 60 incidence rate (95% CI)			
Day 100 incidence rate (95% CI)			
Median time to Platelet Recovery			

EXHIBIT 0901-9: GRAFT FAILURE BY TREATMENT ARM

Primary Graft Failure is defined by lack of neutrophil engraftment by 28 days, e.g. no recovery, or late recovery. Secondary graft failure is defined by initial neutrophil engraftment followed by subsequent decline in neutrophil counts < 500/μL unresponsive to growth factor therapy. P-value using Fisher's test will be provided to compare the numbers of graft failure between the two treatment arms. Results for this endpoint will be summarized in the below table.

Secondary Endpoint: Graft Failure	**Treatment Arm**				**Total**		**P-value**
	MAC		**RIC**				
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	
Primary Graft Failure ANC count did not recover to >500/μL ANC count recovered late - after Day 28							
Secondary Graft Failure							
Total Graft Failure							
Total Transplanted							

EXHIBIT 0901-10: DONOR CELL ENGRAFTMENT BY TREATMENT ARM

Donor cell engraftment will be assessed by donor recipient chimerism studies. For the purposes of this protocol, mixed chimerism will be defined as the presence of donor cells, as a proportion of the total population of < 95% in the peripheral blood or bone marrow. Full donor chimerism is defined as > 95% donor cells. Mixed or full donor chimerism will be evidence of donor engraftment. Graft rejection is defined as the inability to detect or loss of detection of greater than 5% donor cells as a proportion of the total population. Bone marrow is the preferred source for chimerism analysis. If not available, will use peripheral blood. If still not available, will use T cell. P-value using Chi-square test or Fisher's test will be provided to compare the donor chimerism between the two treatment arms.

Results for this endpoint will be summarized in the below table.

Secondary Endpoint: Donor Chimerism	**Treatment Arm**				**Total**		P-value
	MAC		**RIC**				
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	
Day 28 Assay							
Full donor chimerism (>=95% donor)							
Mixed chimerism (5%<donor<95%)							
Graft Rejection (<=5% donor)							
Death prior to Assessment							
Not done /unknown (due to relapse, secondary transplant, missing assay)							
Day 100 Assay							
Full donor chimerism (>=95% donor)							
Mixed chimerism (5%<donor<95%)							
Graft Rejection (<=5% donor)							
Death prior to Assessment							

Secondary Endpoint: Donor Chimerism	Treatment Arm				Total		P-value
	MAC		RIC				
	N	(%)	N	(%)	N	(%)	
Not done /unknown (due to relapse, secondary transplant, missing assay)							
Day 540 Assay							
Full donor chimerism (>=95% donor)							
Mixed chimerism (5%<donor<95%)							
Graft Rejection (<=5% donor)							
Death prior to Assessment							
Not done /unknown (due to relapse, secondary transplant, missing assay)							
Total Transplanted							

EXHIBIT 0901-11: ACUTE GVHD BY TREATMENT ARM

Table to summarize the maximum acute GVHD post transplant. Plots of cumulative incidence of acute GVHD grade II-IV (Panel A) and acute GVHD grade III-IV (Panel B) from the time of transplant. Provide estimates of cumulative incidence of acute GVHD grade II-IV or III-IV at day 100 (as well as Day 180) post transplant, with 95% confidence intervals. Death prior to occurrence of acute GVHD will be considered as a competing risk. Incidence of acute GVHD will be compared between the treatment arms using Gray's test.

Results for this endpoint will be summarized in the below tables, besides the cumulative incidence curves.

Maximum Acute GVHD Grade	Treatment Arm				Total	
	MAC		RIC			
	N	(%)	N	(%)	N	(%)
Grade 0, No aGVHD						

Maximum Acute GVHD Grade	Treatment Arm				Total	
	MAC		RIC			
	N	(%)	N	(%)	N	(%)
Grade I						
Grade II						
Grade III						
Grade IV						
Total Transplanted						

Secondary Endpoint: Acute GVHD	Treatment Arm		P-value
	MAC	RIC	
Day 100 Incidence Rate (95% CI) of Grade II-IV acute GVHD			
Day 100 Incidence Rate (95% CI) of Grade III-IV acute GVHD			
Day 180 Incidence Rate (95% CI) of Grade II-IV acute GVHD			
Day 180 Incidence Rate (95% CI) of Grade III-IV acute GVHD			

