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**NON-MYELOABLATIVE VERSUS REDUCED INTENSITY CONDITIONING FOR ALLOGENEIC
HEMATOPOIETIC STEM CELL TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA PATIENTS AGED
≥65: A STUDY FROM THE ALWP OF EBMT**

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ABSTRACT

The optimal conditioning intensity for allogeneic hematopoietic stem cell transplantation (allo-HCT) in elderly acute myeloid leukemia (AML) remains elusive. We retrospectively analyzed 2,900 AML patients aged ≥ 65 in complete remission who underwent allo-HCT from 2004–2021. Conditioning was classified as reduced-intensity conditioning (RIC: fludarabine with busulfan, melphalan, or treosulfan) or non-myeloablative (NMA: fludarabine with total body irradiation). Primary endpoints were overall survival (OS) and leukemia-free survival (LFS); secondary endpoints included non-relapse mortality (NRM), acute and chronic graft-versus-host disease (GVHD), and GVHD/relapse-free survival (GRFS). With follow-up censored to account for differences between arms, OS, LFS, and NRM at 2 years were similar between RIC and NMA on multivariable analysis. Peripheral blood stem cells (PBSC) were independently associated with superior OS (HR 0.67, $p=0.002$) and LFS (HR 0.71, $p=0.008$) versus bone marrow grafts. GRFS was equivalent between conditioning intensities, although RIC was associated with higher acute GVHD and NMA with higher extensive chronic GVHD. In exploratory analysis, OS and LFS were similar across RIC regimens (Flu/Bu2 as reference: Flu/Mel OS HR 0.91, $p=0.53$; Flu/Treo OS HR 0.89, $p=0.42$). In older AML patients in remission, RIC and NMA

yield comparable survival and NRM; PBSC grafts may be associated with superior outcomes although this warrants validation.

INTRODUCTION

Acute myeloid leukemia (AML) has a median age at diagnosis of ~70 years. For patients with an estimated relapse risk of 35–40% [1], allogeneic stem cell transplantation (allo-HCT) is recommended as standard of care by the European LeukemiaNet [2–4]. In older or comorbid patients, however, the transplant-mediated graft-versus-leukemia (GvL) effect is offset by substantial non-relapse mortality (NRM) [5–7]. Reduced intensity conditioning (RIC) and non-myeloablative (NMA) regimens are therefore central to allo-HCT in this population because high-dose conditioning increases organ toxicity, graft-versus-host disease (GVHD), and infection risk [8–14]. A recent EBMT study [15] and a single-center series [16] did not demonstrate outcome differences between NMA (fludarabine/total body irradiation, Flu/TBI2Gy) and RIC (fludarabine/busulfan) or other RIC regimens. However, no large-scale study has directly compared NMA versus RIC conditioning specifically in patients aged ≥ 65 .

Concurrent advances — broader feasibility of alternative-donor transplants in septuagenarian patients [17, 18], development of reduced-toxicity conditioning (RTC) strategies [11], and the adoption of post-transplant cyclophosphamide (PTCy) as a GVHD-prophylaxis standard in matched-donor transplants [19] — have reshaped contemporary practice. These advances motivated the present large-scale retrospective analysis of 2,900 AML patients aged ≥ 65 years undergoing related or unrelated donor allo-HCT. The primary aim was to compare the prototype Flu/TBI2Gy NMA regimen versus commonly used RIC regimens. Conditioning intensity was stratified as per EBMT consensus criteria [12, 20].

METHODS

Patients

This was a retrospective analysis conducted by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). Data were entered into the EBMT registry's database (ProMISe), following written patient informed consent, according to the guidelines of the Declaration of Helsinki. The study population comprised AML patients aged ≥ 65 years in first or second complete remission (CR1/CR2), who had their first allo-HCT between 2004–2021 from an HLA-matched sibling donor (MSD), 10/10 HLA-matched unrelated donor (MUD), 9/10 HLA-mismatched unrelated donor (MMUD) or a haploidentical donor (Haplo). Patients were conditioned with either intravenous fludarabine/busulfan (Flu/Bu2: total busulfan dose ≤ 6.4 mg/kg IV), fludarabine/melphalan (Flu/Mel: total melphalan dose 110–140 mg/m²), or fludarabine/treosulfan (Flu/Treo: total treosulfan dose 30 g/m²) in the RIC arm [12, 20] whereas NMA conditioning consisted of fludarabine/total body irradiation 2-Gy (Flu/TBI2Gy). The stem cell source was either granulocyte colony-stimulating factor mobilised peripheral blood stem cells (PBSC) or bone marrow (BM). Patients who received cord blood or ex vivo T-cell depletion (TCD) were excluded.

