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Title page

Title: Association between the choice of the conditioning regimen and outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis

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DATA USE STATEMENT

CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

Conflict of interest:

Dr. Guru Subramanian Guru Murthy reports the following outside the submitted work - Cardinal Health (Honoraria), TG Therapeutics (Advisory board), Gilead (Consultancy), Cancerexpert now (Consultancy), Qessential (Consultancy), Techspert (Consultancy), DAVA Oncology (Honoraria), and Curio science (Honoraria), all outside the submitted work.

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Dr. Grunwald reports having worked as a PI with multiple pharmaceutical sponsors and as both consultant and PI for Incyte (manufacturer of ruxolitinib).

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Dr. Rizzieri reports as a consultant and on speaker bureau for Incyte (makers of ruxolitinib used for treatment).

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ABSTRACT

Allogeneic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment for myelofibrosis. However, the optimal conditioning regimen either with reduced intensity conditioning (RIC) or myeloablative conditioning (MAC) is not well known. Using the Center for International Blood and Marrow Transplant Research database, we identified adults aged ≥18 years with myelofibrosis undergoing allo-HCT between 2008-2019 and analyzed the outcomes separately in the RIC and MAC cohorts based on the conditioning regimens used. Among 872 eligible patients, 493 underwent allo-HCT using RIC (Fludarabine/busulfan=166, Fludarabine/melphalan=327) and 379 using MAC (Fludarabine/busulfan=247, Busulfan/cyclophosphamide=132). In multivariable analysis with RIC, Fludarabine/melphalan was associated with inferior overall survival (HR 1.80, 95% CI 1.15-2.81, p=0.009), higher early non-relapse mortality (HR 1.81, 95% CI 1.12-2.91, p=0.01) and higher acute graft versus host disease (GVHD) (grade II-IV- HR 1.45, 95% CI 1.03-2.03, p=0.03; grade III-IV HR 2.21, 95%CI 1.28-3.83, p=0.004) compared to Fludarabine/busulfan. In the MAC setting, Busulfan/cyclophosphamide was associated with a higher acute GVHD (grade II-IV HR 2.33, 95% CI 1.67-3.25, p<0.001; grade III-IV HR 2.31, 95% CI 1.52-3.52, p<0.001) and inferior GVHD-free relapse-free survival (GRFS) (HR 1.94, 95% CI 1.49-2.53, p<0.001) as compared to Fludarabine/busulfan. Hence, our study suggests that Fludarabine/busulfan is associated with better outcomes in RIC (better overall survival, lower early non-relapse mortality, lower acute GVHD) and MAC (lower acute GVHD and better GRFS) in myelofibrosis.

Introduction:

Myelofibrosis is a chronic myeloproliferative neoplasm arising either de-novo (primary) or secondary to antecedent essential thrombocytosis or polycythemia vera. Despite the recent advances in disease biology and treatment options such as Janus Activating Kinase (JAK) inhibitors, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only potentially curative option [1-3]. The availability of reduced intensity conditioning (RIC) and the choice of donors have expanded the scope of allo-HCT for these patients who are often older adults [4]. While several factors influence outcomes of allo-HCT, conditioning intensity and conditioning regimen are aspects that could be tailored to improve the outcomes. Currently, both myeloablative conditioning (MAC) and RIC platforms are available for allo-HCT in myelofibrosis [5-12]. A large study from the European Group for Blood and Marrow Transplant (EBMT) compared the outcomes of allo-HCT with RIC versus MAC in myelofibrosis and demonstrated comparable results with both approaches, but better graft-versus-host disease (GVHD)-and relapse-free survival (GRFS) with MAC [9]. However, the optimal conditioning regimen either with RIC or MAC is not well known. While some studies have previously compared different RIC regimens with varying results [10-12], similar comparative studies with MAC are lacking and no studies have demonstrated a survival difference based on the conditioning regimen. Hence, we sought to determine the outcomes of allo-HCT for myelofibrosis based on the choice of the conditioning regimen, separately with RIC and MAC.

Methods:

Study objective

Our objectives were to compare the overall survival, disease free survival, non-relapse mortality, relapse, incidence of acute GVHD, chronic GVHD and GRFS based on the choice of the conditioning regimen used with RIC or MAC.

Data source

CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program. It comprises a voluntary network of more than 450 transplantation centers worldwide that contribute data on consecutive allo-HCT to a centralized statistical center [13]. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Patients provided written informed consent for research. The institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program approved this study.

Study population

Adults aged ≥18 years with a diagnosis of myelofibrosis (chronic phase) who underwent allo-HCT between the period 2008-2019 and data reported to the CIBMTR were identified. The cohort was then selected to focus on the most common conditioning regimens used in RIC [Fludarabine/busulfan vs. Fludarabine/melphalan] and MAC [Fludarabine/busulfan vs. Busulfan/cyclophosphamide] setting (Supplemental Figure S1). Conditioning regimens were classified in the CIBMTR dataset based on prior published data [14, 15]. The donor groups included matched related donors, 8/8 (HLA-A, -B, -C and -DRB1) matched unrelated donors and 7/8 matched unrelated donors. Key exclusion criteria were allo-HCT from haploidentical donor, syngeneic donor, cord

blood, and ex-vivo T-cell depleted or CD34 selected grafts. In addition, 51 patients in Fludarabine/busulfan MAC group who received post-transplant cyclophosphamide (post-Cy) were excluded as there were no such corresponding patients in Busulfan/cyclophosphamide MAC group.

Statistical analysis:

Baseline characteristics were summarized using descriptive statistics with median and range for continuous variables and proportions for categorical variables. Outcomes were compared separately in RIC and MAC cohorts based on the conditioning regimens. Definitions of the outcomes are provided in Supplement. Cumulative incidence estimates were calculated for competing risks outcomes including acute GVHD, chronic GVHD, non-relapse mortality, and relapse. Kaplan-Meier method was used to estimate the probabilities for survival. To evaluate for other relevant factors that could influence the outcomes, multivariable Cox regression analysis was used (see below for the variables included). The proportional hazards assumption was examined and covariates that violate the proportional hazards assumption were added as time-dependent covariates. In the absence of binary endpoints, hazard ratio (HR) and confidence limits were reported. A pairwise comparison within the non-reference groups was also performed in multivariable models to demonstrate their effect and shown as contrasts. Variables included in multivariable analysis were age, race/ethnicity, disease subtype (primary vs. post ET or PV), dynamic international performance scoring system (DIPSS) score, hematopoietic cell transplantation comorbidity index (HCT-CI), karnofsky performance scale (KPS), systemic symptoms, splenic radiation, splenomegaly, interval from diagnosis to allo-HCT, ruxolitinib use pre-transplant, donor-

recipient HLA-match, gender match, CMV match, stem cell source, GVHD prophylaxis (tacrolimus based vs. cyclosporine based vs. post-Cy vs. others), use of antithymocyte globulin (ATG)/alemtuzumab, and year of transplant. A stepwise selection method was used to identify the final model with a significance level of 0.05 and only variables reaching that statistical significance were shown. In addition, adjusted univariate estimates were provided for outcomes that were significantly associated with conditioning regimen. Fine and Gray model was used for analysis of non-relapse mortality, GVHD and relapse [16]. Center effect was tested using the score test proposed by Commenges and Andersen and marginal Cox models were used for further adjustments [17]. Center effect was noted to be significant only for chronic GVHD and was adjusted accordingly. Missing category was included in the models as one group to avoid loss of data and power [18]. All analyses were performed at a two-sided significance level of 0.05 using SAS 9.4 (SAS Institute, Cary, NC).

Results:

Baseline characteristics

Of 872 eligible patients, 493 underwent allo-HCT using RIC (Fludarabine/busulfan=166, Fludarabine/melphalan=327) and 379 using MAC (Fludarabine/busulfan=247, Busulfan/cyclophosphamide=132). Key baseline characteristics of the patients are summarized (Table 1, Supplemental Tables S1, S2; unadjusted univariate estimates in Tables S3, S4). In the RIC cohort, compared to Fludarabine/busulfan patients, Fludarabine/melphalan patients had longer median interval from diagnosis to allo-HCT (37 vs. 22 months, p=0.02), lower proportion with antithymocyte globulin/alemtuzumab

use (25% vs 52%, p<0.01), and higher proportion with pre-transplant ruxolitinib use (61% vs 49%, p=0.03). In MAC cohort, compared to Fludarabine/busulfan patients, Busulfan/cyclophosphamide patients had younger age (median age 55 vs 60 years p<0.01), higher proportion with low-intermediate risk disease (61% vs 54%, p=0.03), higher proportion with bone marrow graft (12% vs 4%, p<0.01), lower proportion with antithymocyte globulin/alemtuzumab use (5% vs 45%, p<0.01), and lower proportion with pre-transplant ruxolitinib use (43% vs 59%, p<0.01). Median follow-up of the cohort was 26 (3-150) months.

Overall survival

In multivariable analysis (Table 2), overall survival in RIC setting was significantly worse with Fludarabine/melphalan (HR 1.80, 95%CI 1.15-2.81, p=0.009, 2-year adjusted overall survival- 54.4% vs. 60.9%) as compared to Fludarabine/busulfan (Figure 1). In the MAC setting, overall survival was not significantly different between based on the conditioning regimen (Busulfan/cyclophosphamide- HR 1.14, 95%CI 0.75-1.71, p=0.54) (Figure 2). Other factors significantly associated with overall survival were donor-recipient HLA- match (higher risk with unrelated donors in MAC) and the use of antithymocyte globulin/alemtuzumab (higher risk in RIC) (Supplemental Tables S5, S6).

Disease free survival

In multivariable analysis (Table 2), disease free survival was not significantly different based on the conditioning regimen used in RIC (Fludarabine/melphalan- HR 1.03, 95%CI 0.77-1.38, p=0.85) or MAC (Busulfan/cyclophosphamide- HR 1.03, 95%CI 0.77-1.38, p=0.83) settings (Supplemental Figures S2 and S3). Other factors significantly

associated with disease free survival were Karnofsky performance status (higher risk with lower score in MAC) and pre-transplant ruxolitinib use (higher risk in MAC) (Supplemental Tables S5 and S6).

Non-relapse mortality

In RIC setting, there was a significantly higher risk of early non-relapse mortality with Fludarabine/melphalan as compared to Fludarabine/busulfan (17.4% vs. 4.3%, HR 1.81, 95%CI 1.12-2.91, p=0.01). Beyond 6 months the risk of non-relapse mortality was low with fludarabine/melphalan (HR 0.46, 95%CI 0.23-0.91, p=0.02) (Table 2, Supplemental Figure S4) (Cut-off of 6 months was chosen due to non-proportional hazard). No significant differences in non-relapse mortality were seen with MAC based on the conditioning regimens (Busulfan/cyclophosphamide- HR 1.36, 95%CI 0.83-2.21, p=0.22) (Supplemental Figure S5). The other factor significantly associated with non-relapse mortality was donor-recipient HLA-match (higher risk with unrelated donors in MAC) (Supplemental Tables S5, S6).

Relapse

The risk of relapse was not significantly different based on the conditioning regimen used in RIC or MAC (RIC- Fludarabine/melphalan HR 0.85, 95%CI 0.64-1.12, p=0.25; MAC - Busulfan/cyclophosphamide HR 0.92, 95%CI 0.64-1.32, p=0.65) (Supplemental Figures S6, S7, Supplemental Tables S5, S6). Other factors significantly associated with relapse were karnofsky performance status (higher risk with poor score in MAC), pre-transplant ruxolitinib use (higher risk in MAC) and year of transplant (higher risk with recent period in RIC).

GVHD

In the RIC setting, Fludarabine/melphalan was associated with a significantly higher risk of acute GVHD grade II-IV (Fludarabine/melphalan 40%, Fludarabine/busulfan 35.3%, HR 1.45, 95%CI 1.03-2.03, p=0.03) and grade III-IV (Fludarabine/melphalan 21.8%, Fludarabine/busulfan 12.1%, HR 2.21, 95%CI 1.28-3.83, p=0.004) (Supplemental Figures S8, S9). In the MAC setting, Busulfan/cyclophosphamide was associated with a significantly higher risk of acute GVHD grade II-IV (Busulfan/cyclophosphamide 58.9%, Fludarabine/busulfan 34.4%; HR 2.33, 95%CI 1.67-3.25, p<0.001) and grade III-IV (Busulfan/cyclophosphamide 32.6%, Fludarabine/busulfan 11.9%; HR 2.31, 95%CI 1.52-3.52, p<0.001) (Supplemental Figures S10, S11). Chronic GVHD was significantly associated with donor-recipient HLA-match (higher risk with 7/8 matched unrelated donors in RIC) and pre-transplant ruxolitinib use (lower risk in MAC), but not by the conditioning regimen (Supplemental Tables S5, S6).

GRFS:

In the RIC setting, GRFS was not significantly different between Fludarabine/busulfan and Fludarabine/melphalan (HR 1.11, 95%CI 0.90-1.35, p=0.32) (Supplemental Figure S12). However, in the MAC setting, Busulfan/cyclophosphamide was associated with significantly inferior GRFS (HR 1.94, 95%CI 1.49-2.53, p<0.01) (2-year adjusted probability 5.1% vs. 19.4%) as compared to Fludarabine/busulfan (Table 2, Figure 3). Other factors significantly associated with GRFS included recipient age (in MAC) and donor-recipient HLA-match (higher risk with unrelated donors in MAC) (Supplemental Tables S5 and S6).

Engraftment:

The rates of neutrophil engraftment (30 days) were significantly better with Fludarabine/busulfan in RIC (Fludarabine/busulfan 95.1% vs. Fludarabine/melphalan 92.4%, p=0.006) and MAC (Fludarabine/busulfan 95.2% vs. Busulfan/cyclophosphamide 87.2%, p=0.02). The rate of platelet engraftment (100 days) was better with Fludarabine/busulfan in RIC setting (RIC - Fludarabine/busulfan 84.4% vs Fludarabine/melphalan 73.9%, p<0.001; MAC - Fludarabine/busulfan 86.1% vs. Busulfan/cyclophosphamide 83.7%, p=0.27).

Additional analyses:

In the RIC cohort, we investigated whether the outcomes differed based on the dose of melphalan (100 vs 140mg/m^2) used in Fludarabine/melphalan group. As shown in Supplemental Table S7, the outcomes did not significantly vary based on the dose of melphalan (shown as contrasts between melphalan 100 vs 140mg/m^2).

Discussion:

Our study highlights the significant differences in outcomes of allo-HCT for myelofibrosis based on the choice of the conditioning regimen. Fludarabine-busulfan conditioning was associated with superior overall survival, lower early non-relapse mortality and lower acute GVHD (all with RIC), and lower acute GVHD and superior GRFS with MAC. A key aspect of conditioning strategy is its ability be tailored in order to improve the outcomes. Events such as non-relapse mortality and GVHD that affect the morbidity and mortality after allo-HCT could be influenced by the conditioning strategy and efforts to minimize

these complications are vital to improve the long-term success. Although RIC and MAC platforms are clinically decided based on factors such as age, comorbidities, performance status, and other aspects that are often not modifiable, our results illustrate the influence of common conditioning regimens used in these settings and provides valuable information for choosing the appropriate regimen in clinical practice.