EXHIBIT 0901-12: CHRONIC GVHDBY TREATMENT ARM

Table to summarize the maximum grade and overall maximum severity of chronic GVHD by treatment arm. Cumulative incidence of chronic GVHD post transplant will be plotted by treatment arm. Provide incidence rate of chronic GVHD at 1-year and 18 months post transplant, with 95% confidence intervals. Death prior to occurrence of chronic GVHD will be considered as a competing risk. Incidence of acute GVHD will be compared between the treatment arms using Gray's test.

Results for this endpoint will be summarized in the below tables, besides the cumulative incidence curves.

Secondary Endpoint: Chronic GVHD	Treatment Arm		P-value
	MAC	RIC	
12 month Incidence Rate (95% CI)			
18 month Incidence Rate (95% CI)			
Maximum Grade of chronic GVHD **Limited** **Extensive**			
Maximum Severity of chronic GVHD **Mild** **Moderate** **Severe**			

EXHIBIT 0901-13: UNEXPECTED GRADES 3-5 ADVERSE EVENTS

Table listing the unexpected grades 3-5 adverse events (AEs) including onset date, severity, relationship to protocol and medical monitor assessment.

Treatment Arm	Patient ID	Center	AE Onset Date	Days Since Transplant	Adverse Event Description [Medical Monitor Description]	Event Severity	Relationship to Protocol	Effect on Therapy/ Intervention	DCC Expected ?

EXHIBIT 0901-14: CORE AND PROTOCOL-SPECIFIC TOXICITY (GRADE > 2) BY TREATMENT ARM

Use bar graphs to show the toxicity frequency within 18 months post transplant for each treatment arm and each assessment period and overall from transplant through 18 months. And use scatterplot to show the toxicity rate of each toxicity to compare the two treatment arms. Assessment time points include Day 28, Day 56, Day 100, Day 180, Day 365 and Day 540. Also use a summary table to show frequency with maximum toxicity of patients experiencing grade 3-5 toxicities and unexpected adverse events classified by system organ class.

Results for this endpoint will be summarized in the below tables, besides the bar graphs and scatterplots.

Maximum Toxicity of Grades 3-5 by System Organ Class		Treatment Arm		Total
		MAC	RIC	
System Organ Class	Grade			
Blood and lymphatic system disorders	3			
	4			
	5			
	Grades 3-5			
Cardiac disorders	3			
	4			
	5			
	Grades 3-5			
Eye disorders	3			
	4			
	5			
	Grades 3-5			
Gastrointestinal disorders	3			
	4			
	5			
	Grades 3-5			
General disorders and administration site conditions	3			
	4			
	5			
	Grades 3-5			
Hepatobiliary disorders	3			
	4			
	5			
	Grades 3-5			
Immune system disorders	3			
	4			
	5			
	Grades 3-5			
Infections and infestations	3			
	4			
	5			
	Grades 3-5			

Maximum Toxicity of Grades 3-5 by System Organ Class		Treatment Arm		Total
		MAC	RIC	
System Organ Class	**Grade**			
Injury, poisoning and procedural complications	3			
	4			
	5			
	Grades 3-5			
Investigations	3			
	4			
	5			
	Grades 3-5			
Musculoskeletal and connective tissue disorders	3			
	4			
	5			
	Grades 3-5			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3			
	4			
	5			
	Grades 3-5			
Nervous system disorders	3			
	4			
	5			
	Grades 3-5			
Psychiatric disorders	3			
	4			
	5			
	Grades 3-5			
Renal and urinary disorders	3			
	4			
	5			
	Grades 3-5			
Renal and urinary disorders/Reproductive system and breast disorders	3			
	4			
	5			
	Grades 3-5			

Maximum Toxicity of Grades 3-5 by System Organ Class		Treatment Arm		Total
		MAC	RIC	
System Organ Class	**Grade**			
Respiratory, thoracic and mediastinal disorders	3			
	4			
	5			
	Grades 3-5			
Skin and subcutaneous tissue disorders	3			
	4			
	5			
	Grades 3-5			
Surgical and medical procedures	3			
	4			
	5			
	Grades 3-5			
Vascular disorders	3			
	4			
	5			
	Grades 3-5			
Any Organ	3			
	4			
	5			
	Grades 3-5			

EXHIBIT 0901-15: INFECTION SUMMARY BY TREATMENT ARM

Table to summarize the site-reported infections by treatment arm. Number of infections per patient and maximum severity of infections per patient will be tabulated on a per patient basis. Total number of infections by type of organism will also be tabulated.