Endpoints and definitions

The primary endpoints of this study were overall survival (OS), measured as the duration from transplantation until death from any cause, and leukemia-free survival (LFS), defined as the time until either a relapse of leukemia or death from any cause. Secondary endpoints were non-relapse mortality (NRM; time to death without evidence of persistent disease or leukemic relapse, with leukaemia relapse as competing risk event), cumulative incidence of relapse (CIR), engraftment, cumulative incidence (CI) of acute GVHD (aGVHD), CI of chronic GVHD (cGVHD), and GVHD-free, relapse-free survival (GRFS; time to grade III-IV aGVHD, extensive cGVHD, AML relapse, or death from any cause) [21]. Day of engraftment was considered the first of 3 consecutive days with an

absolute neutrophil count $>0.5 \times 10^9/\text{L}$ post-transplant. Modified Glucksberg and NIH criteria were applied to grade aGVHD and cGVHD, respectively [22, 23]. CR was defined as less than 5% blasts in bone marrow without extramedullary disease at the time of allo-HCT.

Statistical analysis

Patient-, disease-, and transplant-related characteristics were compared between conditioning regimens using the chi-square or Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. OS, LFS, and GRFS were calculated using the Kaplan-Meier method. CIR and CI of NRM were analyzed using cumulative incidence competing risk models (Fine-Gray), treating NRM and relapse as mutually competing risks [24]. Similarly, death and relapse were treated as competing events in the CI functions for aGVHD and cGVHD. Median follow-up was estimated using the reverse Kaplan-Meier method. To explicitly address the imbalance in follow-up duration between the NMA and RIC arms, all univariate and multivariate analyses were executed with follow-up administratively censored at 3 years. Univariate analyses were performed using the log-rank test for OS, LFS, and GRFS, and Gray's test for RI and NRM. Multivariate regression was conducted with the Cox proportional-hazards model, and the proportional hazards assumption was visually tested and confirmed. The multivariable model included conditioning intensity, patient age (continuous per 10 years), status at transplant (CR1 vs CR2), type of AML (de novo vs secondary), cytogenetic risk (favorable, intermediate, adverse), donor type, sex matching (female donor to male recipient vs other), Karnofsky performance scale (KPS) ≥ 90 , patient and donor CMV serology, use of in vivo TCD, use of PTCy, year of transplant (continuous), and stem cell source (PBSC vs BM). Most EBMT centers used a combination of validated measurable residual disease (MRD) assays as directed by the presence of specific mutations detectable by PCR and/or aberrant leukemia phenotype assessed by flow cytometry [25]. A random effect (frailty model) for each center was implemented to account for individual center effects [26].

To ensure robustness and account for baseline imbalances, sensitivity analyses were performed by restricting the cohort to contemporary transplants (2016–2021) and by excluding haploidentical and BM recipients. Results were expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). Tests were two-sided, and $p < 0.05$ was deemed statistically significant. No multiplicity adjustment was applied for secondary endpoints. Statistical processes were conducted with SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and R 4.0.3.

RESULTS

Patient Characteristics

Of 2,900 patients, 31.4% ($n=911$) received NMA conditioning with Flu/TBI2Gy, while the remaining 68.6% ($n=1,989$) received RIC regimens — Flu/Bu2 (35.6%, $n=1,033$), Flu/Mel (22.2%, $n=643$), or Flu/Treo (10.8%, $n=313$). Median follow-up was 50.4 months (IQR 46.2–56.4) in the NMA arm versus 35.6 months (IQR 31.8–36.8) in the RIC arm ($p<0.0001$), whereas median age in NMA and RIC was 68.6 and 68.0 years respectively ($p<0.0001$). RIC had more individuals with Karnofsky performance scale ≥ 90 (70% vs 63.4%), female donor to male recipient combination (44.7% vs 16.6%), or in vivo TCD (82.5% vs 10.2%), whereas NMA were more likely to receive haploidentical allo-HCT (19.9% vs 4.3%), bone marrow graft (6.4% vs 3.1%), and PTCy (23.8% vs 7.3%). Baseline patient, disease and transplant characteristics as well as causes of death, are shown in supplementary Table S1.