Prior retrospective studies have evaluated the impact of conditioning intensity and regimen in myelofibrosis, albeit with variable results and certain key differences compared to our study [5-12]. A study by Robin et al. included 160 patients with myelofibrosis from 2 European centers [Paris (Fludarabine-Busulfan) or Hamburg (Fludarabine-Melphalan)], but with antithymocyte globulin given for all patients who received Fludarabine-Busulfan conditioning [11]. Another CIBMTR study by Gupta et al. included only patients with primary myelofibrosis and RIC (Fludarabine-TBI vs Fludarabine-Melphalan vs. Fludarabine-Busulfan) between 1997-2010 with a relatively younger patient population (median age 55 years) [10]. Hence, the differences in the study population, the nature of the cohort (registry vs. individual center based), treatment received and variations in time period included could have contributed to the differences in results noted between the current study and prior studies. To date, prospective studies of conditioning regimen in myelofibrosis are single arm or comparative studies with smaller sample size [19, 20, 21]. For example, a phase II study by Patriarca et al. prospectively compared fludarabine-busulfan and fludarabine-thiotepa for allo-HCT in sixty patients with myelofibrosis and showed similar outcomes with both these regimens [21]. Hence, our study addresses the knowledge gap in this area using a

larger dataset with a comparison of commonly reported conditioning regimens. Unfortunately, due to the limited number of patients receiving other less common conditioning regimens such as fludarabine-thiotepa, these regimens could not be compared in our study. Additionally, given the results of a large EBMT study showing no difference in overall survival between MAC and RIC [9], we did not compare the outcomes of MAC versus RIC in our analysis which also helped to minimize the heterogeneity in comparisons.

Apart from the conditioning regimen, factors such as donor-recipient HLA-match, performance status and use of antithymocyte globulin/alemtuzumab influenced the outcomes similar to prior studies. The imbalances in baseline characteristics were adjusted in multivariable models and there were no significant interactions noted between the baseline characteristics and main effect (conditioning regimen). Antithymocyte globulin/alemtuzumab was associated with worse overall survival in RIC and was more commonly used with Fludarabine/busulfan regimens. Despite this, an early survival advantage was noted with Fludarabine/busulfan in RIC. The association between the outcomes and factors such as the route of busulfan administration (oral vs. intravenous, targeted vs. non-targeted; data not shown) and the dose of melphalan (in RIC) were also investigated and none was found. In MAC, ruxolitinib prior to allo-HCT was associated with higher risk of relapse, inferior disease-free survival, higher risk of acute GVHD and lower risk of chronic GVHD. Although prior studies indicate the feasibility and safety of ruxolitinib therapy prior to allo-HCT [22, 23], we could not evaluate the possible mechanisms behind these differences due to limited information on the

duration, dose, response, and other aspects of ruxolitinib therapy. Other factors such as the role of splenectomy, spleen size or splenic radiation therapy and their association with outcomes could not be evaluated due to the small number of patients with those interventions.

Despite the large sample size, our study is limited by the retrospective design and lack in-depth information on factors such as genomic mutations and therapies for myelofibrosis given pre- and post- allo-HCT that could affect the outcomes [24, 25]. The lack of detailed information on genomic mutations precluded further analyses and calculation of molecular risk scores (such as MIPSS70, MYSEC-PM etc). For example, study by Gagelman et al. investigated the prognostic significance of somatic mutations in myelofibrosis patients undergoing allo-HCT and identified that ASXL1 and non-CALR/MPL driver mutations were associated with poor outcomes. This study also established a prognostic model with variables such as patient age, performance status, white blood count, platelet count, HLA-mismatched donor and molecular mutations. However, due to the lack of information on these aspects, we could not apply this scoring system in our study [24]. We also could not assess the reasons behind the choice of individual conditioning regimens used for these patients, understanding that centers could have their preferences while choosing conditioning regimens. However, we evaluated for center-effects in multivariable analyses and adjustments were made accordingly. As our study mainly focused on patients with chronic phase myelofibrosis, the role of conditioning strategy in advanced phase disease (accelerated/blast phase) was not evaluated. Due to the nature of the GVHD reporting in the dataset, chronic

GVHD was analyzed as a whole outcome without further stratification (mild, moderate, severe).

Our study demonstrates that Fludarabine/busulfan based conditioning is associated with superior overall survival, lower early non-relapse mortality, and lower acute GVHD with RIC and lower acute GVHD and superior GRFS with MAC. The results provide valuable information for tailoring the conditioning strategies to minimize non-relapse mortality and GVHD and improve survival. Prospective comparative studies are warranted to confirm these results and identify the ideal conditioning regimen in myelofibrosis.

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Table 1: Key Baseline characteristics

Characteristic	Reduced intensity conditioning			Myeloablative conditioning		
	Flu/Bu (n=166)	Flu/Mel (n=327)	P-Value	Flu/Bu (n=247)	Bu/Cy (n=132)	P-value
Age	63 (44-75)	63 (38-78)	0.88	60 (27-74)	55 (24-67)	<0.01*
Disease type			0.22			0.85
Primary	132 (80)	242 (74)		191 (77)	100 (76)	
Post ET	14 (8)	45 (14)		20 (8)	13 (10)	
Post PV	20 (12)	40 (12)		36 (15)	19 (14)	
Median time from diagnosis to HCT (months, range)	22 (3-393)	37 (3-594)	0.02*	25 (2-490)	38 (3-377)	0.41
DIPSS Score - no. (%)			0.07			0.03*
Low/Intermediate-1	71 (43)	107 (33)		134 (54)	80 (61)	
Intermediate-2/High	69 (42)	168 (51)		93 (38)	34 (26)	
Missing	26 (16)	52 (16)		20 (8)	18 (14)	
Donor type - no. (%)			0.75			0.15
HLA-identical sibling	48 (29)	94 (29)		79 (32)	53 (40)	
8/8-matched unrelated	107 (64)	205 (63)		142 (57)	62 (47)	
7/8 matched unrelated	11 (7)	28 (9)		26 (11)	17 (13)	
ATG/Alemtuzumab use - no. (%)			<0.01*			<0.01*
No	79 (48)	246 (75)		135 (55)	125 (95)	
Yes	87 (52)	81 (25)		112 (45)	7 (5)	
Graft type - no. (%)			0.84			<0.01*
Bone marrow	6 (4)	13 (4)		11 (4)	16 (12)	
Peripheral blood	160 (96)	314 (96)		236 (96)	116 (88)	
Pre-transplant ruxolitinib			0.03*			<0.01*
No	84 (51)	125 (38)		101 (41)	75 (57)	
Yes	82 (49)	201 (61)		146 (59)	57 (43)	
Missing	0	1		0	0	

*p<0.05-significant

Flu-Fludarabine; Bu-Busulfan; Mel- Melphalan; Cy- Cyclophosphamide; ET- Essential thrombocytosis; PV- polocythemia vera; HCT-hematopoietic cell transplantation; DIPSS- dynamic international prognostic scoring system; ATG – antithymocyte globulin

Table 2: Multivariable analysis of outcomes based on conditioning regimen

Reduced intensity conditioning				**Myeloablative conditioning**			
Outcome	**HR**	**95% CI**	**p-value**	**Outcome**	**HR**	**95% CI**	**p-value**
Overall survival**				**Overall survival**			0.54
≤ 6 months			0.009*	Flu/Bu	1.00	Ref.	
Flu/Bu	1.00	Ref.		Bu/Cy	1.14	0.75-1.71	
Flu/Mel	1.80	1.15-2.81					
> 6 months							
Flu/Bu	1.00	Ref.	0.35				
Flu/Mel	0.82	0.53-1.26					
Disease free survival**				**Disease free survival**			0.83
≤ 6 months				Flu/Bu	1.00	Ref.	
Flu/Bu	1.00	Ref.	0.85	Bu/Cy	1.03	0.77-1.38	
Flu/Mel	1.03	0.77-1.38					
> 6 months							
Flu/Bu	1.00	Ref.	0.76				
Flu/Mel	0.95	0.68-1.34					
NRM**				**NRM**			0.22
≤ 6 months				Flu/Bu	1.00	Ref.	
Flu/Bu	1.00	Ref.	0.01*	Bu/Cy	1.36	0.83- 2.21	
Flu/Mel	1.81	1.12-2.91					
> 6 months							
Flu/Bu	1.00	Ref.	0.02*				
Flu/Mel	0.46	0.23-0.91					
Relapse			0.25	**Relapse**			0.65
Flu/Bu	1.00	Ref.		Flu/Bu	1.00	Ref.	
Flu/Mel	0.85	0.64-1.12		Bu/Cy	0.92	0.64-1.32	
Acute GVHD grade II-IV**				**Acute GVHD grade II-IV****			
≤ 2 months				**≤ 2 months**			
Flu/Bu	1.00	Ref.	0.03*	Flu/Bu	1.00	Ref.	<0.001*
Flu/Mel	1.45	1.03-2.03		Bu/Cy	2.33	1.67-3.25	
> 2 months				**> 2 months**			
Flu/Bu	1.00	Ref.	0.18	Flu/Bu	1.00	Ref.	0.69
Flu/Mel	0.71	0.43-1.17		Bu/Cy	0.88	0.46-1.68	
Acute GVHD grade III-IV**				**Acute GVHD grade III-IV**			
≤ 2 months			0.004*	Flu/Bu	1.00	Ref.	<0.001*
Flu/Bu	1.00	Ref.		Bu/Cy	2.31	1.52-3.52	
Flu/Mel	2.21	1.28-3.83					
> 2 months							
Flu/Bu	1.00	Ref.	0.48				
Flu/Mel	0.89	0.64-1.24					

Chronic GVHD Flu/Bu Flu/Mel	 1.00 0.91	 Ref. 0.67-1.25	0.55	**Chronic GVHD** Flu/Bu Bu/Cy	 1.00 1.21	 Ref. 0.80-1.84	0.36
GRFS Flu/Bu Flu/Mel	 1.00 1.11	 Ref. 0.90-1.35	0.32	**GRFS** Flu/Bu Bu/Cy	 1.00 1.94	 Ref. 1.49-2.53	<0.001*

*p<0.05-significant
**Outcomes separated by timepoints due to non-proportional hazard

Flu-Fludarabine; Bu-Busulfan; Mel- Melphalan; Cy- Cyclophosphamide; NRM – non-relapse mortality; GVHD- graft versus host disease; GRFS – GVHD free relapse free survival

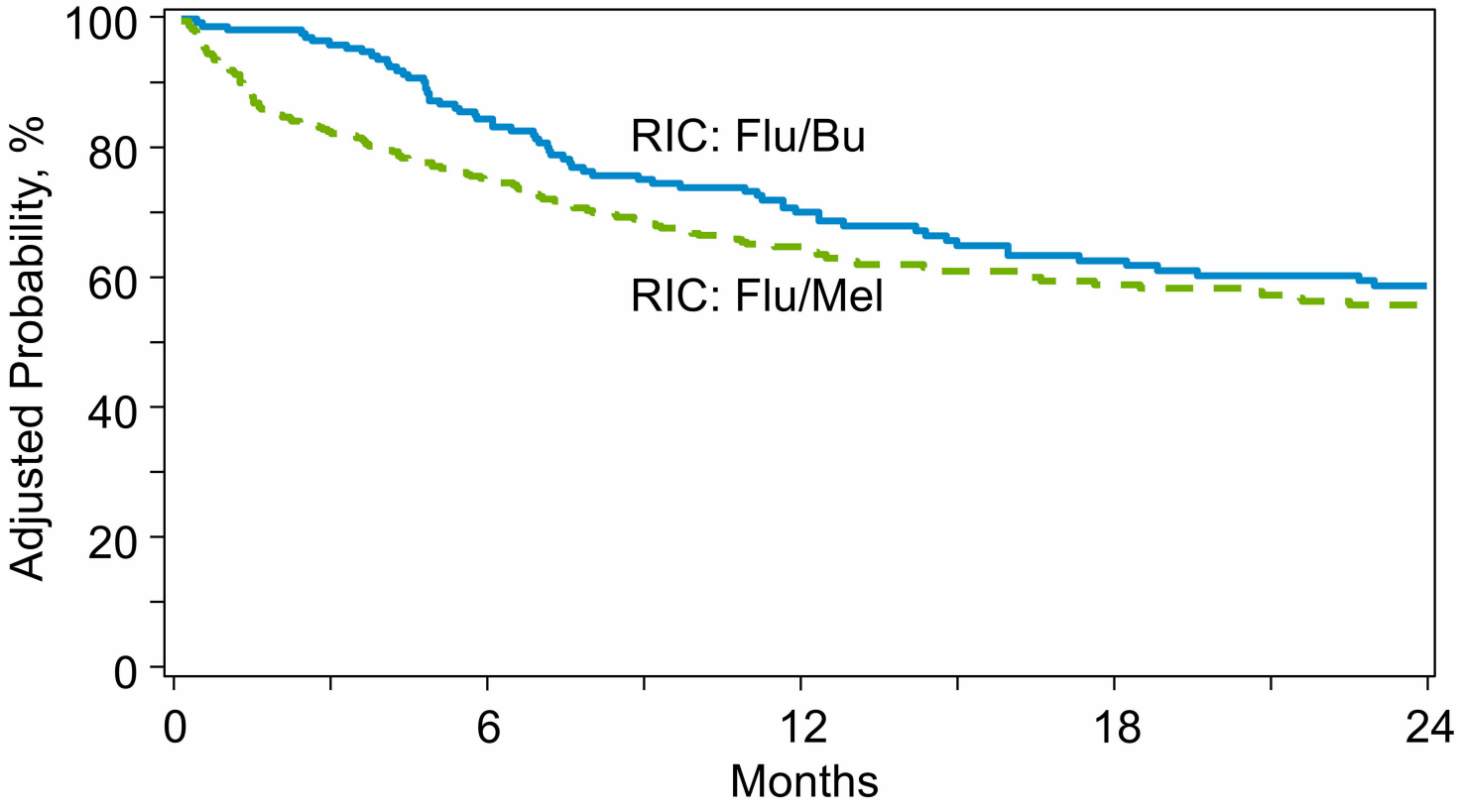
Figure legends:

