# Reduced intensity conditioning for acute myeloid leukemia using melphalan- vs busulfan-based regimens: a CIBMTR report

Zheng Zhou,[1] Rajneesh Nath,[2] Jan Cerny,[3] Hai-Lin Wang,[4] Mei-Jie Zhang,[4,5] Hisham Abdel-Azim,[6] Vaibhav Agrawal,[7] Gulrayz Ahmed,[8] A. Samer Al-Homsi,[9] Mahmoud Aljurf,[10] Hassan B. Alkhateeb,[11] Amer Assal,[12] Ulrike Bacher,[13] Ashish Bajel,[14] Qaiser Bashir,[15] Minocher Battiwalla,[16] Vijaya Raj Bhatt,[17] Michael Byrne,[18] Jean-Yves Cahn,[19] Mitchell Cairo,[20] Hannah Choe,[21] Edward Copelan,[22] Corey Cutler,[23] Moussab B. Damlaj,[24] Zachariah DeFilipp,[25] Marcos De Lima,[26] Miguel Angel Diaz,[27] Nosha Farhadfar,[28] James Foran,[29] César O. Freytes,[30] Aaron T. Gerds,[31] Usama Gergis,[32] Michael R. Grunwald,[22] Zartash Gul,[33] Mehdi Hamadani,[4] Shahrukh Hashmi,[34,35] Mark Hertzberg,[36] Gerhard C. Hildebrandt,[37] Nasheed Hossain,[38] Yoshihiro Inamoto,[39] Luis Isola,[40] Tania Jain,[41] Rammurti T. Kamble,[42] Muhammad Waqas Khan,[43] Mohamed A. Kharfan-Dabaja,[44] Partow Kebriaei,[15] Natasha Kekre,[45] Nandita Khera,[46] Hillard M. Lazarus,[47] Jane L. Liesveld,[48] Mark Litzow,[49] Hongtao Liu,[50] David I. Marks,[51] Rodrigo Martino,[52] Vikram Mathews,[53] Asmita Mishra,[54] Hemant S. Murthy,[44] Arnon Nagler,[55,56] Ryotaro Nakamura,[57] Sunita Nathan,[58] Taiga Nishihori,[54] Rebecca Olin,[59] Richard F. Olsson,[60,61] Neil Palmisiano,[62] Sagar S. Patel,[63] Mrinal M. Patnaik,[11] Attaphol Pawarode,[64] Miguel-Angel Perales,[65] Ioannis Politikos,[65] Uday Popat,[15] David Rizzieri,[66] Brenda M. Sandmaier,[67] Bipin N. Savani,[68] Sachiko Seo,[69] Nirav N. Shah,[70] Geoffrey L. Uy,[71] David Valcárcel,[72] Leo F. Verdonck,[73] Edmund K. Waller,[74] Youjin Wang,[75] Daniel Weisdorf,[76] Baldeep Wirk,[77] Eric Wong,[14] Jean A. Yared,[78] and Wael Saber[4]

[1]Beth Israel Lahey Health, Lahey Hospital and Medical Center, Burlington, MA; [2]Banner MD Anderson Cancer Center, Gilbert, AZ; [3]Division of Hematology/Oncology, Department of Medicine, University of Massachusetts Medical Center, Worcester, MA; [4]Center for International Blood and Marrow Transplant Research, Department of Medicine, and [5]Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI; [6]Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA; [7]Division of Hematology-Oncology, Indiana University School of Medicine, Indianapolis, IN; [8]Internal Medicine, Medical College of Wisconsin, Milwaukee, WI; [9]New York University Langone Medical Center, New York, NY; [10]Department of Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [11]Bone Marrow Transplant Program, Mayo Clinic, Rochester, MN; [12]NYPH/Columbia University Medical Center, New York, NY; [13]Department of Hematology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [14]Royal Melbourne Hospital City Campus, Parkville, VIC, Australia; [15]Department of Stem Cell Transplantation & Cellular Therapy, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; [16]Sarah Cannon Blood Cancer Network, Nashville, TN; [17]The Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE; [18]Vanderbilt University Medical Center, Nashville, TN; [19]Department of Hematology, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; [20]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Department of Pediatrics, New York Medical College, Valhalla, NY; [21]The Ohio University Wexner Medical Center, James Comprehensive Cancer Center, Columbus, OH; [22]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC; [23]Center for Hematologic Oncology, Dana-Farber Cancer Institute, Boston, MA; [24]King Abdulaziz Medical City; King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [25]Blood and Marrow Transplant Program, Massachusetts General Hospital, Boston, MA; [26]Department of Medicine, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH; [27]Department of Hematology/Oncology, Hospital Infantil Universitario Niño Jesus, Madrid, Spain; [28]Division of Hematology/Oncology, University of Florida College of Medicine, Gainesville, FL; [29]Bone Marrow Transplant Program, Mayo Clinic, Jacksonville, FL; [30]Texas Transplant Institute, San Antonio, TX; [31]Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; [32]Hematologic Malignancies & Bone Marrow Transplant, Department of Medical Oncology, New York Presbyterian Hospital/Weill Cornell Medical Center, New York, NY; [33]University of Cincinnati Medical Center, Cincinnati, OH; [34]Department of Internal Medicine, Mayo Clinic, Rochester, MN; [35]Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; [36]Department of Haematology, Prince of Wales Hospital, Randwick, NSW, Australia; [37]Markey Cancer Center, University of Kentucky, Lexington, KY; [38]Stem Cell Transplant Program, Division of Hematology/Oncology, Department of Medicine, Loyola University Chicago Stritch School of Medicine, Maywood, IL; [39]Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan; [40]Mount Sinai Medical Center, New York, NY; [41]Memorial Sloan Kettering Cancer Center, New York, NY; [42]Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX; [43]Bone Marrow Transplant Program, Division of Hematology/Oncology, Louisiana State University, Baton Rouge, LA; [44]Division of Hematology-Oncology, Blood and Marrow Transplantation Program, Mayo Clinic, Jacksonville, FL; [45]The Ottawa Hospital Blood & Marrow Transplant Program, Ottawa, Canada; [46]Department of Hematology/Oncology, Mayo Clinic, Phoenix, AZ; [47]Case Western Reserve University, Cleveland, OH; [48]Department of Medicine, University of Rochester Medical Center, Rochester, NY; [49]Division of Hematology and Transplant Center, Mayo Clinic Rochester, Rochester, MN; [50]University of Chicago Medicine, Chicago, IL; [51]Adult Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom; [52]Divison of Clinical Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [53]Christian Medical College Hospital, Vellore, India; [54]Department of Blood & Marrow Transplant and Cellular Immunotherapy (BMT CI), Moffitt Cancer Center, Tampa, FL; [55]Hematology Division and BMT, Chaim Sheba Medical Center, Tel Hashomer, Israel; [56]Division of Hematology and Bone Marrow Transplantation and Cord Blood Bank, Tel Aviv University, Tel Aviv, Israel; [57]Department of Hematology & Hematopoietic Cell Transplantation, City of Hope, Duarte, CA; [58]Rush University Medical Center, Chicago, IL; [59]University of California San Francisco, San Francisco, CA; [60]Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden; [61]Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden; [62]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; [63]Blood and Marrow Transplant Program, University of Utah, Salt Lake City, UT; [64]Blood and Marrow Transplantation Program, Division of Hematology/Oncology, Department of Internal Medicine, The University of Michigan Medical School, Ann Arbor, MI; [65]Adult Bone

Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [66]Division of Hematologic Malignancies and Cellular Therapy, Duke University, Durham, NC; [67]Division of Medical Oncology, University of Washington and Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [68]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; [69]Department of Haematology and Oncology, Dokkyo Medical University, Tochigi, Japan; [70]Department of Medicine, Medical College of Wisconsin, Milwaukee, WI; [71]Division of Oncology, Washington University School of Medicine, St. Louis, MO; [72]Department of Hematology, Hospital Vall d'Hebron, Barcelona, Spain; [73]Department of Hematology/Oncology, Isala Clinic, Zwolle, The Netherlands; [74]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA; [75]National Cancer Institute, National Institutes of Health, Rockville, MD; [76]Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN; [77]Bone Marrow Transplant Program, Penn State Cancer Institute, Hershey, PA; and [78]Blood & Marrow Transplant Program, Division of Hematology/Oncology, Department of Medicine, Greenebaum Comprehensive Cancer Center, University of Maryland, Baltimore, MD

## Key Points

- FM vs FB in fludarabine-based reduced intensity transplant offers marginally superior long-term survival in AML.

- Compared with FB, FM is associated with higher short-term posttransplant nonrelapse mortality, yet lower long-term leukemia relapse rate.

There is a lack of large comparative study on the outcomes of reduced intensity conditioning (RIC) in acute myeloid leukemia (AML) transplantation using fludarabine/busulfan (FB) and fludarabine/melphalan (FM) regimens. Adult AML patients from Center for International Blood and Marrow Transplant Research who received first RIC allo-transplant between 2001 and 2015 were studied. Patients were excluded if they received cord blood or identical twin transplant, total body irradiation in conditioning, or graft-versus-host disease (GVHD) prophylaxis with in vitro T-cell depletion. Primary outcome was overall survival (OS), secondary end points were leukemia-free survival (LFS), nonrelapse mortality (NRM), relapse, and GVHD. Multivariate survival model was used with adjustment for patient, leukemia, and transplant-related factors. A total of 622 patients received FM and 791 received FB RIC. Compared with FB, the FM group had fewer transplant in complete remission (CR), fewer matched sibling donors, and less usage of anti-thymocyte globulin or alemtuzumab. More patients in the FM group received marrow grafts and had transplantation before 2005. OS was significantly lower within the first 3 months posttransplant in the FM group (hazard ratio [HR] = 1.82, $P < .001$), but was marginally superior beyond 3 months (HR = 0.87, $P = .05$). LFS was better with FM compared with FB (HR = 0.89, $P = .05$). NRM was significantly increased in the FM group during the first 3 months of posttransplant (HR = 3.85, $P < .001$). Long-term relapse was lower with FM (HR = 0.65, $P < .001$). Analysis restricted to patients with CR showed comparable results. In conclusion, compared with FB, the FM RIC showed a marginally superior long-term OS and LFS and a lower relapse rate. A lower OS early posttransplant within 3 months was largely the result of a higher early NRM.

## Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment strategy for patients with acute myeloid leukemia (AML).[1,2] With the conventional myeloablative conditioning (MAC) developed in the 1970 and 1980s, HCT was restricted to younger patients without comorbidities.[3,4] Because the median age of AML patients is ~68 years, most AML patients are not eligible for standard MAC. Because of both antitumor effect of preparative regimens and graft-versus-leukemia immunity in allogeneic HCT, reduced intensity conditioning (RIC) regimens were developed 2 decades ago in an effort to allow allogeneic HCT among older patients and those with comorbidities.[3,5-8] The goal was to reduce nonrelapse mortality (NRM) while relying on graft-versus-leukemia activity for disease control.[6,9-11] In recent years, RIC regimens are also frequently used in younger age group patients.[7,12,13]

Fludarabine/melphalan (FM; M dose ≤140 mg/m$^2$) and fludarabine/busulfan (FB; B dose ≤6.4 mg/kg) are the 2 most commonly used RIC regimens in HCT.[12] There have been several retrospective