Univariate Outcome Analysis

In univariate analysis with censoring at 3 years, RIC showed a 2-year overall survival of 56.5% compared to 53.4% for NMA, which was not statistically significant ($p=0.11$). RIC maintained superior 2-year GRFS (41.2% vs 33.6%, $p=0.001$). Two-year cumulative incidence of relapse, leukemia-free survival, and non-relapse mortality did not differ between conditioning intensities. Graft failure rates

were low and comparable (1.9% vs 1.5%, $p=0.44$), for NMA vs RIC. Comprehensive univariate results are shown in supplementary Table S2.

Multivariate Outcome Analysis

Reduced Intensity vs Non-Myeloablative Conditioning

Results of the multivariate analysis are described in Table 1. RIC did not confer a superior OS, LFS, or NRM compared with NMA conditioning (HR 0.88, $p=0.28$; HR 1.00, $p=0.97$; HR 1.06, $p=0.69$, respectively). RIC was associated with a higher risk of grade II–IV acute GVHD (HR 1.45, $p=0.01$), whereas the risk of extensive chronic GVHD was lower with RIC (HR 0.65, $p=0.029$). GVHD/relapse-free survival (GRFS) did not differ between RIC and NMA (HR 0.94, $p=0.49$) (Figure 1). Tests for interaction indicated that the effect of conditioning intensity remained independent and consistent, as no significant interactions with other clinical covariates were identified ($p > 0.15$).

Adverse Prognostic Factors

In the multivariable analysis, statistically significant adverse factors for OS included increasing age per 10 years (HR 1.37, $p=0.01$), secondary AML (HR 1.19, $p=0.014$), adverse-risk cytogenetics (HR 1.52, $p=0.044$), recipient CMV positivity (HR 1.15, $p=0.049$), and transplantation from a MMUD (HR 1.53, $p=0.0001$). Secondary AML and adverse-risk cytogenetics also increased relapse risk (HR 1.24, $p=0.018$; and HR 2.08, $p=0.008$, respectively). Furthermore, older age, recipient CMV positivity, and MMUD significantly increased NRM (HR 1.62, $p=0.003$; HR 1.27, $p=0.016$; and HR 2.31, $p<0.0001$, respectively) (Table 1).

Favorable Prognostic Factors

Longer OS was significantly associated with KPS ≥ 90 (HR 0.82, $p=0.003$) and PBSC graft (HR 0.67, $p=0.002$). PBSC grafts also demonstrated a trend toward reducing relapse risk (HR 0.71, $p=0.055$), and significantly improved LFS (HR 0.71, $p=0.008$), while KPS ≥ 90 was correlated with improved NRM (HR 0.75, $p=0.002$), as shown in Table 1.

Exploratory Analysis in Reduced Intensity Conditioning Cohort

In a multivariable subset analysis confined to the RIC arm, we assessed outcomes across the three specific regimens: Flu/Bu2, Flu/Mel, and Flu/Treo. Compared with Flu/Bu2, patients receiving Flu/Mel demonstrated a significantly lower risk of relapse (HR 0.54, $p=0.0002$) and a reduced risk of overall chronic GVHD (HR 0.69, $p=0.04$). However, this was nuanced by a trend toward higher NRM in the Flu/Mel group (HR 1.41, $p=0.073$), ultimately resulting in no significant differences in LFS, OS, or GRFS between the two regimens. Outcomes for patients conditioned with Flu/Treo did not differ significantly from the Flu/Bu2 reference group across any of the evaluated endpoints. When directly comparing the remaining two regimens, Flu/Treo was associated with a significantly higher risk of relapse compared to Flu/Mel (HR 1.66, $p=0.017$) but conferred a lower risk of grade II–IV acute GVHD (HR 0.59, $p=0.032$) (supplementary Table S3).