Figure 1: Overall survival with reduced intensity conditioning

Figure 2: Overall survival with myeloablative conditioning

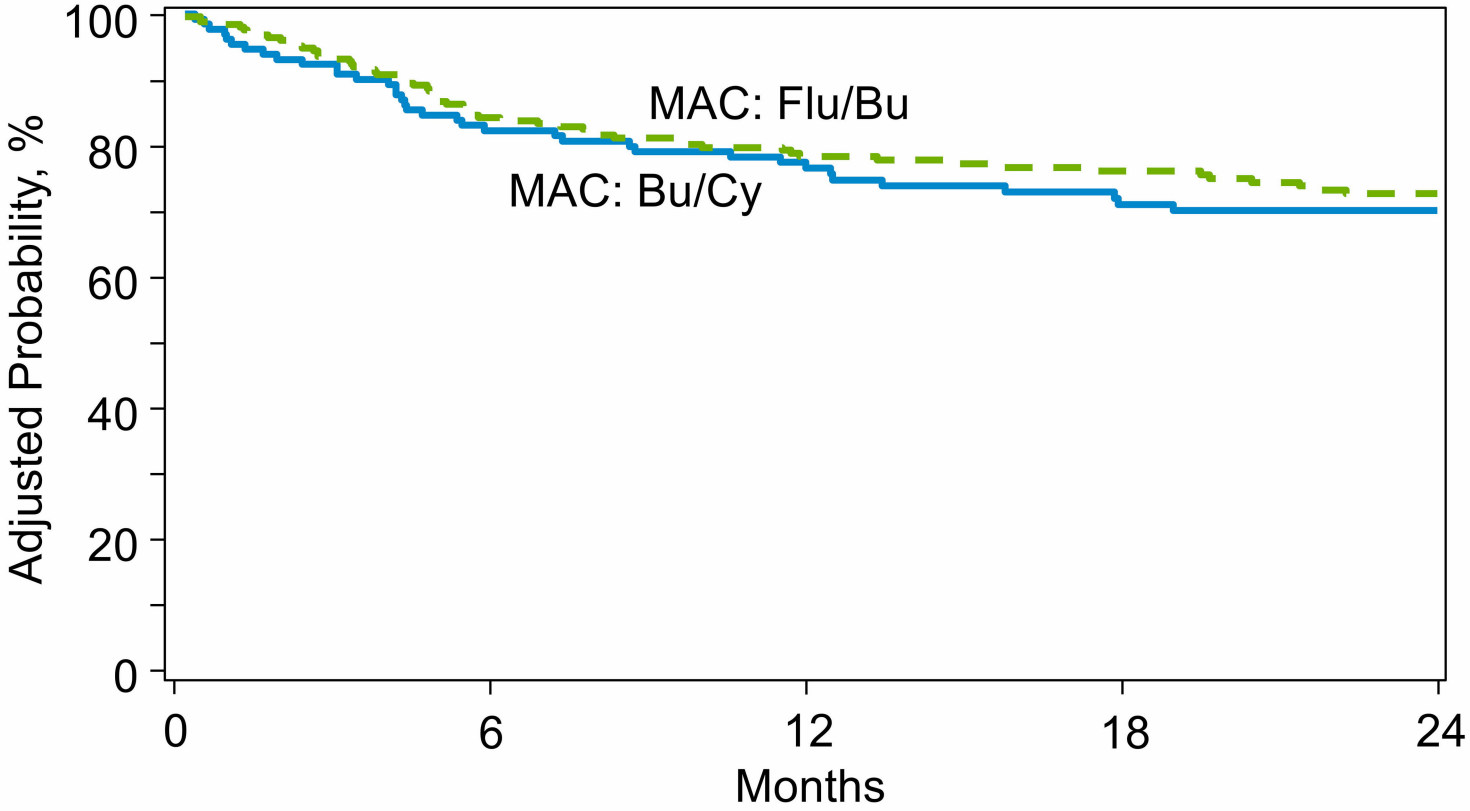
Figure 3: GVHD-free Relapse-Free survival with myeloablative conditioning

Figure 1: Overall Survival with RIC



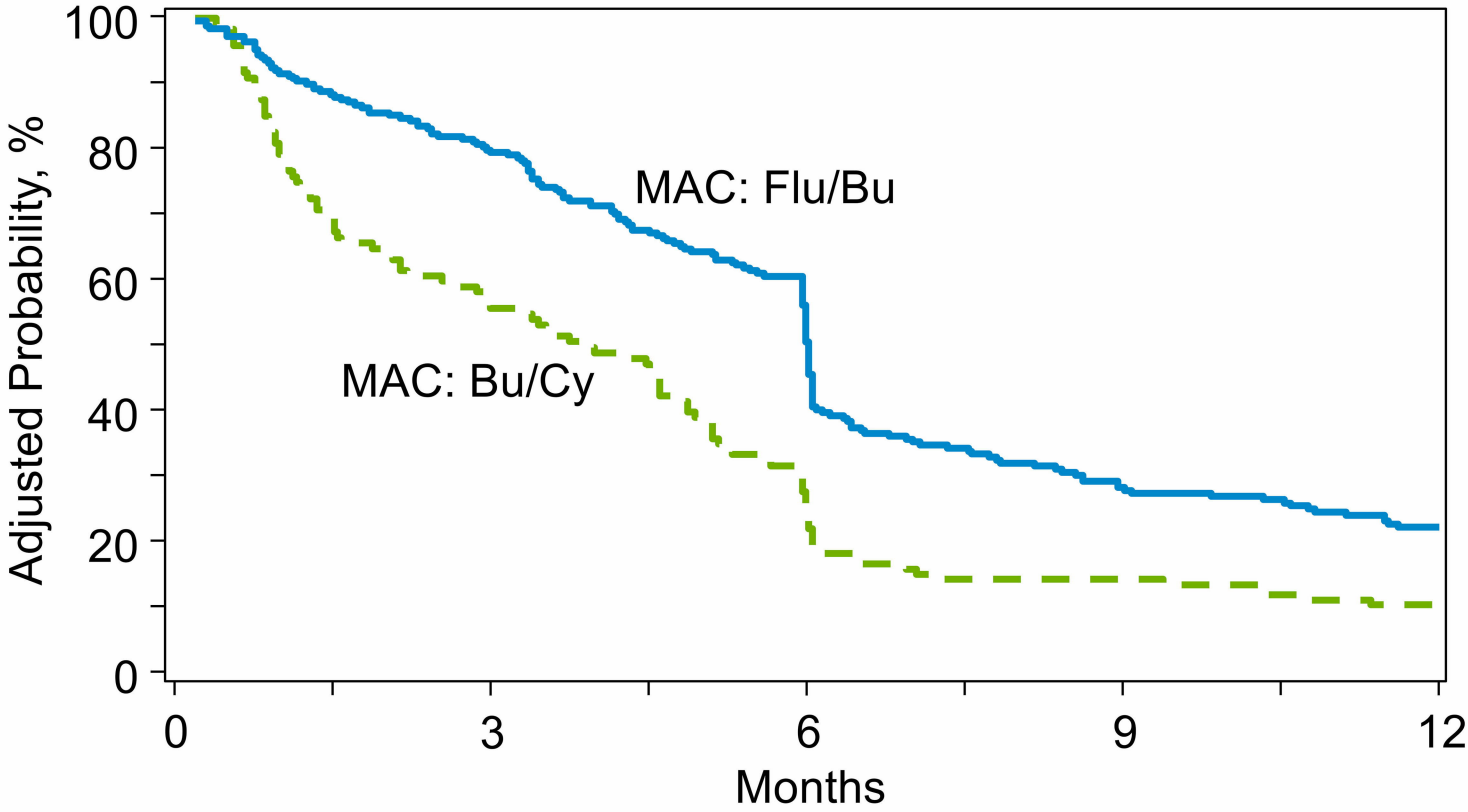
N at Risk	0	6	12	18	24
RIC: Flu/Bu	166	133	104	76	65
RIC: Flu/Mel	327	239	173	116	95

Figure 2: Overall Survival with MAC



N at Risk	0	6	12	18	24
MAC: Flu/Bu	247	196	157	129	109
MAC: Bu/Cy	132	107	95	78	75

Figure 3- GVHD- and Relapse-Free Survival with MAC



N at Risk	0	3	6	9	12
MAC: Flu/Bu	241	110	41	31	26
MAC: Bu/Cy	127	35	15	11	10

Supplement:

Definition of outcomes:

Disease free survival was defined as time from allo-HCT to treatment failure (relapse or death from any cause).

Overall survival was defined as time from allo-HCT to death from any cause.

Acute GVHD [26] and chronic GVHD [27] were graded per standard criteria.

Relapse was defined as disease recurrence as reported by the centers to CIBMTR.

Non-relapse mortality was defined as death from any cause in the first 28 days after allo-HCT or death without evidence of disease recurrence beyond day 28.

GVHD-free relapse-free survival was defined as time from allo-HCT to death, post-transplant relapse, chronic GVHD requiring immunosuppressive treatment, or severe acute GVHD (aGVHD III-IV).

Supplemental Table S1. Baseline characteristics with reduced intensity conditioning

Characteristic	RIC: Flu/Bu	RIC: Flu/Mel	P Value
No. of patients	166	327	
Patient age - median (min-max)	63 (44-75)	63 (38-78)	0.88[a]
Age group - no. (%)			0.50[b]
30-39	0 (0)	1 (0)	
40-49	10 (6)	31 (9)	
50-59	43 (26)	77 (24)	
60-69	99 (60)	182 (56)	
>= 70	14 (8)	36 (11)	
Sex - no. (%)			0.40[b]
Male	105 (63)	194 (59)	
Female	61 (37)	133 (41)	
Region - no. (%)			<.01[b]
US	146 (88)	310 (95)	
Europe	12 (7)	2 (1)	
Australia/New Zealand	8 (5)	15 (5)	
Race/ethnicity - no. (%)			0.16[b]
Hispanic	3 (2)	17 (5)	
Non-Hispanic White	150 (90)	274 (84)	
Non-Hispanic Black/African American	4 (2)	9 (3)	
Other	7 (4)	14 (4)	
Missing	2 (1)	13 (4)	
HCT-CI - no. (%)			0.13[b]
0	23 (14)	72 (22)	
1	22 (13)	34 (10)	
2	29 (17)	52 (16)	
3	34 (20)	71 (22)	
4	24 (14)	40 (12)	
5	16 (10)	17 (5)	
6+	11 (7)	33 (10)	
Missing	7 (4)	8 (2)	
Karnofsky performance score - no. (%)			0.37[b]
90-100	79 (48)	152 (46)	
< 90	85 (51)	164 (50)	
Missing	2 (1)	11 (3)	
Disease type- no. (%)			0.22[b]
Primary Myelofibrosis	132 (80)	242 (74)	

Characteristic	RIC: Flu/Bu	RIC: Flu/Mel	P Value
Post polycythemia vera	14 (8)	45 (14)	
Post Essential thrombocythemia	20 (12)	40 (12)	
Time from diagnosis to HCT - median (min-max)	22 (3-393)	37 (-99-594)	0.02[a]
Time from diagnosis to HCT - no. (%)			0.09[b]
<6 months	32 (19)	44 (13)	
6-11 months	34 (20)	50 (15)	
>=12 months	100 (60)	232 (71)	
Missing	0 (0)	1 (0)	
DIPSS Score - no. (%)			0.07[b]
Low/Intermediate-1	71 (43)	107 (33)	
Intermediate-2/High	69 (42)	168 (51)	
Missing	26 (16)	52 (16)	
Splenomegaly at HCT - no. (%)			0.21[b]
No	66 (40)	107 (33)	
Yes	82 (49)	168 (51)	
Splenectomy	8 (5)	16 (5)	
Missing	10 (6)	36 (11)	
Systemic symptoms prior to HCT. - no. (%)			0.19[b]
No	137 (83)	252 (77)	
Yes	19 (11)	58 (18)	
Missing	10 (6)	17 (5)	
Donor type - no. (%)			0.75[b]
HLA-identical sibling	48 (29)	94 (29)	
8/8 matched unrelated donor	107 (64)	205 (63)	
7/8 matched unrelated donor	11 (7)	28 (9)	
Donor/recipient sex match - no. (%)			0.81[b]
Male-Male	71 (43)	135 (41)	
Male-Female	39 (23)	81 (25)	
Female-Male	34 (20)	58 (18)	
Female-Female	21 (13)	52 (16)	
Missing	1 (1)	1 (0)	
Donor/recipient CMV serostatus - no. (%)			0.73[b]
+/+	54 (33)	102 (31)	
+/-	25 (15)	41 (13)	
-/+	39 (23)	70 (21)	
-/-	47 (28)	111 (34)	
Missing	1 (1)	3 (1)	
Graft type - no. (%)			0.84[b]

Characteristic	RIC: Flu/Bu	RIC: Flu/Mel	P Value
Bone marrow	6 (4)	13 (4)	
Peripheral blood	160 (96)	314 (96)	
GVHD prophylaxis - no. (%)			<.01[b]
Post-CY + other(s)	7 (4)	9 (3)	
TAC + MMF +- other(s) (except post-CY)	28 (17)	36 (11)	
TAC + MTX +- other(s) (except MMF, post-CY)	86 (52)	207 (63)	
TAC + other(s) (except MMF, MTX, post-CY)	7 (4)	36 (11)	
TAC alone	4 (2)	6 (2)	
CSA + MMF +- other(s) (except post-CY)	4 (2)	2 (1)	
CSA + MTX +- other(s) (except MMF, post-CY)	23 (14)	24 (7)	
CSA + other(s) (except MMF, MTX, post-CY)	0 (0)	1 (0)	
CSA alone	1 (1)	5 (2)	
Other(s)	6 (4)	1 (0)	
ATG/alemtuzumab use - no. (%)			<.01[b]
No	79 (48)	246 (75)	
Yes	87 (52)	81 (25)	
ATG/Alemtuzumab - no. (%)			<.01[b]
ATG alone	86 (52)	72 (22)	
Alemtuzumab alone	1 (1)	9 (3)	
No ATG or alemtuzumab	79 (48)	246 (75)	
ATG dose (mg) - median (min-max)	400 (5-4900)	284 (4-2988)	<.01[a]
ATG dose (mg) - no. (%)			0.43[b]
0-5mg	2 (2)	4 (6)	
5-7.5mg	2 (2)	0 (0)	
>7.5mg	78 (91)	65 (90)	
Missing	4 (5)	3 (4)	
Melphalan dose - no. (%)			
Melphalan 100mg/m^2	-	52 (16)	
Melphalan 140mg/m^2	-	275 (84)	
Busulfan Administration - no. (%)			
Oral	7 (4)	-	
IV	159 (96)	-	
Ruxolitinib use prior to HCT- no. (%)			0.03[b]
No	84 (51)	125 (38)	
Yes	82 (49)	201 (61)	
Missing	0 (0)	1 (0)	
Splenic radiation prior HCT - no. (%)			0.36[b]
No	161 (97)	308 (94)	
Yes	5 (3)	18 (6)	

Characteristic	RIC: Flu/Bu	RIC: Flu/Mel	P Value
Missing	0 (0)	1 (0)	
Year of HCT - no. (%)			0.01[b]
2008	11 (7)	17 (5)	
2009	9 (5)	14 (4)	
2010	4 (2)	2 (1)	
2011	0 (0)	1 (0)	
2012	0 (0)	1 (0)	
2013	4 (2)	4 (1)	
2014	27 (16)	23 (7)	
2015	11 (7)	20 (6)	
2016	21 (13)	32 (10)	
2017	32 (19)	64 (20)	
2018	22 (13)	73 (22)	
2019	25 (15)	76 (23)	
Follow-up - median (range)	36 (3-143)	24 (3-122)	

Hypothesis testing: [a] Kruskal-Wallis test [b] Pearson chi-square test

Other race include: Asian (n= 15), Native Hawaiian or other Pacific Islander (n=4), More than 1 race (n=1)

RIC-Reduced intensity conditioning; Flu-Fludarabine; Bu-Busulfan; Mel- Melphalan; HCTCI-hematopoietic cell transplantation comorbidity index; HCT-hematopoietic cell transplantation; DIPSS- dynamic international prognostic scoring system; CMV – cytomegalovirus; TAC-tacrolimus, CSA – cyclosporine; MMF- mycophenolate mofetil; MTX- methotrexate; CY-cyclophosphamide; ATG – antithymocyte globulin; GVHD- graft versus host disease