studies and a meta-analysis comparing the 2; however, these studies were limited by the inclusion of various age groups, disease-related factors, and graft-versus-host disease (GVHD) prophylaxis regimens.[14-16] In general, the results suggested a higher NRM but better disease control with FM RIC compared with FB and a variable effect on overall survival (OS). In the current study, we analyzed individual level data from a large cohort of AML transplantation patients from Center for International Blood and Marrow Transplant Research (CIBMTR) to compare the 2 RIC regimens. We studied characteristics associated with regimen utility and comparative effectiveness. Efforts were also made to identify subgroups of patients that could derive greater benefit from either of the 2 regimens.
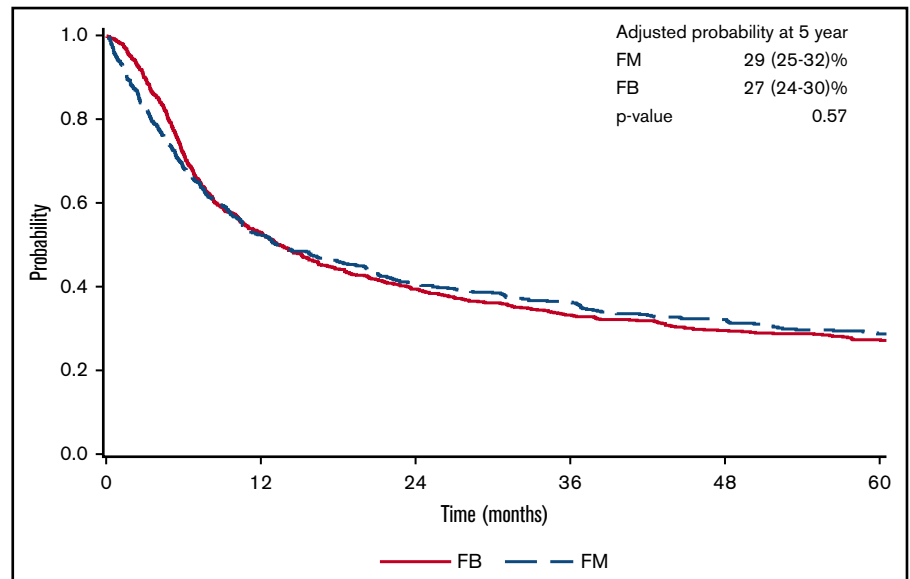
## Patients, materials, and methods

### Patient cohort

The data were from the CIBMTR transplant registry, which included AML patients aged ≥18 years that had their first allogeneic HCT using FM- or FB (IV busulfan)-based RIC regimen between 2001 and 2015 in the United States. Patients were excluded if they received cord blood, identical twin or haploidentical donors, total

**Table 1. Baseline characteristics in AML patients receiving FM, FB RIC regimen for allogeneic HCT (full cohort)**

| | FM | FB | P |
|---|---|---|---|
| **Patient-related** | | | |
| No. of patients | 622 | 791 | |
| No. of centers | 73 | 80 | |
| Age at transplant, y | | | |
| Median (range) | 59 (18-76) | 61 (18-77) | <.001 |
| Male sex, n (%) | 359 (58) | 445 (56) | .58 |
| Karnofsky score, n (%) | | | .19 |
| <90 | 290 (47) | 336 (43) | |
| ≥90 | 311 (50) | 416 (52) | |
| **Disease status before HCT, n (%)** | | | |
| Primary induction failure | 120 (19) | 86 (11) | <.001 |
| CR1 | 285 (46) | 484 (62) | |
| ≥CR2+ | 110 (18) | 163 (20) | |
| Relapse | 106 (17) | 57 (7) | |
| MRD status before transplant | | | <.001 |
| Negative | 127 (20) | 257 (33) | |
| Positive | 40 (6) | 63 (8) | |
| Not in CR1 | 138 (22) | 190 (24) | |
| NA before 2007 | 310 (50) | 244 (31) | |
| Cytogenetic score | | | .96 |
| Favorable | 36 (6) | 50 (6) | |
| Intermediate | 323 (52) | 425 (54) | |
| Poor | 200 (32) | 266 (34) | |
| Therapy-related/secondary AML | | | .56 |
| No | 533 (86) | 689 (87) | |
| Yes | 75 (12) | 88 (11) | |
| **Transplant-related, n (%)** | | | |
| Donor type | | | <.001 |
| HLA-identical sibling | 130 (21) | 241 (30) | |
| Well-matched unrelated (8/8) | 335 (54) | 427 (54) | |
| Partially-matched unrelated (7/8) | 115 (18) | 95 (12) | |
| Mismatched unrelated (≤6/8) | 18 (3) | 5 (< 1) | |
| Donor age at HCT (for URD only) | | | .006 |
| Median (range) | 38 (16-85) | 39 (11-82) | |
| GVHD prophylaxis | | | <.001 |
| TAC-based + MTX | 238 (38) | 493 (63) | |
| TAC-based + MMF | 132 (21) | 158 (20) | |
| CsA-based + MTX | 49 (8) | 18 (2) | |
| CsA-based + MMF | 70 (11) | 32 (4) | |
| ATG/alemtuzumab use | 259 (42) | 413 (52) | <.001 |
| Graft type | | | <.001 |
| Bone marrow | 119 (19) | 73 (9) | |
| Peripheral blood | 503 (81) | 726 (91) | |
| Year of transplant | | | <.001 |
| 2001-2005 | 180 (29) | 98 (12) | |
| 2006-2015 | 442 (71) | 693 (88) | |
| Median follow-up (range), mo | 85 (6-168) | 72 (6-169) | |

**Figure 1. Adjusted survival curve comparing FM vs FB RIC on OS (full cohort).**



Adjusted probability at 5 year
FM        29 (25-32)%
FB        27 (24-30)%
p-value             0.57

body irradiation as a part of conditioning, ex vivo T-cell depletion or CD34 selected grafts, or GVHD prophylaxis using posttransplant cyclophosphamide.

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry, the Autologous Blood and Marrow Transplant Registry, and the National Marrow Donor Program established in 2004, which collects data from more than 450 transplantation centers worldwide. The CIBMTR transplant registry collects transplant essential data as well as comprehensive patient, disease, and other clinical information pre- and poststem transplantation per CIBMTR data collection form. Data are collected pretransplantation, 100 days posttransplantation, 6 months posttransplantation, and annually thereafter or until death.