Sensitivity Analyses

To ensure the robustness of these findings against baseline patient arm imbalances, sensitivity analyses were performed. The multivariate analysis restricted to patients transplanted between 2016 and 2021, confirmed no statistically significant differences between the two regimens regarding OS (HR 0.82, $p=0.22$), LFS (HR 0.92, $p=0.55$), NRM (HR 1.18, $p=0.45$), relapse (HR 0.78, $p=0.15$), or GRFS (HR 0.92, $p=0.49$). RIC remained associated with a significantly higher risk of grade II–IV acute GVHD (HR 1.57, $p=0.024$) albeit grade III–IV acute GVHD (HR 1.26, $p=0.47$) and extensive chronic GVHD (HR 0.65, $p=0.12$) did not differ significantly between conditioning intensity arms

(supplementary Table S4). A similar statistical approach excluding haploidentical donors and bone marrow grafts, corroborated no statistically significant differences between NMA versus RIC concerning OS (HR 0.86, $p=0.26$), LFS (HR 0.97, $p=0.79$), NRM (HR 0.94, $p=0.75$), or GRFS (HR 0.96, $p=0.71$). (supplementary Table S5).

Finally, among 248 NMA and 753 RIC patients with known pre-transplant MRD, no statistically significant interaction was observed between conditioning intensity and MRD status (supplementary Table S6).

DISCUSSION

In this study, we analyzed 2,900 AML patients aged ≥ 65 years who underwent their first allo-HCT in CR1 or CR2 between 2004 and 2021. Transplants were performed from MSD, MUD, MMUD, or Haplo donors, using Flu/Bu2, Flu/Mel, or Flu/Treo (RIC) versus Flu/TBI2Gy (NMA). Our findings show that neither conditioning intensity (NMA vs. RIC) nor individual RIC regimens significantly influenced NRM, LFS, or OS. To date, this is the largest retrospective registry study [15, 16] showing that, among RIC strategies, less intensive NMA conditioning does not compromise disease control in elderly AML patients receiving related or unrelated donor allo-HCT. Further, we did not restrict this study to CR1, as both arms had similar CR1/CR2 distributions and no differences by CR1 versus CR2 on multivariate analysis. It is prudent to highlight that these results should be interpreted with caution, because a null result in a retrospective study does not definitively prove equivalence. For example, the 95% CI for OS (HR 0.71–1.10) between RIC and NMA arms (Table 1) means a clinically meaningful benefit of up to 29% for RIC cannot be definitively excluded. Nevertheless, our findings are consistent with Heinicke et al., who compared Flu/Bu2 and Flu/TBI2Gy in AML patients ≥ 65 years [15], and with several retrospective and prospective trials comparing MAC and RIC in younger myeloid cohorts [9, 27–32]. Finally, a French randomized trial demonstrated that Flu/Bu2 was associated with higher long-term NRM, and Flu/TBI2Gy with graft failure and inferior LFS [33]. Differences in patient age,

characteristics and disease distribution (<20% AML in the French study) likely explain the observed discrepancies.

The role of pre-transplant MRD in allo-HCT for AML remains of primary interest. In our sensitivity analysis, conditioning intensity did not interact with MRD status. Hourigan et al. showed that MAC reduced relapse in MRD positive patients with AML/MDS using NGS [32], while the UK FIGARO trial found no benefit of augmented conditioning in MRD+ AML by flow cytometry [9], aligning more closely with our results and those of Walter et al. [16]. One must state that the quest for optimizing conditioning regimens for MRD-positive elderly AML will require future prospective, randomized studies stratified by genetic subsets, donor type, and methods of GVHD prophylaxis.