Supplemental Table S2. Baseline characteristics with myeloablative conditioning

Characteristic	MAC: Flu/Bu	MAC: Bu/Cy	P Value
No. of patients	247	132	
No. of centers	61	30	
Patient age - median (min-max)	60 (27-74)	55 (24-67)	<.01[a]
Age group - no. (%)			<.01[b]
18-29	1 (0)	1 (1)	
30-39	2 (1)	7 (5)	
40-49	25 (10)	24 (18)	
50-59	96 (39)	78 (59)	
60-69	110 (45)	22 (17)	
>= 70	13 (5)	0 (0)	
Sex - no. (%)			0.17[b]
Male	126 (51)	77 (58)	
Female	121 (49)	55 (42)	
Region - no. (%)			0.62[b]
US	240 (97)	130 (98)	
Canada	1 (0)	1 (1)	
Europe	2 (1)	0 (0)	
Australia/New Zealand	4 (2)	1 (1)	
Race/ethnicity - no. (%)			<.01[b]
Hispanic	16 (6)	3 (2)	
Non-Hispanic White	209 (85)	113 (86)	
Non-Hispanic Black/African American	15 (6)	3 (2)	
Other	7 (3)	10 (8)	
Missing	0 (0)	3 (2)	
HCTCI - no. (%)			0.32[b]
0	62 (25)	45 (34)	
1	38 (15)	21 (16)	
2	40 (16)	19 (14)	
3	47 (19)	26 (20)	
4	31 (13)	13 (10)	
5	12 (5)	5 (4)	
6+	16 (6)	2 (2)	
Missing	1 (0)	1 (1)	
Karnofsky performance score - no. (%)			0.42[b]
90-100	151 (61)	89 (67)	

Characteristic	MAC: Flu/Bu	MAC: Bu/Cy	P Value
< 90	92 (37)	42 (32)	
Missing	4 (2)	1 (1)	
Disease type - no. (%)			0.85[b]
Primary Myelofibrosis	191 (77)	100 (76)	
Post polycythemia vera	20 (8)	13 (10)	
Post essential thrombocythemia	36 (15)	19 (14)	
Time from diagnosis to HCT - median (min-max)	25 (2-490)	38 (3-377)	0.41[a]
Time from diagnosis to HCT - no. (%)			0.65[b]
<6 months	38 (15)	24 (18)	
6-11 months	51 (21)	23 (17)	
>=12 months	158 (64)	85 (64)	
DIPSS Score - no. (%)			0.03[b]
Low/Intermediate-1	134 (54)	80 (61)	
Intermediate-2/High	93 (38)	34 (26)	
Missing	20 (8)	18 (14)	
Splenomegaly at HCT - no. (%)			0.19[b]
No	85 (34)	38 (29)	
Yes	133 (54)	73 (55)	
Splenectomy	10 (4)	12 (9)	
Missing	19 (8)	9 (7)	
Systemic symptoms prior to HCT- no. (%)			0.53[b]
No	185 (75)	105 (80)	
Yes	51 (21)	21 (16)	
Missing	11 (4)	6 (5)	
Donor type - no. (%)			0.15[b]
HLA-identical sibling	79 (32)	53 (40)	
8/8-matched unrelated	142 (57)	62 (47)	
7/8-matched unrelated	26 (11)	17 (13)	
Donor/recipient sex match - no. (%)			0.17[b]
Male-Male	87 (35)	44 (33)	
Male-Female	72 (29)	31 (23)	
Female-Male	39 (16)	33 (25)	
Female-Female	49 (20)	24 (18)	
Donor/recipient CMV serostatus - no. (%)			0.37[b]
+/+	66 (27)	26 (20)	
+/-	42 (17)	19 (14)	
-/+	64 (26)	40 (30)	

Characteristic	MAC: Flu/Bu	MAC: Bu/Cy	P Value
-/-	71 (29)	46 (35)	
Missing	4 (2)	1 (1)	
Graft type - no. (%)			<.01[b]
Bone marrow	11 (4)	16 (12)	
Peripheral blood	236 (96)	116 (88)	
GVHD prophylaxis - no. (%)			0.03[b]
TAC + MMF +- other(s) (except post-CY)	26 (11)	5 (4)	
TAC + MTX +- other(s) (except MMF, post-CY)	193 (78)	111 (84)	
TAC + other(s) (except MMF, MTX, post-CY)	12 (5)	3 (2)	
TAC alone	4 (2)	0 (0)	
CSA + MMF +- other(s) (except post-CY)	3 (1)	2 (2)	
CSA + MTX +- other(s) (except MMF, post-CY)	9 (4)	11 (8)	
ATG/Alemtuzumab use - no. (%)			<.01[b]
No	135 (55)	125 (95)	
Yes	112 (45)	7 (5)	
ATG/alemtuzumab - no. (%)			<.01[b]
ATG + alemtuzumab	1 (0)	0 (0)	
ATG alone	107 (43)	6 (5)	
Alemtuzumab alone	4 (2)	1 (1)	
No ATG or alemtuzumab	135 (55)	125 (95)	
ATG dose (mg) - median (min-max)	338 (3-6000)	250 (150-500)	0.32[a]
ATG dose (mg) - no. (%)	3(3)	0(0)	0.10[c]
0-5mg	0(0)	0(0)	
5-7.5mg	98(92)	4(67)	
>7.5mg	6(6)	2(33)	
Missing			
Busulfan pharmacokinetics performed - no. (%)			0.62[b]
No	102 (41)	51 (39)	
Yes	145 (59)	81 (61)	
Busulfan Administration - no. (%)			0.02[b]
Oral	2 (1)	6 (5)	
IV	245 (99)	126 (95)	
Ruxolitinib use prior to HCT - no. (%)			<.01[b]
No	101 (41)	75 (57)	
Yes	146 (59)	57 (43)	
Splenic radiation prior HCT - no. (%)			0.07[b]
No	237 (96)	131 (99)	

Characteristic	MAC: Flu/Bu	MAC: Bu/Cy	P Value
Yes	10 (4)	1 (1)	
Year of HCT - no. (%)			<.01[b]
2008	9 (4)	15 (11)	
2009	12 (5)	21 (16)	
2010	5 (2)	8 (6)	
2011	2 (1)	6 (5)	
2012	1 (0)	3 (2)	
2013	9 (4)	6 (5)	
2014	35 (14)	6 (5)	
2015	27 (11)	15 (11)	
2016	25 (10)	11 (8)	
2017	47 (19)	15 (11)	
2018	39 (16)	15 (11)	
2019	36 (15)	11 (8)	
Follow-up - median (range)	25 (3-122)	49 (6-150)	

Hypothesis testing: [a] Kruskal-Wallis test [b] Pearson chi-square test

Other race include: Asian (n= 11), Native Hawaiian or other Pacific Islander (n=6), American Indian or Alaska Native (n=1), More than 1 race (n=1)

MAC-Myeloablative conditioning; Flu-Fludarabine; Bu-Busulfan; Cy- Cyclophosphamide; HCTCI-hematopoietic cell transplantation comorbidity index; HCT-hematopoietic cell transplantation; DIPSS- dynamic international prognostic scoring system; CMV – cytomegalovirus; TAC- tacrolimus, CSA – cyclosporine; MMF- mycophenolate mofetil; MTX- methotrexate; CY- cyclophosphamide; ATG – antithymocyte globulin; GVHD- graft versus host disease

Supplemental Table S3. Univariable analysis with reduced intensity conditioning (Unadjusted, censored at 24 months)

		RIC: Flu/Bu (N = 166)		RIC: Flu/Mel (N = 327)		
Outcomes		**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**	**P Value**
Non-relapse mortality		164		321		0.21
100-day	Censored	10	4.3 (1.7-7.9)%	6	17.4 (13.5-21.8)%	<0.001
	Event	7		56		
	N at risk	148		261		
1-year	Censored	73	19.9 (14.1-26.5)%	146	27.3 (22.5-32.3)%	0.06
	Event	25		30		
	N at risk	51		86		
2-year	Censored	13	26.8 (20-34.2)%	28	28.7 (23.7-33.9)%	0.67
	Event	9		3		
	N at risk	27		52		
Relapse		164		321		0.08
1-year	Censored	37	48.8 (41-56.6)%	109	41.7 (36.2-47.2)%	0.14
	Event	78		129		
	N at risk	51		86		
2-year	Censored	21	49.6 (41.8-57.4)%	26	44 (38.4-49.7)%	0.26
	Event	1		5		
	N at risk	27		52		
Disease Free-Survival		164		321		0.99
1-year	Censored	5	31.3 (24.3-38.7)%	23	31.1 (26-36.4)%	0.96
	Event	110		215		
	N at risk	49		83		
2-year	Censored	12	23.6 (17.2-30.8)%	23	27.3 (22.2-32.6)%	0.40
	Event	10		8		
	N at risk	27		52		
Overall Survival		166		327		0.43
1-year	Censored	12	68.7 (61.3-75.7)%	45	65.6 (60.2-70.7)%	0.49
	Event	50		109		
	N at risk	104		173		
2-year	Censored	24	56.9 (48.7-64.8)%	60	56.7 (50.8-62.6)%	0.98
	Event	15		18		
	N at risk	65		95		
Acute GVHD II-IV		164		325		0.63
100-day	Censored	9	35.5 (28.3-43)%	42	40.1 (34.8-45.5)%	0.32
	Event	58		130		
	N at risk	98		154		

Outcomes		RIC: Flu/Bu (N = 166) N	RIC: Flu/Bu (N = 166) Prob (95% CI)	RIC: Flu/Mel (N = 327) N	RIC: Flu/Mel (N = 327) Prob (95% CI)	P Value
6 months	Censored	18	43.9 (36.3-51.6)%	14	43.6 (38.2-49)%	0.95
	Event	13		11		
	N at risk	68		130		
1-year	Censored	13	46.7 (38.9-54.5)%	31	45.4 (40-50.9)%	0.79
	Event	4		5		
	N at risk	50		96		
Acute GVHD III-IV		165		326		0.12
6 months	Censored	33	18.5 (12.9-24.9)%	64	22.8 (18.4-27.5)%	0.26
	Event	30		75		
	N at risk	103		190		
1-year	Censored	19	18.5 (12.9-24.9)%	49	23.9 (19.4-28.7)%	0.16
	Event	1		3		
	N at risk	83		141		
2-year	Censored	31	18.5 (12.9-24.9)%	61	23.9 (19.4-28.7)%	0.16
	Event	0		0		
	N at risk	51		74		
Chronic GVHD		165		323		0.15
1-year	Censored	56	44.6 (36.7-52.6)%	139	35.2 (29.8-40.8)%	0.05
	Event	68		104		
	N at risk	42		83		
2-year	Censored	15	50.1 (41.8-58.4)%	32	47.8 (41.7-54)%	0.66
	Event	6		24		
	N at risk	20		24		
GRFS		164		320		0.30
1-year	Censored	5	12.3 (7.6-17.9)%	19	11.6 (8.2-15.6)%	0.84
	Event	140		273		
	N at risk	19		28		
2-year	Censored	5	8.9 (4.8-14.2)%	7	4.7 (2.2-7.9)%	0.12
	Event	4		13		
	N at risk	10		8		

RIC-Reduced intensity conditioning; Flu-Fludarabine; Bu-Busulfan; Mel- Melphalan; GVHD-Graft-versus-host disease; GRFS- GVHD-Free Relapse-Free survival

Supplemental Table S4. Univariable analysis with myeloablative conditioning (Unadjusted, censored at 24 months)

		MAC: Flu/Bu (N = 247)		MAC: Bu/Cy (N = 132)		
Outcomes		**N**	**Prob (95% CI)**	**N**	**Prob (95% CI)**	**P Value**
Non-relapse mortality		242		132		0.28
100-day	Censored	12	6.2 (3.5-9.6)%	4	9.1 (4.8-14.6)%	0.32
	Event	15		12		
	N at risk	216		117		
1-year	Censored	102	15.7 (11.3-20.6)%	43	19 (12.8-26.2)%	0.42
	Event	22		13		
	N at risk	92		61		
2-year	Censored	24	16.8 (12.2-21.9)%	3	21.5 (14.8-29)%	0.28
	Event	2		3		
	N at risk	65		54		
Relapse		242		132		0.24
1-year	Censored	63	38.2 (32-44.6)%	29	32.9 (25.1-41.2)%	0.31
	Event	88		43		
	N at risk	92		61		
2-year	Censored	22	40.5 (34.1-47)%	5	33.7 (25.8-42.1)%	0.20
	Event	4		1		
	N at risk	65		54		
Disease-Free Survival		242		132		0.81
1-year	Censored	26	46.2 (39.7-52.6)%	4	48.1 (39.6-56.7)%	0.72
	Event	125		68		
	N at risk	91		60		
2-year	Censored	20	42.7 (36.3-49.3)%	2	44.8 (36.4-53.4)%	0.70
	Event	6		4		
	N at risk	65		54		
Overall Survival		247		132		0.71
1-year	Censored	38	78 (72.5-83.1)%	8	77.8 (70.4-84.5)%	0.96
	Event	52		29		
	N at risk	157		95		
2-year	Censored	38	72.1 (65.9-78)%	12	70.7 (62.4-78.3)%	0.77
	Event	10		8		
	N at risk	109		75		
Acute GVHD II-IV		244		129		<0.001
100-day	Censored	13	34.1 (28.3-40.2)%	7	58.9 (50.3-67.3)%	<0.001
	Event	83		76		
	N at risk	149		47		

Outcomes		MAC: Flu/Bu (N = 247) N	MAC: Flu/Bu (N = 247) Prob (95% CI)	MAC: Bu/Cy (N = 132) N	MAC: Bu/Cy (N = 132) Prob (95% CI)	P Value
6 months	Censored	18	43 (36.8-49.3)%	1	62.8 (54.2-71)%	<0.001
	Event	21		5		
	N at risk	111		41		
1-year	Censored	26	47.5 (41.1-53.9)%	1	62.8 (54.2-71)%	0.004
	Event	9		0		
	N at risk	75		40		
Acute GVHD III-IV		244		127		<0.001
6 months	Censored	39	16.6 (12.1-21.5)%	10	34.6 (26.6-43.2)%	<0.001
	Event	40		44		
	N at risk	168		75		
1-year	Censored	33	19.5 (14.6-24.8)%	8	34.6 (26.6-43.2)%	0.002
	Event	6		0		
	N at risk	127		67		
2-year	Censored		19.5 (14.6-24.8)%		34.6 (26.6-43.2)%	0.002
	Event					
	N at risk	82		53		
Chronic GVHD		242		131		0.29
1-year	Censored	73	46.1 (39.4-52.8)%	30	47.6 (38.9-56.3)%	0.78
	Event	100		61		
	N at risk	70		41		
2-year	Censored	21	53.3 (46.3-60.1)%	9	58.1 (49.1-66.8)%	0.40
	Event	12		11		
	N at risk	36		20		
GRFS		241		127		<0.001
1-year	Censored	14	19.2 (14.3-24.6)%	3	13.4 (8-19.9)%	0.15
	Event	186		109		
	N at risk	41		15		
2-year	Censored	6	14.9 (10.5-20)%	0	8.9 (4.5-14.7)%	0.09
	Event	9		5		
	N at risk	26		10		

MAC-Myeloablative conditioning; Flu-Fludarabine; Bu-Busulfan; Cy- Cyclophosphamide; GVHD-Graft-versus-host disease; GRFS-GVHD-Free Relapse-Free survival

Supplemental Table S5. Multivariable Analyses - reduced intensity conditioning

Overall Survival			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect (<= 6 months)						
RIC: Flu/Bu	166	1.00	Reference			0.009
RIC: Flu/Mel	326	1.80	1.15	2.81	0.009	
Main Effect (> 6 months)						
RIC: Flu/Bu	133	1.00	Reference			0.35
RIC: Flu/Mel	239	0.82	0.53	1.26	0.35	
ATG/alemtuzumab						
No	324	1.00	Reference			0.03
Yes	168	1.39	1.03	1.88	0.03	