### Study end points

The primary study end point was OS defined as time from transplant to death from any cause. Patients were censored at time of last follow-up. The secondary end points included leukemia-free survival (LFS) defined as time to leukemia relapse or death from any cause. Patients were censored at last follow-up. NRM was defined as time to death without evidence of persistent disease or leukemia relapse, with leukemia relapse as competing risk event. Patients were censored at last follow-up. Relapse was defined as recurrence of leukemia after transplant, meeting 1 or more of the following criteria per CIBMTR: ≥5% blasts in the marrow or peripheral blood, extramedullary disease, or disease presence determined by a physician upon clinical assessment. NRM is considered as a competing risk event and patients were censored at last follow-up. Hematological complete remission (CR) was defined by CIBMTR as meeting all of the following response criteria for at least 4 weeks: <5% blasts in the bone marrow; no blast in blood; normal maturation of all cellular components in the bone marrow; no extramedullary disease (eg, central nervous system, soft-tissue disease); absolute neutrophil count (ANC) ≥1000/μL, platelets ≥100 000/μL; and transfusion independent. Acute GVHD (aGVHD) included occurrence of grade 2, 3, and/or 4 skin, gastrointestinal, or liver abnormalities fulfilling the consensus criteria

of aGVHD.[17] Chronic GVHD (cGVHD) was defined as occurrence of symptoms in any organ system fulfilling the diagnostic criteria of cGVHD.[18] For both acute and chronic GVHD, patients were censored at time of subsequent transplant or last follow-up. GVHD-free and relapse-free survival (GRFS) is a composite end point in which events include grade 3-4 aGVHD, cGVHD, relapse or death, whichever occurs first. Patients were censored at time of subsequent HCT or last follow-up.

### Statistical methods

***Busulfan and melphalan dosing.*** In the FB group, because of having too few patients (n = 50) receiving oral busulfan who were all transplanted in early years, only patients received IV busulfan were included in the analysis. The 2 most commonly used dosing regimens, 3.2 (n = 122) and 6.4 mg/kg (n = 402), were identified. We compared demographics characteristics between the 2 groups and respective survival at 5 years and did not detect any statistically significant difference. Therefore, the 2 dose groups were combined in the analysis.

Similarly, the 2 most common dosing groups of melphalan, 100 (n = 69) and 140 mg/m$^2$ (n = 493) in the FM group were compared with respect to demographics and survival outcomes. Similarly, in univariate analysis, no statistically significant differences were detected and therefore the 2 dose groups were combined.

***Baseline characteristics.*** Patient, disease, and transplant-related factors were compared between the FM and FB using the $\chi^2$ test for categorical variables and the Wilcoxon 2-sample test for continuous variables. The probabilities of disease-free and OS were calculated using the Kaplan-Meier estimator and were plotted using adjusted Kaplan-Meier curves. The probabilities of the secondary end points were generated using cumulative incidence estimates that were accounted for competing. Cox proportional hazards regression were used to estimate hazard ratio (HR) for outcomes between the 2 treatment groups. The variables to be considered in the multivariate models included age, sex, Karnofsky Performance Scale at time of HCT, clinical onset of AML, cytogenetics, disease status before HCT, time to achieve CR1, year of HCT, donor type,
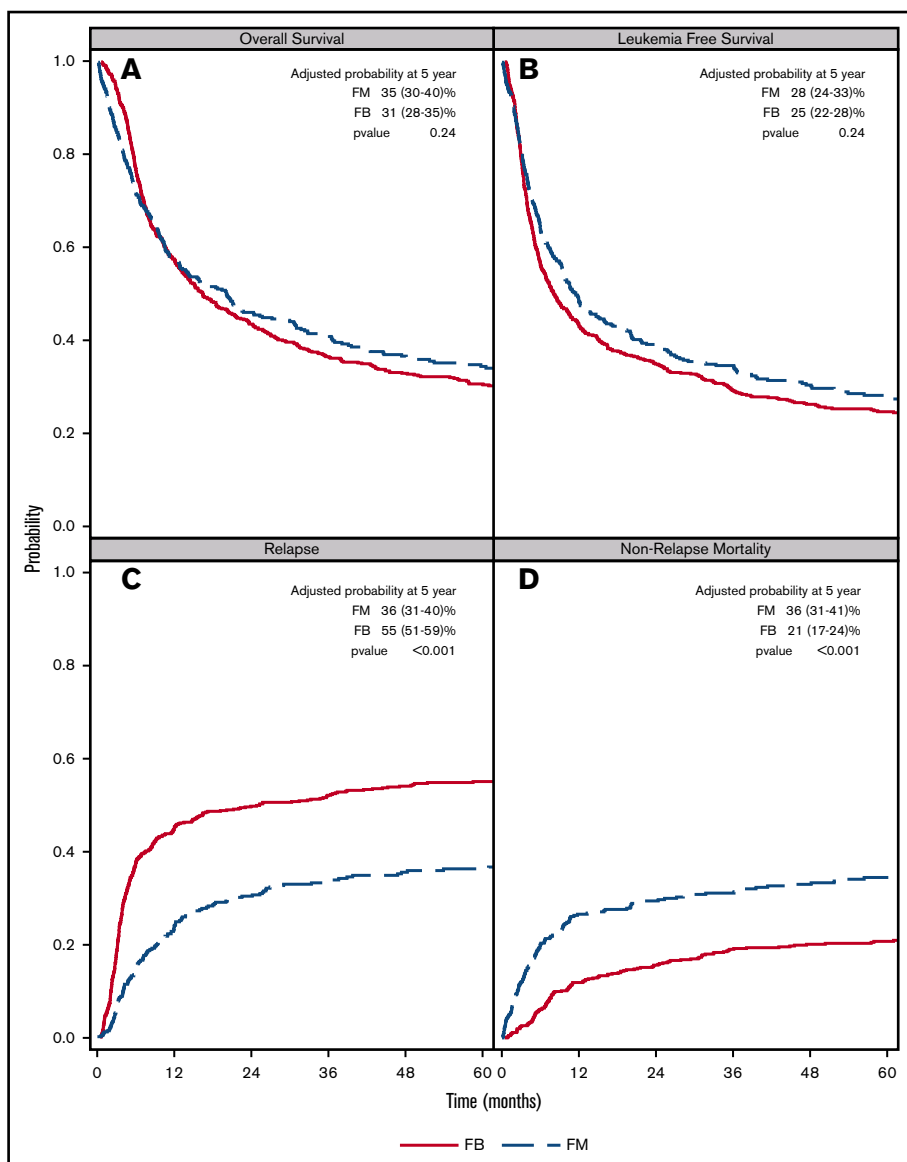
**Figure 2. FM vs FB on AML transplant outcomes.** Adjusted survival: OS (A) and LFS (B). CIF curves: relapse (C) and NRM (D).