Results for this endpoint will be summarized in the below table.

	Treatment Arm		Total
	MAC	RIC	
	N %	N %	N %
# Patients Transplanted			
# Patients with Infections			
# Patients with Infection Reports =1 =2 =3 =4 =5 >=6			
Total Infection Events			
Maximum Severity by Patient None Moderate Severe Life Threatening/Fatal			
Infection by Type (# of patients) Bacterial Viral Fungal Protozoal Other			

EXHIBIT 0901-16: IMMUNE RECONSTITUTION BY TREATMENT ARM

Quantitative assessment of peripheral blood CD3, CD4, CD8, CD19 and CD56 by flow cytometric analysis will be tabulated by time period after transplant. The concentration of lymphocyte subsets will be compared between treatment arms at 100 days, 12 and 18 months from transplant using a nonparametric Mann-Whitney test. To account for potential imbalances caused by differences in survival probabilities, the concentration of lymphocyte subsets for patients who died prior to the assessment period will be assigned as zero.

Table to summarize the descriptive statistics for survivors (mean, standard deviation, median etc.) at each time point.

Box plots by treatment arm to show the distribution across various time points for each cell, corresponding to the table.

Results for this endpoint will be summarized in the below table besides the box plots.

		Treatment Arm								All				P-value
		MAC				RIC								
		N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	
CD3 (cells/µL)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
CD4 (cells/µL)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
CD8 (cells/µL)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
CD19 (cells/µL)	**Day 0**													

		Treatment Arm								All				P-value
		MAC				RIC								
		N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	
	Day 100													
	Day 365													
	Day 540													
CD56+ (cells/µL)	Day 0													
	Day 100													
	Day 365													
	Day 540													
CD45+ (cells/µL)	Day 0													
	Day 100													
	Day 365													
	Day 540													

EXHIBIT 0901-17: QUALITY OF LIFE BY TREATMENT ARM

QOL will be described and compared between the two treatment arms utilizing the FACT-BMT Trial Outcome Index (comprised of the physical, functional and BMT-specific items), the MOS-SF36 Physical Component Score (PCS) and Mental Component Score (MCS), the MDASI interference and symptom subscales, the EQ-5D utility score, and the categorical components of the occupational functioning, global quality of life, and chronic GVHD self reported scales. The questionnaires will be scored according to standard procedures. The self report questionnaires will be completed prior to transplantation and subsequently at 100 days, 12 months, and 18 months from randomization or until death. HQL will be described and compared between the two treatment arms over time.

Differences in quality of life will be assessed in several ways. For the descriptive analysis, only QOL scores for survivors at specific time points will be compared between treatment arms using simple T-tests. In the primary analysis, linear mixed models will be used to assess differences in QOL scores over time and to explore covariates associated with QOL in survivors. Additional secondary analysis to account for differences in survival rates between treatment groups will be performed using the Integrated Quality Adjusted Survival. The Integrated Quality Adjusted Survival approach aggregates QOL over the entire period of observation. Finally, if missing data occur for survivors, mechanism and patterns of missing data will be analyzed. In addition, the joint mixed-effects model for informatively censored longitudinal data developed by Schluchter will be explored to identify clinical events associated with changes in QOL overtime.

Results for this endpoint from exploratory analyses will be summarized in the below table.