Disease Free Survival			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect (<= 6 months)						0.85
RIC: Flu/Bu	164	1.00	Reference			
RIC: Flu/Mel	320	1.03	0.77	1.38	0.85	
Main Effect (> 6 months)						0.76
RIC: Flu/Bu	92	1.00	Reference			
RIC: Flu/Mel	181	0.95	0.68	1.34	0.76	

Relapse			95% CI	95% CI		Overall p-value
Variable	N	HR	Lower Limit	Upper Limit	p-value	
Main Effect						0.25
RIC: Flu/Bu	165	1.00	Reference			
RIC: Flu/Mel	320	0.85	0.64	1.12	0.25	
Year of transplant						0.01
2008-2014	116	1.00	Reference			
2015-2019	369	1.53	1.08	2.17	0.01	

Non-Relapse Mortality			95% CI	95% CI		
Variable	N	HR	Lower Limit	Upper Limit	p-value	Overall p-value
Main Effect (<=6 months)						0.01
RIC: Flu/Bu	164	1.00	Reference			
RIC: Flu/Mel	320	1.81	1.12	2.91	0.01	
Main Effect (> 6 months)						0.02
RIC: Flu/Bu	92	1.00	Reference			
RIC: Flu/Mel	181	0.46	0.23	0.91	0.02	

Acute GVHD II-IV			95% CI	95% CI		
Variable	N	HR	Lower Limit	Upper Limit	p-value	Overall p-value
Main Effect (<=2 months)						0.03
RIC: Flu/Bu	164	1.00	Reference			

RIC: Flu/Mel	324	1.45	1.03	2.03	0.03	
Main Effect (> 2 months)						0.18
RIC: Flu/Bu	111	1.00	Reference			
RIC: Flu/Mel	174	0.71	0.43	1.17	0.18	

Acute GVHD III-IV			**95% CI**	**95% CI**		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect (<=2 months)						0.004
RIC: Flu/Bu	165	1.00	Reference			
RIC: Flu/Mel	325	2.21	1.28	3.83	0.004	
Main Effect (>2 months)						0.48
RIC: Flu/Bu	143	1.00	Reference			
RIC: Flu/Mel	226	0.89	0.64	1.24	0.48	

Chronic GVHD (adjusted center effect)			**95% CI**	**95% CI**		**Overall p-value**
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	
Main Effect						0.55
RIC: Flu/Bu	165	1.00	Reference			
RIC: Flu/Mel	322	0.91	0.67	1.25	0.55	
Donor type						
HLA-identical sibling	139	1.00	Reference			0.03

8/8-matched unrelated donor	309	0.97	0.69	1.35	0.83	
7/8-matched unrelated donor	39	1.89	1.15	3.12	0.01	
Contrast						
8/8-matched unrelated vs 7/8-matched unrelated donor		0.51	0.30	0.88	0.01	

GRFS			**95% CI**	**95% CI**		**Overall p-value**
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	
Main Effect						0.32
RIC: Flu/Bu	164	1.00	Reference			
RIC: Flu/Mel	319	1.11	0.90	1.35	0.32	

**RIC- reduced intensity conditioning; Flu/Bu – Fludarabine/busulfan; Flu/Mel- Fludarabine/melphalan; HCT- hematopoietic cell transplantation; ATG – antithymocyte globulin; GVHD- graft versus host disease; GRFS – GVHD-free relapse-free survival

The following factors were considered in the multivariable analysis - patient age, race/ethnicity, disease subtype, dynamic international performance scoring system (DIPSS) score, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Karnofsky Performance Scale (KPS), splenic radiation, splenomegaly at HCT, ruxolitinib use pre-transplant, donor-recipient HLA-match, gender match, CMV match, stem cell source, GVHD prophylaxis, use of antithymocyte globulin (ATG)/alemtuzumab, and year of transplant. Significant covariates are shown in table.

Supplemental Table S6. Multivariable Analyses for patients who received myeloablative conditioning

Overall Survival			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect						0.54
MAC: Flu/Bu	247	1.00	Reference			
MAC: Bu/Cy	132	1.14	0.75	1.71	0.54	
Donor type						<0.001
HLA-identical sibling	132	1.00	Reference			
8/8-matched unrelated	204	1.78	1.09	2.89	0.02	
7/8-matched unrelated	43	3.33	1.83	6.06	<0.001	
Contrast						
8/8-matched unrelated vs 7/8-matched unrelated donor		0.53	0.32	0.89	0.01	

Disease Free Survival			95% CI	95% CI		Overall p-value
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	
Main Effect						0.83
MAC: Flu/Bu	238	1.00	Reference			
MAC: Bu/Cy	131	1.03	0.77	1.38	0.83	
Karnofsky score						0.006
90-100	238	1.00	Reference			

< 90	131	1.47	1.11	1.95	0.006	
Ruxolitinib use prior to HCT						0.04
No	170	1.00	Reference			
Yes	199	1.33	1.01	1.77	0.04	

Relapse			**95% CI**	**95% CI**		**Overall p-value**
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	
Main Effect						0.65
MAC: Flu/Bu	238	1.00	Reference			
MAC: Bu/Cy	131	0.92	0.64	1.32	0.65	
Karnofsky score						0.006
90-100	238	1.00	Reference			
< 90	131	1.61	1.14	2.26	0.006	
Ruxolitinib use prior to HCT						0.01
No	170	1.00	Reference			
Yes	199	1.56	1.10	2.21	0.01	

Non Relapse Mortality			**95% CI**	**95% CI**		**Overall p-value**
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	
Main Effect						0.22
MAC: Flu/Bu	242	1.00	Reference			

MAC: Bu/Cy	132	1.36	0.83	2.21	0.22	
Donor type						<0.001
HLA-identical sibling	131	1.00	Reference			
8/8-matched unrelated	201	2.66	1.36	5.18	0.004	
7/8-matched unrelated	42	5.33	2.44	11.61	<0.001	
Contrast						
8/8-matched unrelated vs 7/8-matched unrelated donor		0.50	0.28	0.90	0.02	

Acute GVHD II-IV			**95% CI**	**95% CI**		**Overall p-value**
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	
Main Effect (<=2 months)						<0.001
MAC: Flu/Bu	244	1.00	Reference			
MAC: Bu/Cy	129	2.33	1.67	3.25	<0.001	
Main Effect(> 2 months)						0.69
MAC: Flu/Bu	163	1.00	Reference			
MAC: Bu/Cy	53	0.88	0.46	1.68	0.69	
Donor type						<0.001
HLA-identical sibling	130	1.00	Reference			
8/8-matched unrelated	200	1.45	1.05	1.99	0.02	
7/8-matched unrelated	43	2.53	1.63	3.93	<0.001	

Contrast						
8/8-matched unrelated vs 7/8-matched unrelated donor		0.57	0.38	0.86	0.007	

Acute GVHD III-IV			95% CI	95% CI		Overall p-value
Variable	N	HR	Lower Limit	Upper Limit	p-value	
Main Effect						<0.001
MAC: Flu/Bu	244	1.00	Reference			
MAC: Bu/Cy	127	2.31	1.52	3.52	<0.001	
Ruxolitinib use prior to HCT						0.02
No	170	1.00	Reference			
Yes	201	1.67	1.08	2.58	0.02	

Chronic GVHD (adjusted center effect)			95% CI	95% CI		Overall p-value
Variable	N	HR	Lower Limit	Upper Limit	p-value	
Main Effect						
MAC: Flu/Bu	242	1.00	Reference			0.36
MAC: Bu/Cy	131	1.21	0.80	1.84	0.36	
Ruxolitinib use prior to HCT						
No	172	1.00	Reference			0.02
Yes	201	0.74	0.57	0.96	0.02	

GRFS			95% CI	95% CI		Overall p-value
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	
Main Effect						<0.001
MAC: Flu/Bu	241	1.00	Reference			
MAC: Bu/Cy	127	1.94	1.49	2.53	<.0001	
Recipient age						0.001
18-49	56	1.00	Reference			
50-59	171	0.74	0.53	1.03	0.07	
>=60	141	1.22	0.85	1.74	0.27	
Donor type						<0.001
HLA-identical sibling	127	1.00	Reference			
8/8-matched unrelated	198	1.31	1.02	1.69	0.03	
7/8-matched unrelated	43	2.41	1.66	3.51	<0.001	
Contrast						
Age 50-59 vs >=60		0.61	0.47	0.79	<0.001	
8/8-matched unrelated vs 7/8-matched unrelated donor		0.54	0.38	0.77	<0.001	

**MAC- myeloablative conditioning; Flu/Bu – Fludarabine/busulfan; Bu/Cy-Busulfan/cyclophosphamide; HCT- hematopoietic cell transplantation; ATG – antithymocyte globulin; GVHD- graft versus host disease; GRFS – GVHD-free relapse-free survival

The following factors were considered in the multivariable analysis - patient age, race/ethnicity, disease subtype, dynamic international performance scoring system (DIPSS) score, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Karnofsky Performance Scale (KPS), splenic radiation, splenomegaly at HCT, ruxolitinib use pre-transplant, donor-recipient HLA-match, gender match, CMV match, stem cell source, GVHD prophylaxis, use of antithymocyte globulin (ATG)/alemtuzumab, and year of transplant. Significant covariates are shown in table.

Supplemental Table S7. Multivariable Analyses with RIC – analyzed based on melphalan dose

Overall Survival			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect (<= 6 months)						0.02
RIC: Flu/Bu	166	1.00	Reference			
RIC: Flu/Mel-100	52	2.07	1.08	3.97	0.02	
RIC: Flu/Mel-140	274	1.75	1.11	2.77	0.01	
Main Effect (> 6 months)						0.45
RIC: Flu/Bu	133	1.00	Reference			
RIC: Flu/Mel-100	32	1.12	0.50	2.52	0.78	
RIC: Flu/Mel-140	207	0.78	0.49	1.22	0.27	
ATG/alemtuzumab						0.03
No	324	1.00	Reference			
Yes	168	1.38	1.03	1.88	0.03	
Contrast						
<=6 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		1.18	0.66	2.11	0.56	
>6 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		1.44	0.64	3.21	0.37	

Disease Free Survival			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**

Main Effect (<= 6 months)						
RIC: Flu/Bu	164	1.00	Reference			0.87
RIC: Flu/Mel-100	51	1.14	0.70	1.85	0.61	
RIC: Flu/Mel-140	269	1.01	0.75	1.37	0.94	
Main Effect (> 6 months)						0.91
RIC: Flu/Bu	92	1.00	Reference			
RIC: Flu/Mel-100	24	1.03	0.55	1.93	0.92	
RIC: Flu/Mel-140	157	0.94	0.66	1.33	0.72	
Contrast						
<=6 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		1.12	0.71	1.79	0.62	
>6 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		1.10	0.60	2.01	0.76	

Relapse			**95% CI**	**95% CI**		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect						0.47
RIC: Flu/Bu	164	1.00	Reference			
RIC: Flu/Mel-100	51	0.76	0.45	1.30	0.32	
RIC: Flu/Mel-140	269	0.86	0.64	1.14	0.30	
Year of transplant						0.01
2008-2014	116	1.00	Reference			
2015-2019	368	1.53	1.08	2.18	0.01	

Contrast						
RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		0.89	0.53	1.48	0.66	

Non relapse mortality			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect (<=6 months)						0.03
RIC: Flu/Bu	164	1.00	Reference			
RIC: Flu/Mel-100	51	2.28	1.17	4.47	0.01	
RIC: Flu/Mel-140	269	1.71	1.05	2.80	0.03	
Main Effect (>6 months)						
RIC: Flu/Bu	92	1.00	Reference			0.07
RIC: Flu/Mel-100	24	0.55	0.12	2.37	0.42	
RIC: Flu/Mel-140	157	0.44	0.22	0.91	0.02	

Contrast					
<=6 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140	1.33	0.74	2.38	0.33	
>6 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140	1.23	0.27	5.45	0.78	

Acute GVHD II-IV			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect (<= 2 months)						0.10
RIC: Flu/Bu	164	1.00	Reference			
RIC: Flu/Mel-100	52	1.47	0.85	2.54	0.16	
RIC: Flu/Mel-140	272	1.44	1.01	2.04	0.04	
Main Effect (> 2 months)						0.34
RIC: Flu/Bu	111	1.00	Reference			
RIC: Flu/Mel-100	29	0.91	0.37	2.19	0.83	
RIC: Flu/Mel-140	145	0.67	0.39	1.14	0.14	
Contrast						
<=2 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		1.02	0.61	1.69	0.92	
>2 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		1.34	0.55	3.26	0.51	

Acute GVHD III-IV			95% CI	95% CI		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect (<= 2						0.005

months)						
RIC: Flu/Bu	165	1.00	Reference			
RIC: Flu/Mel-100	52	1.31	0.51	3.35	0.57	
RIC: Flu/Mel-140	273	2.38	1.36	4.15	0.002	
Main Effect (>2 months)						0.42
RIC: Flu/Bu	143	1.00	Reference			
RIC: Flu/Mel-100	41	0.47	0.10	2.08	0.32	
RIC: Flu/Mel-140	185	0.67	0.32	1.39	0.28	
Contrast						
<=2 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		0.55	0.23	1.27	0.16	
>2 mon: RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		0.70	0.16	3.11	0.64	
Chronic GVHD (adjusted center effect)			**95% CI**	**95% CI**		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect						0.73
RIC: Flu/Bu	165	1.00	Reference			
RIC: Flu/Mel-100	52	0.80	0.44	1.42	0.45	
RIC: Flu/Mel-140	270	0.92	0.67	1.27	0.64	