graft type, donor/recipient sex match and cytomegalovirus serostatus, GVHD prophylaxis, and in vivo T-cell depletion. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. When the test indicated differential effects over time (nonproportional hazards), models were constructed breaking the posttransplant time course into 2 periods, using the maximized partial likelihood method to find the most appropriate breakpoint. Backward stepwise model selection was used to identify all significant risk factors. Each step of model building contained the main effect of conditioning regimen. Factors of significance level <5% were kept in the final model. Potential interactions between main effect and significant risk factors were also tested. Direct adjusted probabilities of OS and LFS, and direct adjusted cumulative incidence probability function (CIF) of relapse and NRM were generated from the final regression models stratified by conditioning regimen and weighted averages of covariate values using the pooled sample proportion as the weight function. These adjusted probabilities estimated likelihood

of outcomes in populations with similar prognostic factors. Among the secondary outcomes, GRFS and GVHD comparing FM vs FB were also reported.

**Outcome reporting.** For both primary and secondary outcomes, OS, LFS, relapse, NRM, and GVHD (acute and chronic) were reported for the entire cohort and patients who achieved CR pretransplant (CR cohort). For reporting OS and NRM, outcomes were divided into short- (≤3 months) and long-term (>3 months) periods. The 2 survival curves crossed at 3 months, suggesting model-defined time dependence resulting from violation of the proportionality assumption of the Cox model. We therefore reported early vs late period divided at 3-month posttransplant.

**Sensitivity analyses.** The analyses included comparison limited to patients with reported comorbidity index (HCT-CI) available who were transplanted in 2007 and beyond, and among patients who received matched sibling or well-matched unrelated donors. Center effect in the comparison was studied in the comparison using

**Table 2. Transplant outcomes in AML patients receiving FM vs FB RIC for allogeneic HCT**

| | FM vs FB (entire cohort), HR (95% CI) | FM vs FB (CR only cohort), HR (95% CI) |
|---|---|---|
| **OS** | | |
| ≤3 mo | 1.82 (1.36-2.45), $P < .001$* | 2.70 (1.80-4.07), $P < .001$* |
| >3 mo | 0.87 (0.76-1.00), $P = .05$ | 0.81 (0.68-0.95), $P = .01$* |
| LFS | 0.89 (0.78-1.00), $P = .05$ | 0.87 (0.75-1.01), $P = .06$ |
| **NRM** | | |
| ≤3 mo | 3.85 (2.46-6.03), $P < .001$* | 5.09 (2.83-9.14), $P < .001$* |
| >3 mo | 1.14 (0.88-1.47), $P = .32$ | 1.17 (0.88-1.57), $P = .28$ |
| Relapse | 0.65 (0.55-0.76), $P < .001$* | 0.60 (0.49-0.73), $P < .001$* |
| GRFS | 1.03 (0.91-1.15), $P = .66$ | 1.01 (0.87-1.16), $P = .92$ |

*Significant $P$ value.

random-effects model in the framework of extended Cox multivariate regression analysis and for OS and LFS; center effect was not a statistically significant factor ($P > .05$).

## Results

### Baseline characteristics

The cohort consisted of 622 AML patients who received transplant with the FM RIC and 791 with the FB RIC regimen. Baseline characteristics of the 2 treatment groups in the entire cohort and CR cohort are summarized in Table 1 and supplemental Table 1, respectively. In the entire cohort, the median age of the FM group was 59 years (range, 18-76); and the median age of FB group was 61 years (range, 18-77). Notably, compared with the FB group, the FM group had more patients with active disease (36% vs 18%), with mismatched donors (24% vs 15%), with bone marrow grafts (19% vs 9%), received transplant before 2005 (29% vs 12%), and without anti-thymocyte globulin (ATG)/alemtuzumab (58% vs 48%). However, there were fewer patients in CR1 (46% vs 62%) and matched sibling donor grafts (21% vs 30%) in the FM group compared with that of FB group. The remaining characteristics were comparable between the 2 groups for both entire cohort and CR cohort.

### Transplant outcomes

***OS and LFS.*** There was a lower OS associated with FM group compared with FB group within 3 months posttransplant (HR = 1.82; 95% confidence interval [CI], 1.36-2.45; $P < .001$). OS was marginally superior with FM compared with FB beyond 3 months (HR = 0.87; 95% CI, 0.76-1.00; $P = .05$). At 5 years posttransplant, the survival rate was 29% (95% CI, 25-32) for FM and 27% (95% CI, 24-30) for FB ($P = .57$) (Figure 1). The results were shown to be consistent in patients with CR pretransplant (Figure 2; Table 2) for an increased early mortality in the FM group within 3 months posttransplant (HR = 2.70; 95% CI, 1.80-4.07; $P < .001$), and a better OS beyond 3 months compared with the FB group (HR = 0.81; 95% CI, 0.68-0.95; $P = .01$) (Table 2). Regarding the LFS, again there was a marginal advantage with FM compared with FB (entire cohort: HR = 0.89; 95% CI, 0.78-1.00; $P = .05$; and CR cohort: HR = 0.87; 95% CI, 0.75-1.01; $P = .06$) (Table 2). Adjusted probabilities (at specific time points) among patients in CR at transplant showed comparable OS at 1, 3, and 5 years posttransplant. Similarly, LFS was similar between the FM and FB groups (Figure 2; supplemental Table 2).

### NRM

NRM was significantly higher in the FM compared with the FB group during the early period (<3 months) posttransplant. This was found in both the entire cohort (HR = 3.85; 95% CI, 2.46-6.03; $P < .001$) and CR cohort (HR = 5.09; 95% CI, 2.83-9.14; $P < .001$). In the multivariate survival analysis, excess in NRM in the FM group did not persist beyond 3 months (entire cohort: HR = 1.14; 95% CI, 0.88-1.47; $P = .32$; CR cohort only: HR = 1.17; 95% CI, 0.88-1.57; $P = .28$) (Table 2). CIF comparing FM vs FB at 1-, 3-, and 5-year time points in patients with pretransplant CR showed higher NRM in the FM group, largely owing to increased early NRM occurring within the first 3 months posttransplant (Figure 2; supplemental Table 2).