HQL		Treatment Arm								All				P-value
		MAC				RIC								
		N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	
Global QOL														
Overall feeling	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
Overall health	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
FACT BMT														
Physical Well-Being (7 Items)	**Day 0**													
	Day 100													
	Day 365													

HQL		Treatment Arm								All				P-value
		MAC				RIC								
		N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	
	Day 540													
Social / Family Well-Being (7 Items)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
Emotional Well-Being (6 Items)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
Functional Well-Being (7 Items)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
FACT BMT Concerns (10 Items)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
FACT-G Total (27 Items)	**Day 0**													
	Day 100													
	Day 365													

HQL		Treatment Arm								All				P-value
		MAC				RIC								
		N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	
	Day 540													
FACT-BMT Total (37 Items)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
FACT-BMT Trial Outcome Index (24 Items)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
SF36														
Physical Component Score (PCS)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
Mental Component Score (MCS)	**Day 0**													
	Day 100													
	Day 365													
	Day 540													
MDASI interference and symptom subscales	**Day 0**													
	Day 100													

HQL		Treatment Arm								All				P-value
		MAC				RIC								
		N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	N	Mean	Std Dev	Median	
	Day 365													
	Day 540													
EQ-5D utility score	Day 0													
	Day 100													
	Day 365													
	Day 540													

Notes/Concerns: For ASH abstract, will only do exploratory analyses for the abstract. So the final results from multivariate analysis will be provided until the final dataset available to prepare for the manuscript and ASH presentation, or even a secondary paper.

EXHIBIT 0901-18: ACCRUAL OVER TIME

Table showing accrual numbers for each participating center, actual accrual versus projected accrual number.

EXHIBIT 0901-19: SIGNIFICANT PROTOCOL DEVIATIONS

Table listing the cumulative significant protocol deviations occurred during the study, including transplant center, patient ID, description of the protocol deviations.

EXHIBIT 0901-20: MULTIVARIATE ANALYSIS FOR PRIMARY AND SECONDARY ENDPOINTS

Will run COX model for the primary endpoint and some secondary endpoints like OS, DFS, relapse and TRM in multivariate analyses.

Disease risk, donor type, primary disease, conditioning regimen and all demographic and baseline characteristic shown to be significantly different between treatment arms will be likely included in the Cox model to adjust for potential imbalances. A gender effect will be examined as well as interaction with the treatment arm. The proportional hazards assumption will be checked for all covariates. Treatment arm will be forced to be included in the COX model. Backward selection will be used for model building.

Notes/Concerns: For ASH abstract, will not do any multivariate analyses. Multivariate models will not be run until final dataset is closed, which is expected to be in October 2015. So the final results from multivariate analysis will be provided for the manuscript and ASH presentation.

EXHIBIT 0901-21: SUBGROUP ANALYSES OF PRIMARY ENDPOINT BY CONDITIONING REGIMEN AND DISEASE

We will utilize the data on conditioning regimen choice pre-specified prior to randomization to examine specific myeloablative conditioning regimen comparisons on the primary endpoint - OS. First we will summarize the 6 different combinations of myeloablative and RIC regimen choices that a center might pre-specify prior to randomization as in the table below:

	Treatment Arm (per randomization)		
Prespecified regimen pair (MAC vs. RIC)	**MAC (n, %)**	**RIC (n, %)**	**Total (n, %)**
Bu/Flu vs. Flu/Bu			
Bu/Flu vs. Flu/Mel			
Bu/Cy vs. Flu/Bu			
Bu/Cy vs. Flu/Mel			
Cy/TBI vs. Flu/Bu			
Cy/TBI vs. Flu/Mel			

Next we will do a forest plot of the difference in survival probabilities at 18 months for each pre-specified regimen pair, showing the difference and the confidence interval for each regimen pair. We will formally assess interaction between conditioning intensity and choice of regimen pairs by testing whether the differences in survival probabilities between MAC and RIC are consistent across all regimen pairs.

We will also utilize the data on primary disease to examine if the primary outcome – OS varies by disease (MDS or AML). We will estimate survival probabilities at 18 months for each disease with each intensity, will show the difference in survival in a forest plot, and will formally test for interaction between conditioning intensity and disease.

Disease	**Primary Endpoint: OS**	**Treatment Arm**		**P-value**
		MAC	**RIC**	
MDS patients	18 month OS (95% CI)			
AML patients	18 month OS (95% CI)			

Note: Analyses in this exhibit are exploratory analyses (not defined in the protocol) and patients number in some groups may be relatively small.

Additional exploratory subgroup analyses by patient age, performance score, cytogenetics risk and comorbility will also be conducted in a similar manner.