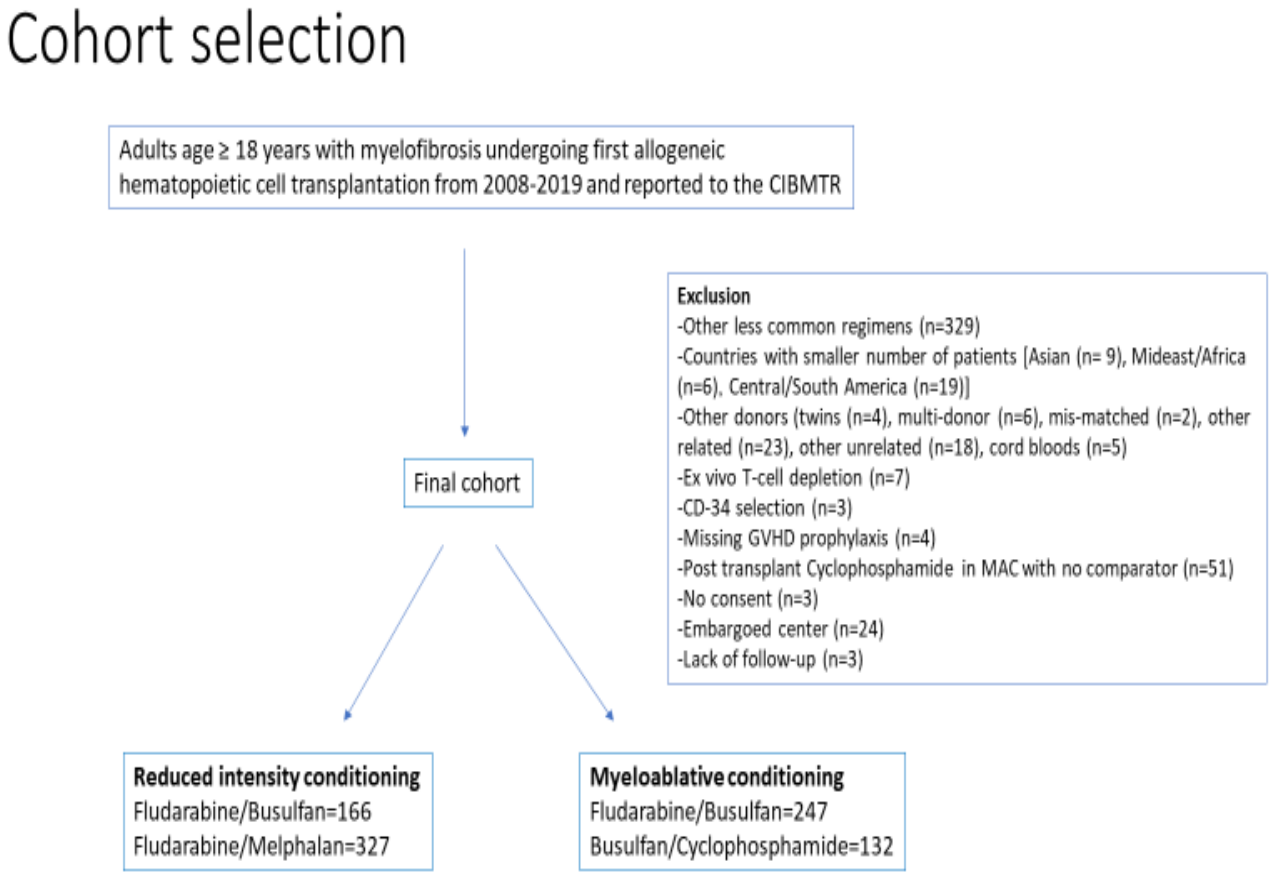
Donor type						0.03
HLA-identical sibling	139	1.00	Reference			
8/8-matched unrelated	309	0.97	0.70	1.34	0.86	
7/8-matched unrelated	39	1.92	1.17	3.16	0.009	
Contrast						
8/8-matched unrelated vs 7/8-matched unrelated		0.50	0.29	0.87	0.01	
RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		0.86	0.50	1.48	0.59	

GRFS			**95% CI**	**95% CI**		
Variable	**N**	**HR**	**Lower Limit**	**Upper Limit**	**p-value**	**Overall p-value**
Main Effect						0.60
RIC: Flu/Bu	164	1.00	Reference			
RIC: Flu/Mel-100	51	1.07	0.76	1.52	0.67	
RIC: Flu/Mel-140	268	1.11	0.90	1.36	0.32	
Contrast						
RIC: Flu/Mel-100 vs RIC: Flu/Mel-140		0.97	0.69	1.35	0.85	

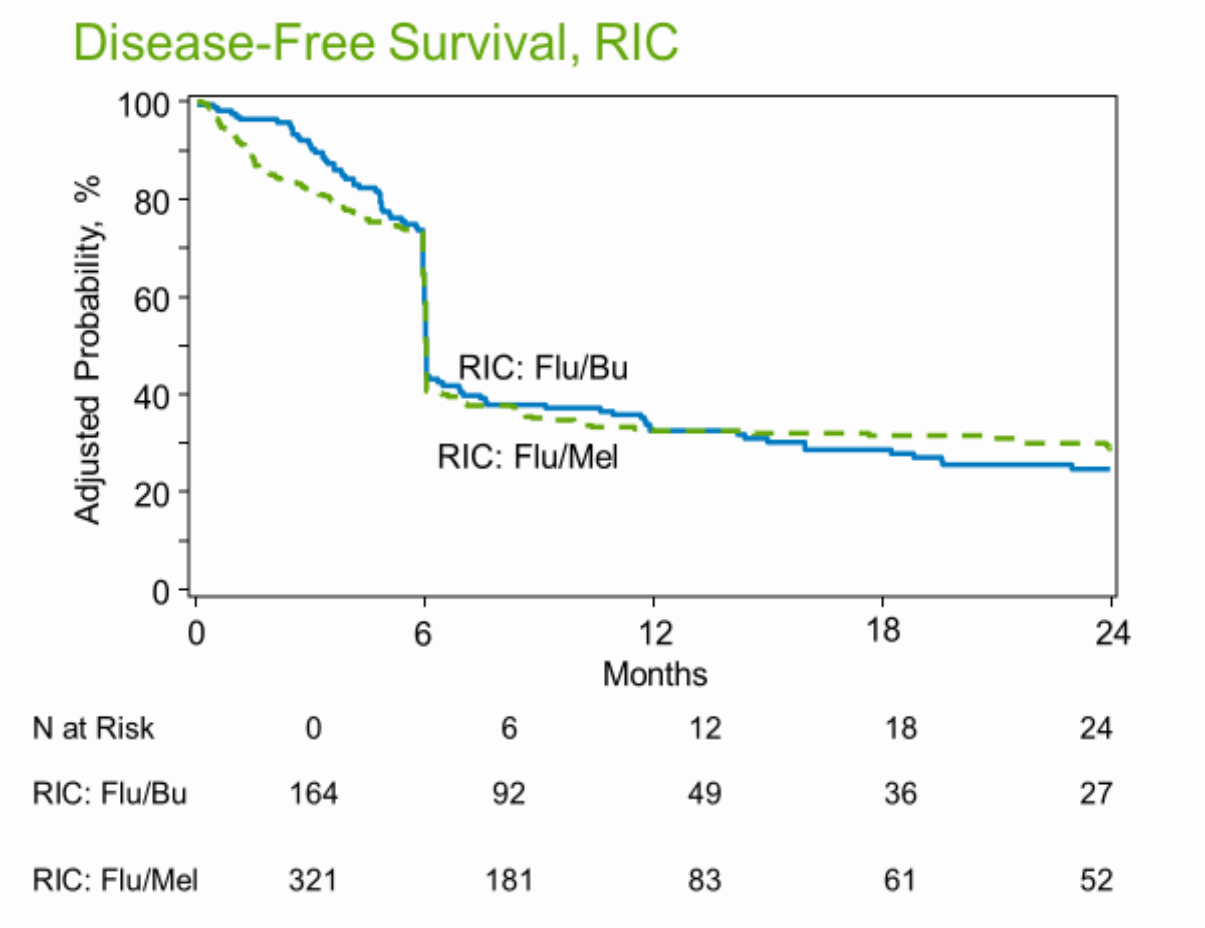
*RIC- reduced intensity conditioning; Flu/Bu – Fludarabine/busulfan; Flu/Mel- Fludarabine/melphalan; HCT- hematopoietic cell transplantation; ATG – antithymocyte globulin; GVHD- graft versus host disease; GRFS – GVHD-free relapse-free survival

The following factors were considered in the multivariable analysis - patient age, race/ethnicity, disease subtype, dynamic international performance scoring system (DIPSS) score, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), Karnofsky Performance Scale (KPS), splenic radiation, splenomegaly at HCT, ruxolitinib use pre-transplant, donor-recipient HLA-match, gender match, CMV match, stem cell source, GVHD prophylaxis, use of antithymocyte globulin (ATG)/alemtuzumab, and year of transplant. Significant covariates are shown in table.

Supplemental Figure S1- Consort diagram

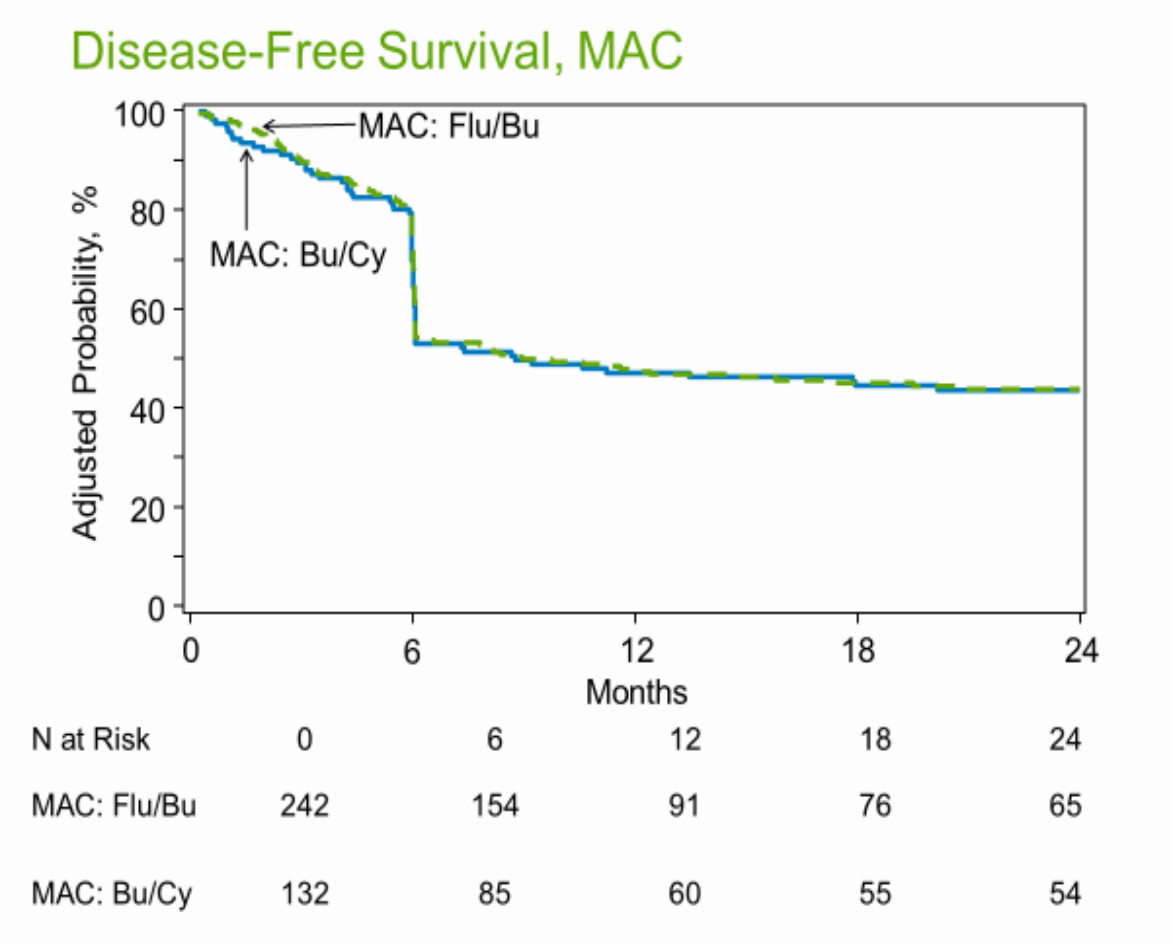


Supplemental Figure S2 – Disease free survival with reduced intensity conditioning



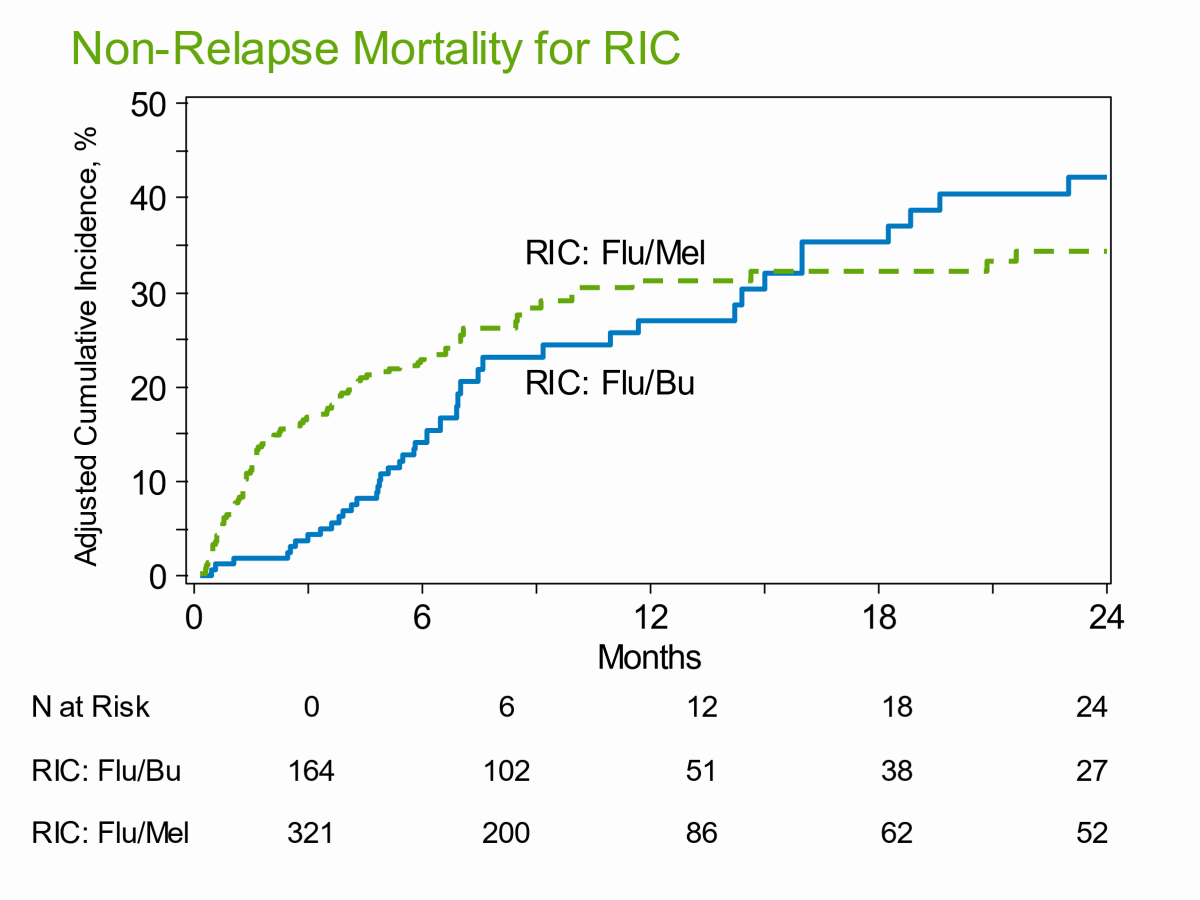
N at Risk	0	6	12	18	24
RIC: Flu/Bu	164	92	49	36	27
RIC: Flu/Mel	321	181	83	61	52