### Relapse and GRFS

In both the full and the CR cohorts, there were an overall significant decrease in relapse associated with the FM group compared with the FB group (entire cohort: HR = 0.65; 95% CI, 0.55-0.76; $P < .001$; and CR cohort: HR = 0.60, 95% CI, 0.49-0.73; $P < .001$). CIF at respective time points posttransplant showed a consistent lower relapse rate in the FM compared with the FB group, $P < .001$ (Figure 2; supplemental Table 2). There was no detectable difference with regard to GRFS when comparing the 2 conditioning regimens, either in the entire cohort or the CR cohort (Table 2).

### Multivariable analysis comparing FM with FB based on patient, leukemia, and transplant-related characteristics

Effect of baseline characteristics on overall mortality comparing the 2 treatment groups were reported in forest plots according to the early (<3 months) and late (>3 months) time periods (Figures 3 and 4), as well as with the multivariate models (supplemental Tables 3 and 4). The results showed a uniformly increased early mortality associated with FM group irrespective of patient-, disease-, and transplant-specific factors. These included age, Karnofsky Performance Scale, cytogenetics risk, secondary AML, or remission status. Differences in mortality between the 2 regimens diminished beyond 3 months posttransplant without influence from specific baseline characteristics. Those included well-established adverse risk groups. In other words, there was consistency of the results within all subgroups (all $P$ values for interaction >.05).
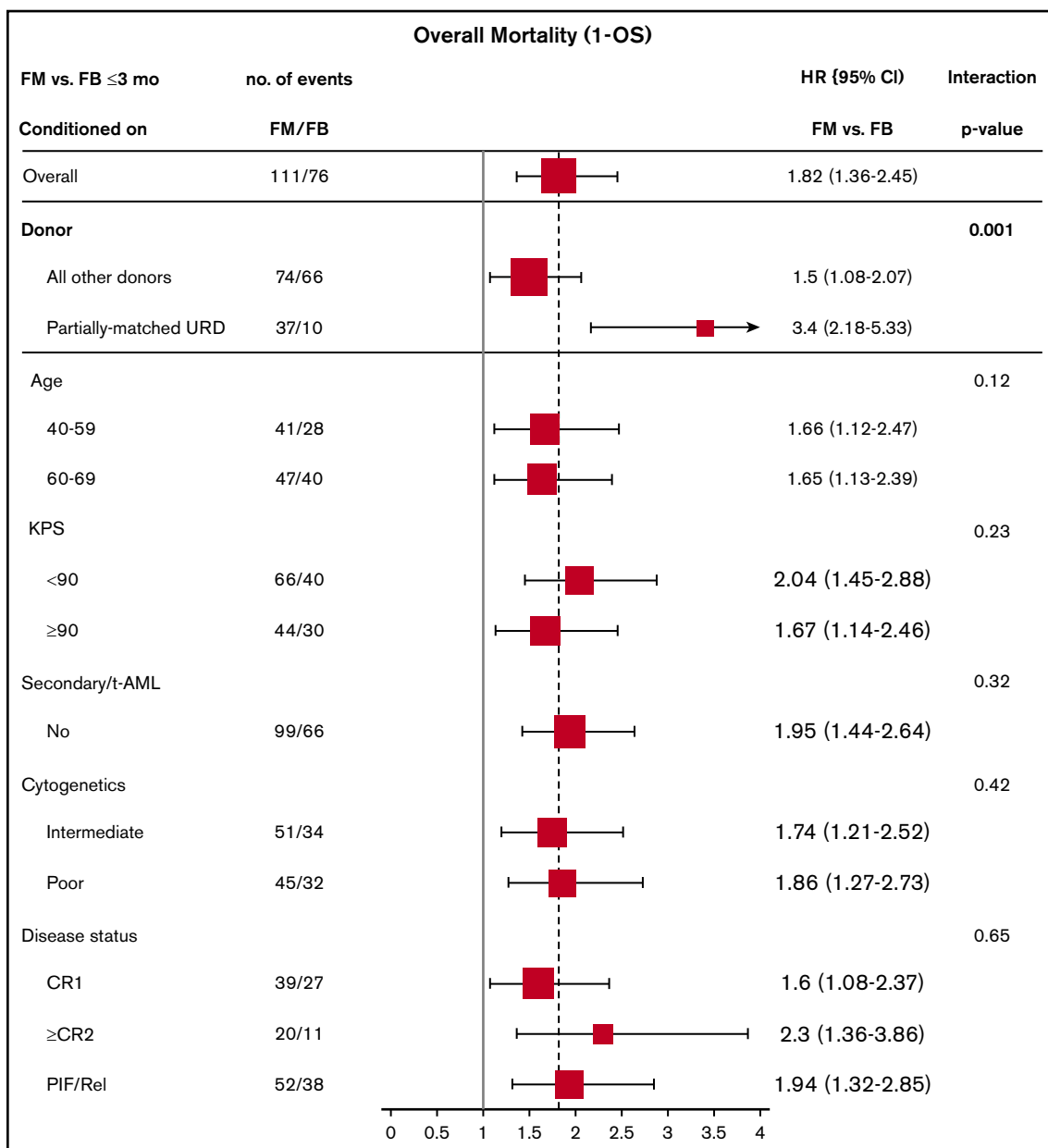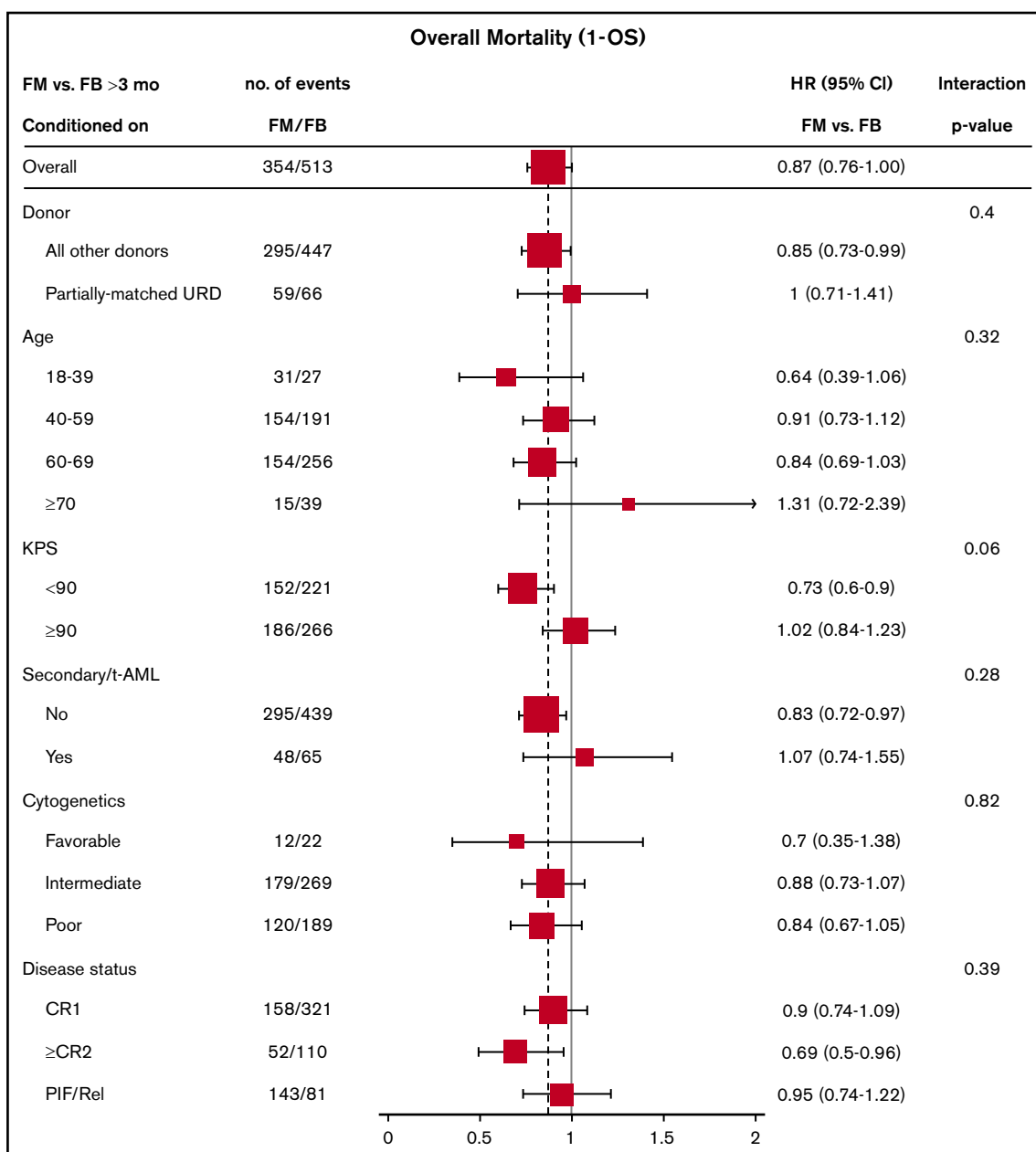
**Figure 3. Early overall mortality (1 − OS) (≤3 months) comparing FM vs FB based on patient-, disease-, and transplant-related characteristics (full cohort).**