Unlike conditioning intensity, the use of PBSC was independently associated with improved OS, primarily through a trend in reduced relapse and significantly improved LFS, without adversely affecting GRFS. An EBMT activity survey reported that the shift from BM to PBSC for allo-HCT, which began during the first year of the SARS-CoV-2 pandemic, was reversed in 2021; in that year BM was used in 9.4%, 18.9%, and 5.2% of MSD, MUD, and Haplo allo-HCT procedures, respectively, among patients with myeloid malignancies [34]. EBMT and Blood and Marrow Transplant Clinical Trials Network studies have examined the impact of stem cell source on transplant outcomes. In RIC allo-HCT for AML between 2002 and 2012, PBSC was associated with increased cGVHD [35], while two subsequent EBMT studies observed higher rates of aGVHD with PBSC in haploidentical transplants for acute leukemia [36, 37]. Ultimately, Rocha et al. demonstrated that PBSC was associated with increased NRM (HR 1.22) and decreased OS (HR 1.13) compared to BM in a substantial cohort of 8,854 adults undergoing Haplo-PTCy [37]. In contrast, a prospective randomized trial in MUD allo-HCT demonstrated that PBSC reduced graft failure whereas BM protected against cGVHD, with both sources yielding comparable OS [38]. In their seminal paper, Luznik et al. reported low GVHD and NRM for older patients receiving NMA PTCy Haplo transplants, although disease recurrence was high in that setting [39]. Taken together, our data suggest that PBSC may enhance disease control in older AML recipients receiving attenuated conditioning, likely because PBSC grafts contain a higher

number of donor T cells compared with BM grafts [40]. Further research is needed to elucidate how T-cell and other lymphocyte subsets within stem cell grafts modulate GvL while limiting GVHD.

In this analysis, the RIC arm demonstrated a higher incidence of aGVHD, whereas NMA recipients experienced more cGVHD; despite these differences there were no significant differences in GRFS or OS, consistent with prior reports [15, 32]. RIC Flu/Mel and Flu/Treo with a transplant conditioning index (TCI) ≥ 2.0 are associated with a higher risk of acute GVHD than Flu/TBI2Gy (TCI 1.5) [41], which may in turn contribute to a GVHD-related increase in non-relapse mortality [42]. The greater burden of cGVHD in the NMA cohort reflects significantly lower utilization of TCD (10.2% vs 82.5% in RIC arm, $p < 0.0001$) and higher Haplo donor allo-HCT (19.9% vs 4.3% in RIC arm, $p < 0.0001$) which would be expected to affect chronic GVHD incidence [43-45]. Indeed, our sensitivity analysis of patients transplanted between 2016 and 2021 showed that the initial difference in extensive chronic GVHD between study arms disappeared (HR 0.65, $p = 0.12$). This may reflect wider adoption of modern GVHD prophylaxis platforms such as PTCy in NMA-conditioned allo-HCT [46]. Nonetheless, it should be emphasized that this study was not designed to compare outcomes between specific RIC regimens or GVHD prophylaxis strategies. Rather, the exploratory analyses were intended to assess the validity of the overall NMA versus RIC comparison across a heterogeneous population.

Within the RIC cohort, exploratory analyses revealed that melphalan-based conditioning significantly reduced relapse risk compared to fludarabine/busulfan (HR 0.54 [0.39–0.75], $p = 0.0002$), consistent with prior EBMT/ALWP [47] and CIBMTR reports [48] demonstrating the superior anti-leukemic activity of Flu/Mel whereas this relapse benefit was abrogated by higher non-relapse mortality, such that these competing risks resulted in equivalent long-term leukemia-free and overall survival across these two widely utilised RIC regimens. Similarly, Flu/Treo demonstrated higher relapse rates compared to Flu/Mel, but was associated with lower acute GVHD compared to Flu/Mel, consistent with the retrospective, propensity-matched analysis by Beelen et al. who found no difference in relapse incidence between Flu/Treo and Flu/Mel ($p = 0.28$) but identified significantly lower NRM with Flu/Treo ($p = 0.019$), resulting in superior OS for Flu/Treo ($p = 0.04$) [49]. Intriguingly, a recent meta-

analysis by Wannaphut et al. suggested that in elderly patients (≥ 60 years) with AML/MDS, Flu/Mel may improve overall survival without significantly increasing transplant-related mortality [50]. These divergent findings illustrate the multifaceted task of regimen selection, necessitating prospective, randomized trials to guide individualized conditioning strategies.