Supplemental Figure S3 – Disease free survival with myeloablative conditioning



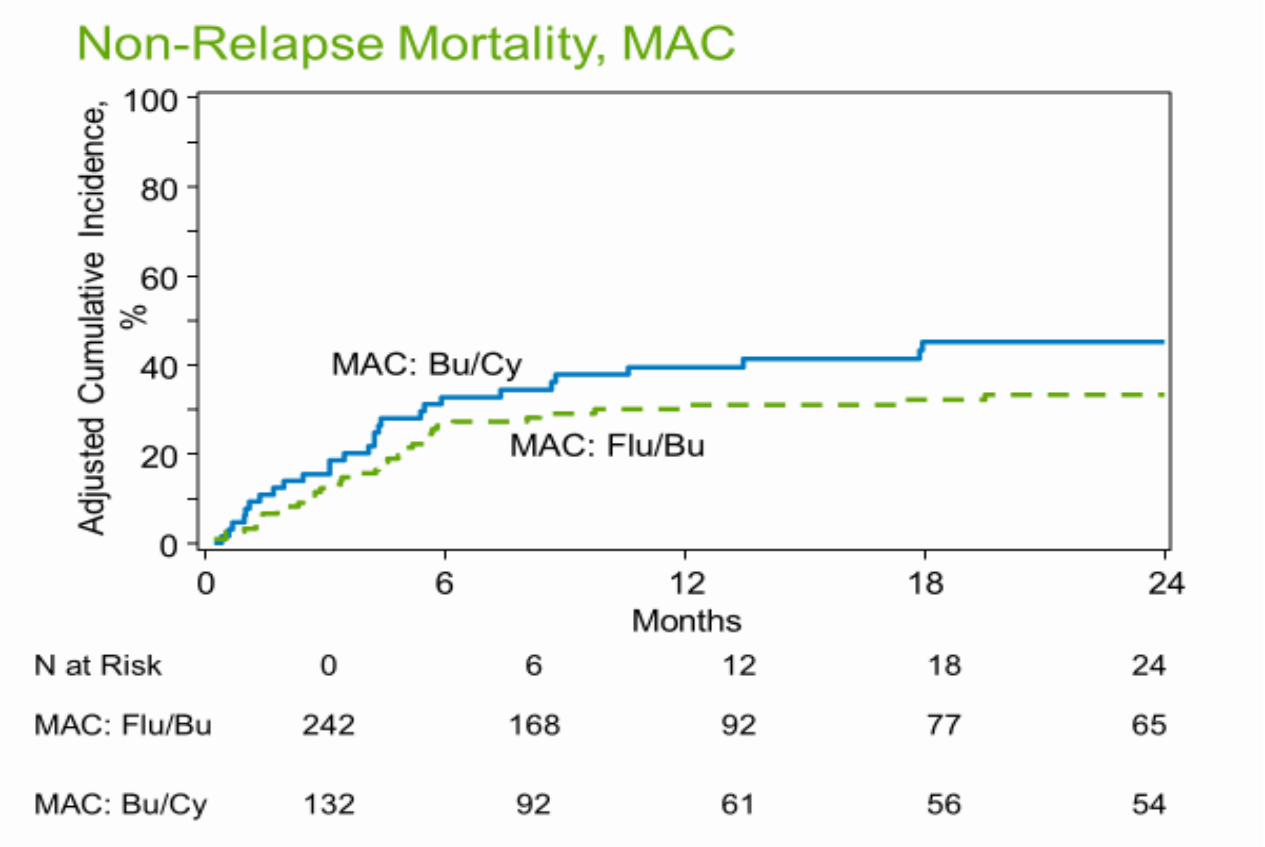
N at Risk	0	6	12	18	24
MAC: Flu/Bu	242	154	91	76	65
MAC: Bu/Cy	132	85	60	55	54

Supplemental Figure S4 – Non-relapse mortality with reduced intensity conditioning



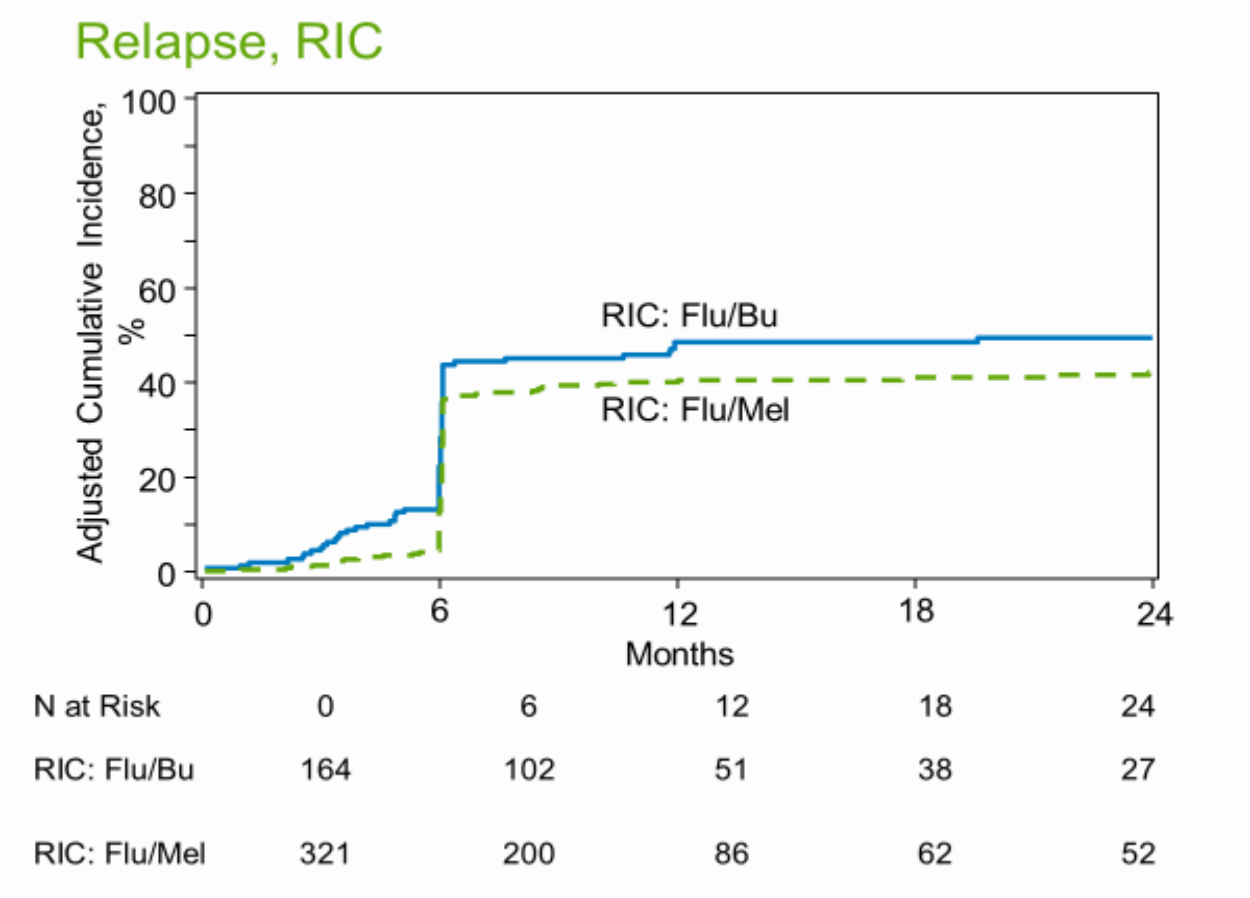
N at Risk	0	6	12	18	24
RIC: Flu/Bu	164	102	51	38	27
RIC: Flu/Mel	321	200	86	62	52

Supplemental Figure S5 – Non-relapse mortality with myeloablative conditioning



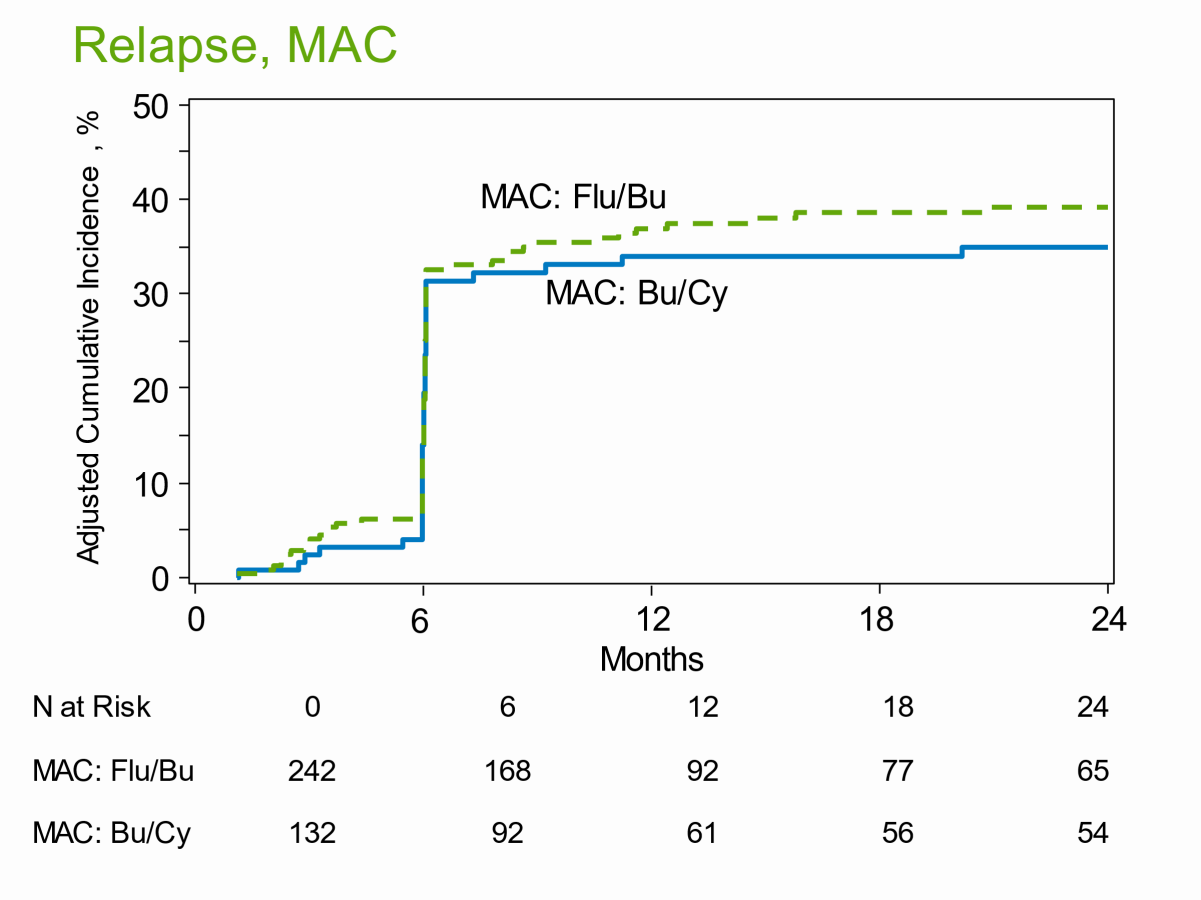
N at Risk	0	6	12	18	24
MAC: Flu/Bu	242	168	92	77	65
MAC: Bu/Cy	132	92	61	56	54

Supplemental Figure S6 – Relapse with reduced intensity conditioning



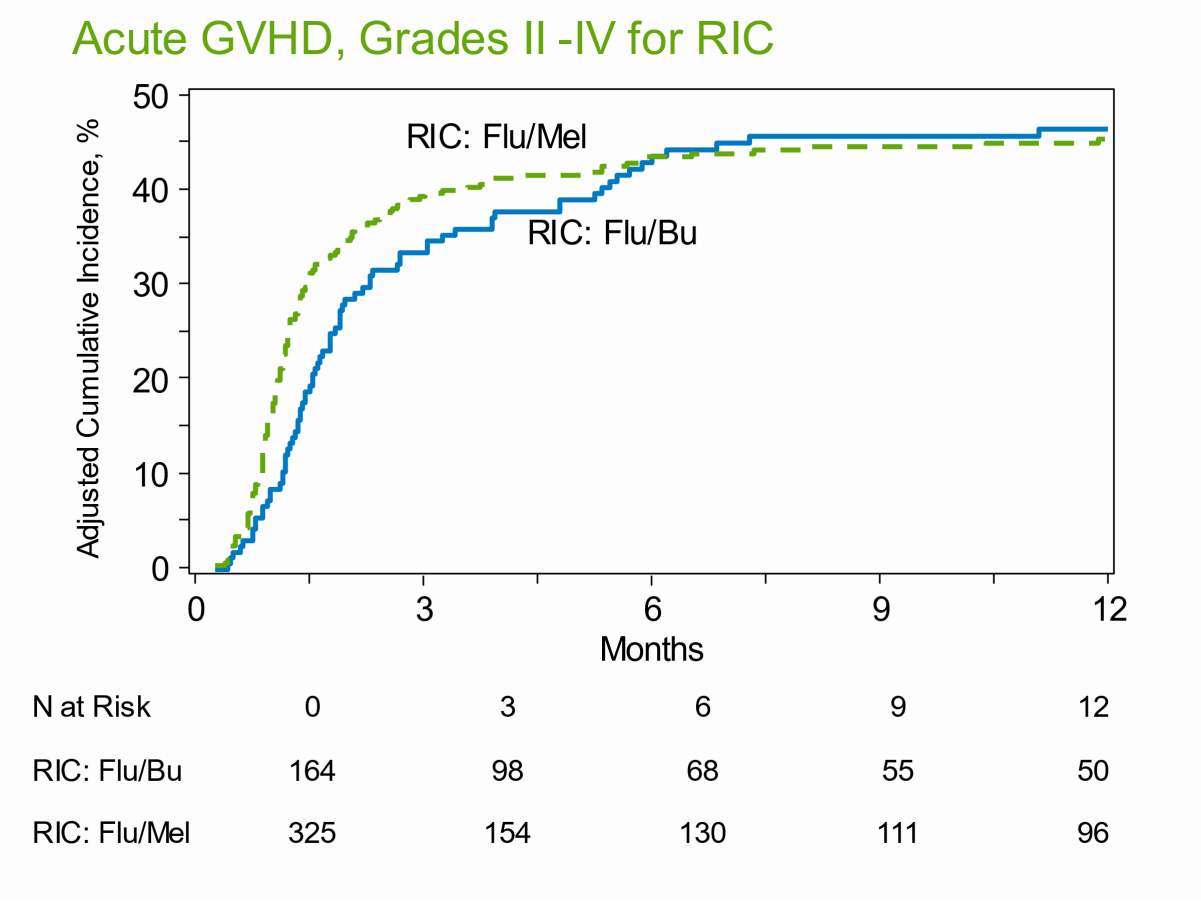
N at Risk	0	6	12	18	24
RIC: Flu/Bu	164	102	51	38	27
RIC: Flu/Mel	321	200	86	62	52