In sensitivity analyses, there was no evidence showing superior outcome associated with either the FM or FB group, especially when restricted to patients with HCT-CI available for multivariate adjustment. There was also no difference in outcomes when limiting analysis to patients who received sibling or well-matched unrelated donors (supplemental Tables 5 and 6).

## GVHD

Based on the multivariable model of the entire cohort, after adjusting for all other characteristics, FM was associated with higher grade 2-4 and grade 3-4 aGVHD (supplemental Table 3). This was true both in the full and CR cohorts (supplemental Tables 3 and 4). With regard to cGVHD, for the full cohort, FM was associated with higher cGVHD in absence of in vivo T-cell

depletion, but effect was not seen in its presence, suggesting presence of interaction. For the CR cohort, this effect modification with in vivo T-cell depletion on the outcome of cGVHD was not seen.

Compared with tacrolimus and mycophenolate (TAC/MMF), GVHD prophylaxis using calcineurin inhibitor (TAC or cyclosporine [CsA]) and methotrexate (MTX) led to a lower incidence of grade 2-4 aGVHD (TAC/MTX vs TAC/MMF: HR = 0.65; 95% CI, 0.52-0.80; $P < .001$; CsA/MTX vs TAC/MMF: HR = 0.59; 95% CI, 0.37-0.93; $P = .02$). Notably, in vivo T-cell depletion by either ATG or alemtuzumab consistently showed a benefit in reducing both grade II-IV aGVHD (HR = 0.80; 95% CI, 0.66-0.96; $P = .02$) and cGVHD (HR = 0.65; 95% CI. 0.51-0.81; $P < .001$), as well as a lower NRM (HR = 0.78; 95% CI, 0.63-0.97; $P = .02$).

**Figure 4. Late overall mortality (1 – OS) (>3 months) comparing FM vs FB based on patient-, disease-, and transplant-related characteristics (full cohort).**

## Engraftment

Data on neutrophil (ANC) and platelet engraftment of the 2 regimens is shown in supplemental Table 7. There appeared to be notably faster engraftment of counts in the FB compared with the FM group, but with both groups achieving at least 95% probability of ANC recovery by day 100.

## Cause of death

Finally, details on cause of death between the FM and FB group were shown in supplemental Table 8. Notably, in comparing to FB, patients who received FM condition experienced relatively higher rates of infection and organ failure as their cause of death.