This study is limited by its retrospective design, which prevents definitive attribution of causality and makes it impossible to decipher the clinical reasoning that led centers to select NMA versus RIC for individual patients. Firstly, median follow-up was substantially longer in the NMA arm. To explicitly assess the potential impact of this imbalance on late endpoints (relapse, chronic GVHD, LFS, and OS), follow-up was estimated using the reverse Kaplan-Meier method, and all analyses were administratively censored at 3 years (or 2 years for subgroups). This rigorous adjustment confirmed our initial findings. Secondly, selection bias and center-level practice heterogeneity produced important baseline imbalances between arms. The markedly higher use of haploidentical donors with PTCy and bone marrow grafts in the NMA arm may independently influence relapse risk and GVHD incidence, representing a significant confounding factor when interpreting the comparable outcomes. The NMA cohort also contained more patients with higher comorbidity (HCT-CI >2), while the RIC cohort included greater use of T-cell depletion, more adverse-risk AML, and lower HCT-CI. To directly address these confounders, robust sensitivity analyses restricting the cohort to recent transplant years (2016–2021) and completely excluding haploidentical and bone marrow recipients were conducted, which demonstrated consistent outcomes and strengthened the scientific rigor of our conclusions regarding conditioning intensity. Thirdly, while the PBSC finding is compelling, BM grafts comprised only ~4% of the cohort; this small absolute number of BM recipients raises concerns regarding the stability of the PBSC benefit estimate. Furthermore, the dataset lacks information on post-relapse therapies such as donor lymphocyte infusions, which could confound overall survival estimates, and potential immortal time bias regarding the time from CR1/CR2 to transplant cannot be entirely excluded. Comparisons within the RIC cohort must be interpreted with circumspection, as individual center preferences, infrastructure, and local elderly AML population

characteristics decidedly affect the selection of RIC regimens. Lastly, given the high rate of missing pre-transplant MRD data (72.8% in NMA, 62.1% in RIC), our stratified analyses lack granularity, rendering these specific findings purely exploratory.

In conclusion, among older patients with AML receiving related or unrelated-donor allo-HCT, conditioning intensity (NMA versus RIC) produced comparable survival and relapse outcomes. In contrast, peripheral-blood stem cell grafts were independently associated with improved leukemia-free and overall survival, supporting the prioritization of graft source and the incorporation of contemporary GVHD-prophylaxis data [51–53] when planning allo-HCT for older or frail patients. Furthermore, these findings may support the design of prospective, MRD-stratified trials—for example, randomized non-inferiority studies of NMA versus RIC in MRD-negative AML patients aged ≥ 65 years.

Ethics Approval and Consent to Participate

All methods in this study were performed in accordance with the relevant guidelines and regulations, including the principles of the Declaration of Helsinki. This retrospective registry analysis was conducted under the auspices of the EBMT Acute Leukemia Working Party. The EBMT registry (ProMiSe) operates under ethics approval granted to the EBMT by the relevant national and institutional ethics committees of participating centers. Written informed patient consent for data use in registry-based research was obtained prior to data entry into the registry. No additional institutional ethics committee approval was required for this retrospective analysis.

Author contributions

AK designed the study, interpreted the data, and wrote the draft manuscript. AS and MM designed the study, supervised the project and contributed to the manuscript. ML performed the statistical analyses, supervised the project, and contributed to the manuscript. EN, UP, DB, HS, FK, TS, GC, ET,

PD, VP, GS, AECB, JP, ME, GO, JHB, GVG, MS, JOB, JLB, PC, JAS, BNS, EB, FC, and AN contributed to retrospective patient recruitment, writing, critical review, and approval of the manuscript.

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Conflict of interest

The authors declare no competing interests.

Data Availability

The data were allocated by the EBMT registry in Paris. The datasets are available upon data-specific request.

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Figure Legends

Figure 1: Post-transplant outcomes for 2,900 adults ≥65 years with AML transplanted in first or second complete morphologic remission according to conditioning intensity.

NRM non-relapse mortality, RI relapse incidence, LFS leukemia-free survival, OS overall survival, NMA non-myeloablative, RIC reduced-intensity conditioning.