Supplemental Figure S7 – Relapse with myeloablative conditioning



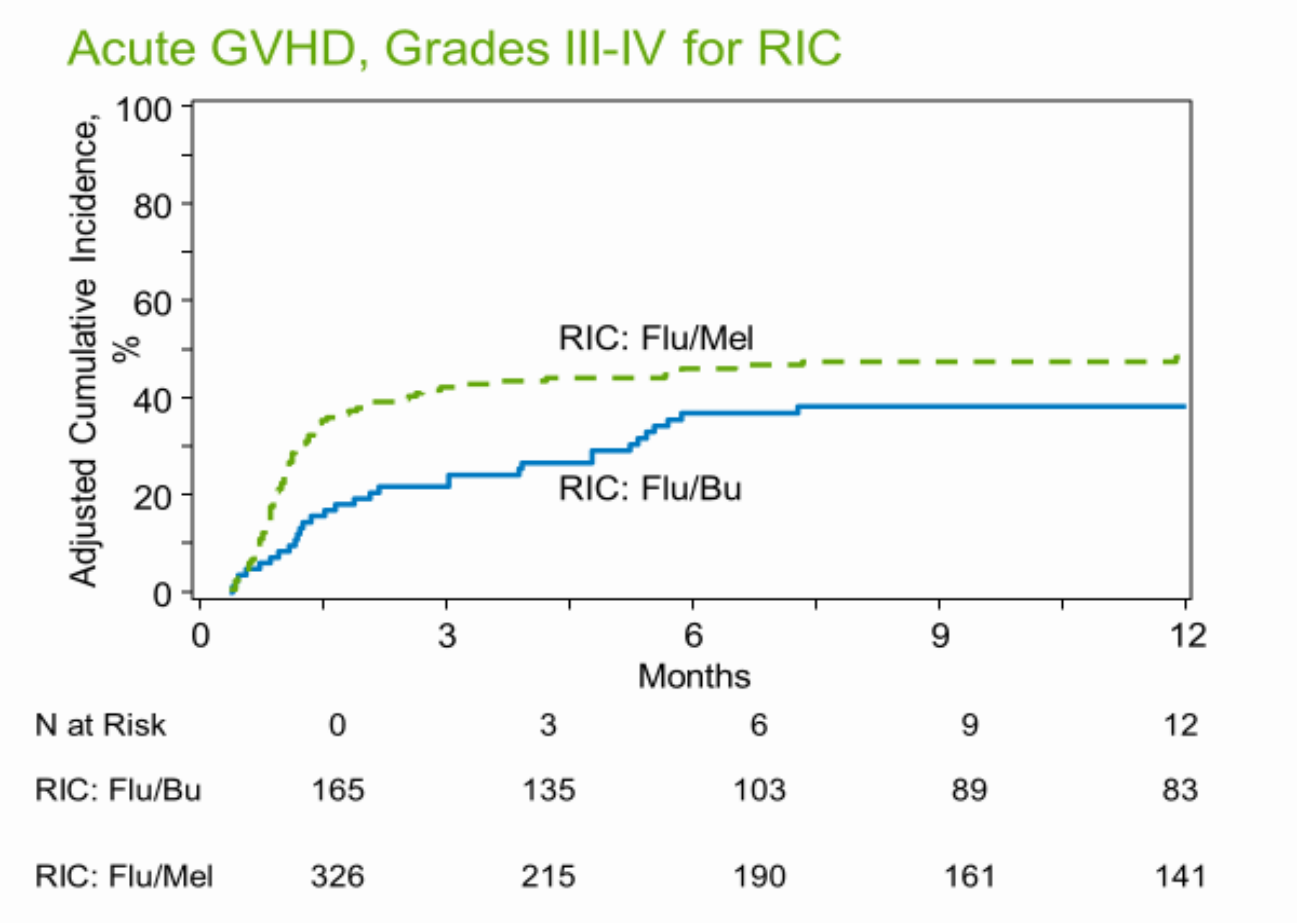
N at Risk	0	6	12	18	24
MAC: Flu/Bu	242	168	92	77	65
MAC: Bu/Cy	132	92	61	56	54

Supplemental Figure S8 – Acute GVHD grade II-IV with reduced intensity conditioning



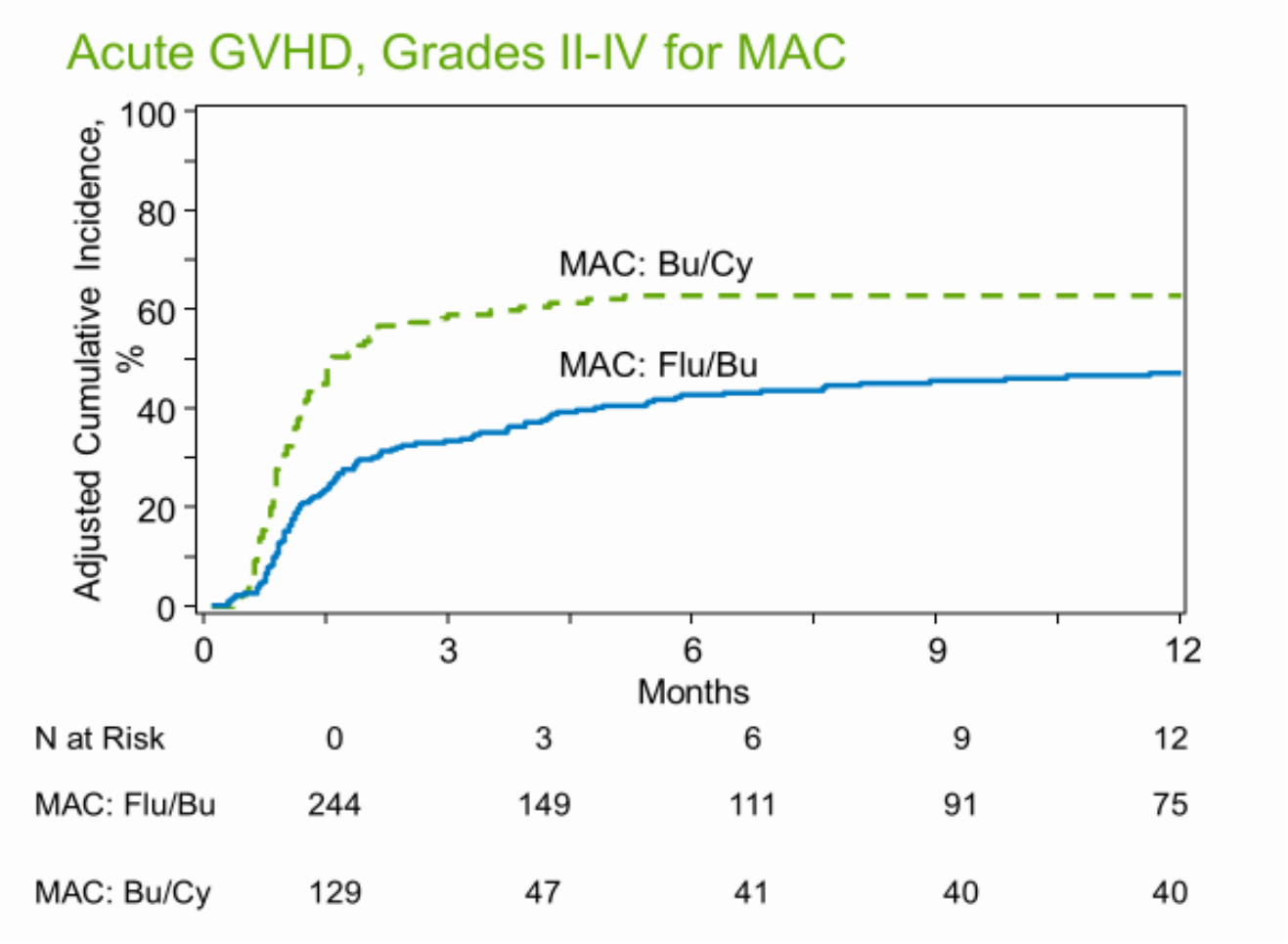
N at Risk	0	3	6	9	12
RIC: Flu/Bu	164	98	68	55	50
RIC: Flu/Mel	325	154	130	111	96

Supplemental Figure S9 – Acute GVHD grade III-IV with reduced intensity conditioning



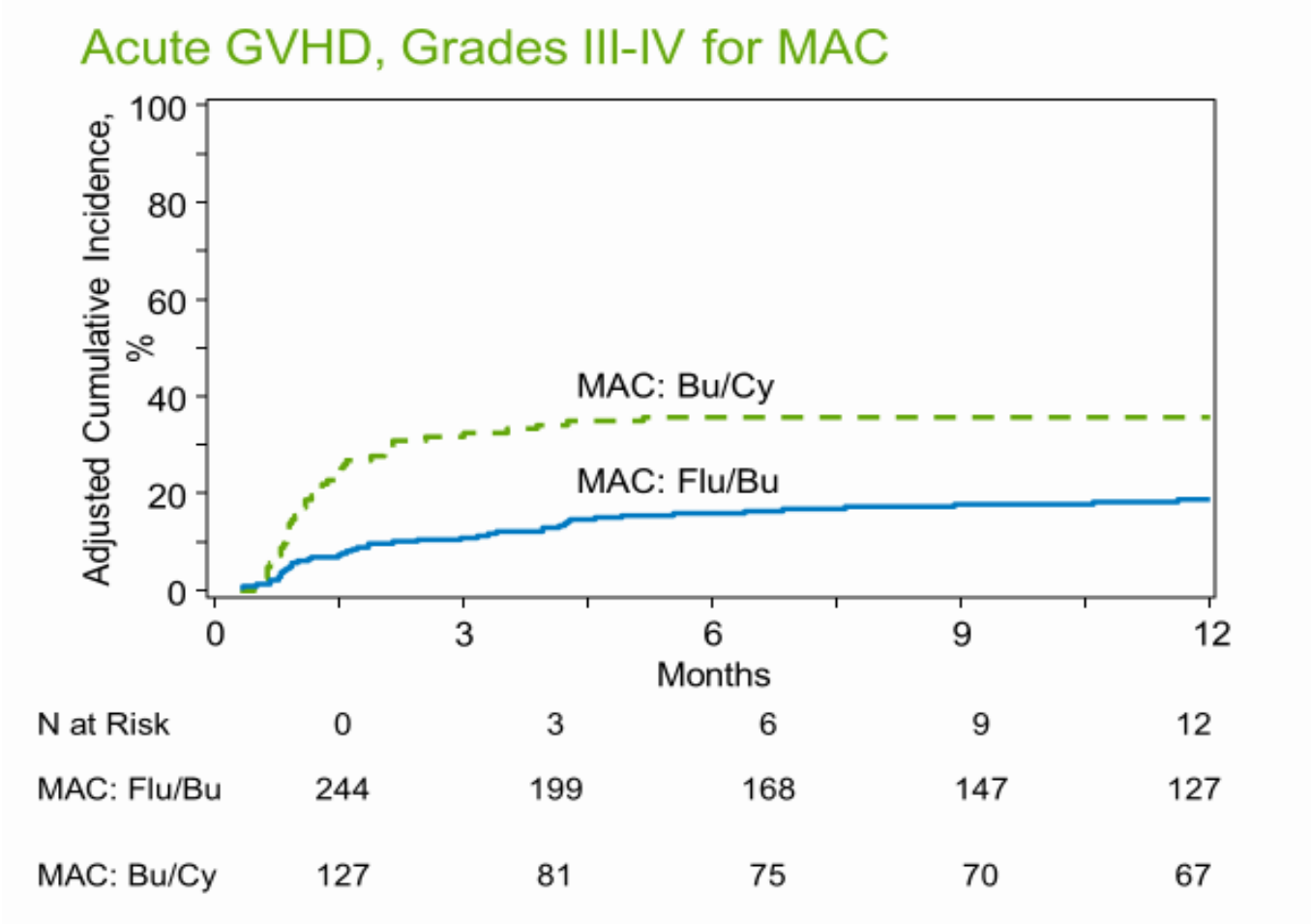
N at Risk	0	3	6	9	12
RIC: Flu/Bu	165	135	103	89	83
RIC: Flu/Mel	326	215	190	161	141

Supplemental Figure S10 – Acute GVHD grade II-IV with myeloablative conditioning



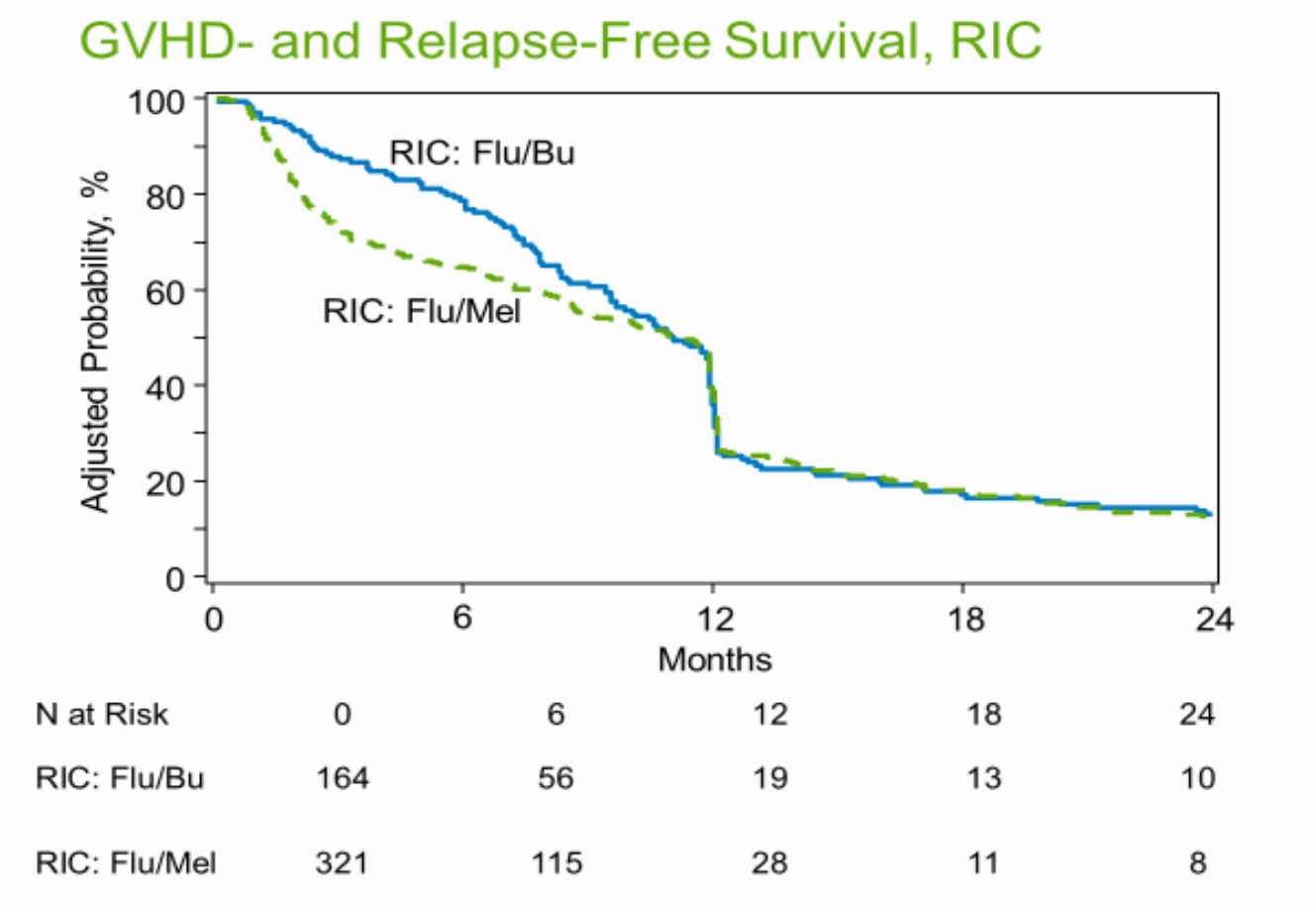
N at Risk	0	3	6	9	12
MAC: Flu/Bu	244	149	111	91	75
MAC: Bu/Cy	129	47	41	40	40

Supplemental Figure S11 – Acute GVHD grade III-IV with myeloablative conditioning



N at Risk	0	3	6	9	12
MAC: Flu/Bu	244	199	168	147	127
MAC: Bu/Cy	127	81	75	70	67

Supplemental Figure S12 – GVHD-free Relapse-free Survival with reduced intensity conditioning



N at Risk	0	6	12	18	24
RIC: Flu/Bu	164	56	19	13	10
RIC: Flu/Mel	321	115	28	11	8