## Discussion

The current CIBMTR study is the largest cohort to date comparing the 2 most common RIC regimens for AML allogeneic transplantation. The initial CIBMTR report by Luger et al comparing RIC and MAC regimens for myelodysplastic syndrome and AML showed similar survival.[19] A more recent randomized Clinical Trials Network study 0901 comparing RIC (FB and FM) vs MAC regimens for AML was stopped early because of significant increase in relapse in the RIC arm (48.3% vs 13.5%)[18,20]; however, only 19% of the RIC transplants in the study were FM. Although there is no prospective trial comparing the utility of FB- and FM-based RIC regimens, several observational studies have looked at the outcomes of using the 2 RIC regimens, including single-center retrospective

analyses,[7,10,14,15] 1 Blood and Marrow Transplantation registry analysis,[21] and 1 meta-analysis of ~2000 patients pooled from various studies and disease settings.[16] The study by Shimoni et al[15] of 151 patients included several hematological malignancies signified a higher NRM for FM (40% vs 16%). Patients transplanted in remission had a better OS with FM compared with FB (72% vs 36%) because of less relapse in the FM group, whereas patients transplanted with active disease showed a similar survival where increased NRM in the FM group was compensated by a lower relapse rate. Registry study from the Blood and Marrow Transplantation Clinical Trials Network restricted to AML patients transplanted from MSD without T-cell-depleting agents and with oral and intravenous FB RIC regimen also showed similar OS between the 2 RIC regimens, where higher NRM with FM was compensated by better disease control. Both groups experienced similar rate of acute and chronic GVHD. For the patients in CR, FM had a better OS (54% vs 32%, $P = .02$) and LFS (46% vs 30%, $P = .03$). Similar outcomes were found in a French study of myelofibrosis[12] and another from the Mayo Clinic using only IV busulfan, suggesting a better disease control with FM at the expense of increased NRM. The Mayo study also suggested a better OS in the FM group with Karnofsky ≥90 (78.3% vs 48.3%; $P = .03$) but a threefold increase in 2-year NRM among patients with Karnofsky <90, leading the authors to speculate the need of individualization of RIC regimens for HCT.[14]

The results of current study indicate a marginal long-term OS advantage beyond 3 months as well as LFS advantage in association with the FM regimen group, especially in patients with CR and well-matched sibling and unrelated donor recipient. There was yet a statistically significant lower survival during the early period posttransplant resulting from excess NRM of the FM regimen. Long-term OS and LFS advantage with FM were driven by a marked reduction in leukemia relapse with the FM regimen. This held true in younger patients with high-risk disease in adjusted analysis.

There are several notable findings, in particular, the strategy to reduce GVHD using calcineurin inhibitors combined with methotrexate, as well as approaches for in vivo T-cell depletion using ATG or alemtuzumab have led to significant reduction of both acute and chronic GVHD, but no significant improvement in GRFS when comparing the 2 RIC regimens. There was not enough data to study prophylaxis regimen such as posttransplant Cytoxan and effect on the study outcomes.

Our results based on rather comprehensive analyses endorsed findings by the previous reports. Using this large study cohort, we were able to apply additional approaches to reduce confounding. These included analyses limited to only patients in CR, and with matched sibling and full-matched unrelated donor, as well as in a subcohort (2007 and beyond) in which HCT-CI was available for adjustment. In addition, we were able to examine the effect of leukemia and transplant specific factors on the main comparison (FM vs FB) with respect to the study outcomes. Using a multivariate regression survival model, factors such as AML disease risk, degree of donor matching and regimens for GVHD prophylaxis were studied. There are several limitations that are intrinsic to the retrospective cohort design and database-based study, such as missing data and uncollected information that could introduce residual confounding. Information related to more recent transplant strategies is limited or not available, such as

knowledge related to minimal residual disease, pre- or post-transplant utilization of novel targeted therapy, as well as haploidentical donor transplantation.

In conclusion, the results of this large comparative study from CIBMTR suggest that long-term OS and LFS are marginally superior with FM compared with FB regimen but at the expense of higher early NRM with FM. It is reasonable to postulate in those with high HCT-CI for NRM, FB is likely a preferred regimen, whereas in younger patients with higher risk of relapse, FM could be a better option. Our analysis did not identify strong evidence in support of using FM over FB to prevent relapse in higher risk group, such as in those with later remission, worse cytogenetics, or treatment-related AML. On the other hand, it is possible that the observed lower risk of relapse associated with FM could be also due to patient assignment driven by unmeasured confounding factors or extreme competing risk from NRM associated with FM, both early and late. The choice of FM over FB remains an individualized decision based on perceived risk and benefit of an AML patient undergoing transplant.

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## Authorship

ORCID profiles: Z.Z., 0000-0002-3620-4721; J.C., 0000-0002-6602-5505; V.A., 0000-0002-6383-3777; G.A., 0000-0001-6873-9571; A.A., 0000-0003-4707-9265; U.B., 0000-0001-8771-947X; Q.B., 0000-0002-4086-6453; Z.D., 0000-0002-7994-8974; M.D.L., 0000-0002-8568-4522; C.O.F., 0000-0003-2880-6797; A.T.G., 0000-0002-3422-1309; M. Hamadani, 0000-0001-5372-510X; S.H., 0000-0002-8914-7927; G.C.H., 0000-0003-0478-3340; T.J., 0000-0001-6854-773X; N. Kekre, 0000-0001-8394-0855; H.M.L., 0000-0002-1159-5607; M.L., 0000-0002-9816-6302; H.L., 0000-0002-3190-7807; R.M., 0000-0001-5143-4042; V.M., 0000-0001-9417-2353; R. Nakamura, 0000-0002-9082-0680; T.N., 0000-0002-2621-7924; R.F.O., 0000-0001-5970-2128; S.S.P., 0000-0001-9949-3615; U.P., 0000-0002-7592-2224; B.M.S., 0000-0002-9767-9739; G.L.U., 0000-0002-7809-0996; E.K.W., 0000-0003-0816-6729; D.W., 0000-0001-8078-8579; J.A.Y., 0000-0002-5346-6299.

Correspondence: Zheng Zhou, Beth Israel Lahey Health, Lahey Hospital and Medical Center, Division of Hematology/Oncology and Bone Marrow Transplant, Department of Medicine, Burlington, MA 01805; e-mail: zheng.x.zhou@lahey.org.

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