Table 1: Multivariate Analysis of Clinical Outcomes Between Conditioning Intensity Arms

	RELAPSE		NRM		LFS		OS		GRFS		Acute GVHD II-IV		Acute GVHD III-IV		chronic GVHD		extensive chronic GVHD	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
RIC vs NMA	0.94 (0.72-1.21)	0.62	1.06 (0.79-1.43)	0.69	1 (0.82-1.22)	0.97	0.88 (0.71-1.1)	0.28	0.94 (0.78-1.12)	0.49	1.45 (1.09-1.93)	0.01	1.34 (0.86-2.1)	0.19	0.79 (0.61-1.01)	0.063	0.65 (0.44-0.96)	0.029
Age (per 10y)	1.13 (0.83-1.53)	0.43	1.62 (1.17-2.24)	0.003	1.34 (1.07-1.67)	0.01	1.37 (1.08-1.74)	0.01	1.29 (1.05-1.57)	0.013	1.14 (0.84-1.55)	0.4	1.4 (0.84-2.32)	0.2	1.31 (0.99-1.74)	0.059	1.51 (1.26-2.26)	0.048
CR2 vs CR1	1.09 (0.88-1.34)	0.45	1.12 (0.91-1.39)	0.28	1.12 (0.96-1.3)	0.15	1.06 (0.9-1.25)	0.46	1.06 (0.92-1.22)	0.4	0.93 (0.75-1.15)	0.49	0.76 (0.51-1.12)	0.17	1.1 (0.91-1.32)	0.33	1.18 (0.9-1.54)	0.24
secondary AML	1.24 (1.04-1.48)	0.018	1.18 (0.97-1.43)	0.1	1.21 (1.06-1.38)	0.005	1.19 (1.04-1.38)	0.014	1.24 (1.1-1.39)	0.0005	1.24 (1.03-1.48)	0.021	1.35 (1-1.81)	0.05	1.2 (1.01-1.42)	0.035	1.37 (1.08-1.75)	0.011
Cytogenetic favorable (ref)	1		1		1		1		1		1		1		1		1	
intermediate risk	1.14 (0.68-1.93)	0.61	1.03 (0.61-1.76)	0.9	1.11 (0.76-1.61)	0.58	0.99 (0.67-1.46)	0.94	1.22 (0.87-1.71)	0.26	1.43 (0.84-2.43)	0.19	2.07 (0.65-6.6)	0.22	0.95 (0.63-1.42)	0.79	1.01 (0.55-1.85)	0.97
adverse risk	2.08 (1.21-3.57)	0.008	1.28 (0.73-2.26)	0.39	1.73 (1.17-2.55)	0.006	1.52 (1.01-2.28)	0.044	1.66 (1.16-2.37)	0.005	1.53 (0.88-2.68)	0.14	2.23 (0.68-7.34)	0.19	0.9 (0.57-1.4)	0.63	0.99 (0.51-1.9)	0.97
NA/failed	1.39 (0.81-2.39)	0.23	1.23 (0.71-2.13)	0.45	1.33 (0.9-1.95)	0.15	1.17 (0.78-1.75)	0.45	1.24 (0.87-1.77)	0.23	1.2 (0.69-2.09)	0.51	1.41 (0.43-4.62)	0.57	0.8 (0.52-1.23)	0.31	0.8 (0.42-1.52)	0.49
Year of HSCT	1 (0.98-1.02)	0.97	0.98 (0.95-1.01)	0.11	0.99 (0.97-1.01)	0.27	0.99 (0.97-1.01)	0.19	0.99 (0.97-1)	0.14	0.96 (0.94-0.99)	0.004	0.93 (0.89-0.97)	#### #	0.99 (0.96-1.01)	0.25	1.02 (0.98-1.05)	0.33
Donor MSD (reference)	1		1		1		1		1		1		1		1		1	
UD 10/10	0.73 (0.6-0.88)	0.001	1.39 (1.09-1.77)	0.007	0.96 (0.83-1.12)	0.64	1.06 (0.9-1.24)	0.51	0.95 (0.83-1.09)	0.5	1.77 (1.4-2.23)	< 1	1.47 (1-2.16)	0.04 7	1 (0.83-1.2)	0.97	0.88 (0.68-1.16)	0.37
UD 9/10	0.81 (0.61-1.08)	0.16	2.31 (1.71-3.12)	< 0.0001	1.33 (1.08-1.63)	0.007	1.53 (1.23-1.9)	0.0001	1.27 (1.06-1.54)	0.011	1.87 (1.38-2.53)	0.000 1	2.17 (1.35-3.49)	0.00 1	1.09 (0.83-1.44)	0.53	1.2 (0.82-1.76)	0.35
Haplo	0.91 (0.59-1.4)	0.66	1.75 (1.1-2.77)	0.018	1.2 (0.87-1.65)	0.26	1.27 (0.9-1.78)	0.17	1.01 (0.76-1.33)	0.95	1.95 (1.29-2.94)	0.001	1.44 (0.72-2.89)	0.3	0.84 (0.57-1.22)	0.35	0.54 (0.31-0.94)	0.03
KPS>=90	0.89 (0.75-1.05)	0.17	0.75 (0.62-0.9)	0.002	0.83 (0.73-0.94)	0.003	0.82 (0.71-0.93)	0.003	0.84 (0.75-0.94)	0.002	0.9 (0.75-1.07)	0.22	0.89 (0.67-1.19)	0.44	0.9 (0.77-1.06)	0.2	0.83 (0.66-1.05)	0.12
Female D to male R	0.66 (0.55-0.79)	< 0.0001	1.5 (1.24-1.82)	< 0.0001	0.99 (0.87-1.13)	0.89	1.09 (0.95-1.26)	0.23	0.97 (0.86-1.1)	0.65	1.25 (1.04-1.51)	0.017	1.28 (0.95-1.71)	0.11	0.89 (0.75-1.05)	0.17	0.9 (0.69-1.18)	0.44
Pat. CMV pos	0.94 (0.79-1.13)	0.52	1.27 (1.05-1.55)	0.016	1.08 (0.94-1.23)	0.27	1.15 (1-1.33)	0.049	1.04 (0.93-1.17)	0.49	0.99 (0.83-1.19)	0.95	0.77 (0.57-1.03)	0.08 1	1.13 (0.96-1.33)	0.16	1.13 (0.89-1.43)	0.33
Don. CMV pos	1.18 (1-1.39)	0.057	0.91 (0.76-1.09)	0.29	1.06 (0.93-1.19)	0.38	1 (0.88-1.14)	0.94	1.03 (0.92-1.15)	0.65	1.06 (0.9-1.25)	0.49	1.22 (0.92-1.63)	0.17	0.99 (0.85-1.16)	0.92	0.96 (0.77-1.2)	0.72
in vivo TCD	1.1 (0.85-1.43)	0.45	0.99 (0.74-1.32)	0.93	1.04 (0.86-1.26)	0.69	1.07 (0.86-1.33)	0.53	0.88 (0.74-1.05)	0.14	0.66 (0.5-0.87)	0.003	0.8 (0.51-1.24)	0.31	0.65 (0.51-0.83)	0.000 6	0.51 (0.35-0.74)	0.0004
PTCy	0.72 (0.49-1.05)	0.088	0.97 (0.66-1.42)	0.87	0.82 (0.63-1.08)	0.15	0.9 (0.67-1.19)	0.45	0.82 (0.65-1.04)	0.1	1.52 (0.87-2.64)	0.051	1.52 (0.87-2.64)	0.14	0.65 (0.48-0.88)	0.006	0.46 (0.3-0.72)	0.0007
PBSC vs BM	0.71 (0.51-1.01)	0.055	0.72 (0.5-1.03)	0.069	0.71 (0.56-0.91)	0.008	0.67 (0.51-0.86)	0.002	0.8 (0.63-1.02)	0.067	1.37 (0.9-2.08)	0.15	1.53 (0.7-3.32)	0.28	1.29 (0.86-1.92)	0.22	0.99 (0.57-1.71)	0.96

NMA non myeloablative, RIC reduced intensity conditioning, NRM non relapse mortality, LFS leukemia free survival, OS overall survival, GRFS graft-versus-host disease-free and relapse-free survival, GVHD graft-versus-host disease, y years, AML acute myeloid leukemia, NA not applicable, HSCT hematopoietic stem cell transplantation, CR1 first complete remission, CR2 second complete remission, MSD matched sibling donor, UD unrelated donor, Haplo haploidentical donor, KPS Karnofsky performance scale, D donor, R recipient, CMV cytomegalovirus, Pat. patient, Don. donor, pos positive, TCD T-cell depletion, PTCy post-transplant cyclophosphamide, PBSC peripheral blood stem cells, BM bone marrow.



