original reports

Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome

Ryotaro Nakamura, MD[1]; Wael Saber, MD, MS[2]; Michael J. Martens, PhD[2]; Alyssa Ramirez, BS[3]; Bart Scott, MD[4]; Betul Oran, MD[5]; Eric Leifer, PhD[6]; Roni Tamari, MD[7]; Asmita Mishra, MD[8]; Richard T. Maziarz, MD[9]; Joseph McGuirk, DO[10]; Peter Westervelt, MD, PhD[11]; Sumithira Vasu, MBBS[12]; Mrinal Patnaik, MBBS[13]; Rammurti Kamble, MD[14]; Stephen J. Forman, MD[1]; Mikkael A. Sekeres, MD, MS[15]; Frederick Appelbaum, MD[4]; Adam Mendizabal, PhD[3]; Brent Logan, PhD[2]; Mary Horowitz, MD, MS[2]; and Corey Cutler, MD, MPH[16]; on behalf of the Blood and Marrow Transplant Clinical Trials Network

abstract

PURPOSE Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative therapy for myelodysplastic syndromes (MDS), although it is infrequently offered to older patients. The relative benefits of HCT over non-HCT therapy in older patients with higher-risk MDS have not been defined.

METHODS We conducted a multicenter biologic assignment trial comparing reduced-intensity HCT to hypomethylating therapy or best supportive care in subjects 50-75 years of age with intermediate-2 or high-risk de novo MDS. The primary outcome was overall survival probability at 3 years. Between January 2014 and November 2018, we enrolled 384 subjects at 34 centers. Subjects were assigned to the Donor or No-Donor arms according to the availability of a matched donor within 90 days of study registration.

RESULTS The median follow-up time for surviving subjects was 34.2 months (range: 2.3-38 months) in the Donor arm and 26.9 months (range: 2.4-37.2 months) in the No-Donor arm. In an intention-to-treat analysis, the adjusted overall survival rate at 3 years in the Donor arm was 47.9% (95% CI, 41.3 to 54.1) compared with 26.6% (95% CI, 18.4 to 35.6) in the No-Donor arm ($P = .0001$) with an absolute difference of 21.3% (95% CI, 10.2 to 31.8). Leukemia-free survival at 3 years was greater in the Donor arm (35.8%; 95% CI, 29.8 to 41.8) compared with the No-Donor arm (20.6%; 95% CI, 13.3 to 29.1; $P = .003$). The survival benefit was seen across all subgroups examined.

CONCLUSION We observed a significant survival advantage in older subjects with higher-risk MDS who have a matched donor identified and underwent reduced-intensity HCT, when compared with those without a donor. HCT should be included as an integral part of MDS management plans in fit older adults with higher-risk MDS.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Myelodysplastic syndrome (MDS) is predominantly a disease of older adults, with a median age at onset of 76 years.[1] Although there are few available therapeutic options, DNA hypomethylating agents (HMA) can improve hematologic parameters, reduce transfusion requirements, delay transformation to acute myelomonocytic leukemia (AML), and prolong progression-free survival and overall survival (OS) in individuals with higher-risk disease.[2-5] However, fewer than half of the patients with MDS achieve objective responses to hypomethylating therapy, and these responses are usually of limited duration. When patients develop HMA resistance, prognosis is dismal with few treatment options.[6,7] Allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy for MDS and an established therapy for younger patients with MDS.[8-10] Although transplantation outcomes among selected older individuals with MDS are similar to those in younger patients with MDS,[11,12] early transplantation for older individuals is not broadly accepted. Statistical modeling analyses demonstrate the benefits of early HCT in older populations,[13,14] and two prospective studies from European groups showed a benefit of HCT over non-HCT therapy when a suitable donor is available.[15,16]

We designed a clinical trial to address the research question regarding the appropriateness of allogeneic HCT in this older population within the guidelines set forth by Centers for Medicare and Medicaid Services' (CMS) decision memo.[17,18] Although a randomized study comparing transplantation to nontransplant

CONTEXT

Key Objective

To determine whether having a suitable HLA-matched donor improves outcomes for older patients with higher-risk myelodysplastic syndrome (MDS) who are candidates for reduced-intensity allogeneic stem-cell transplantation.

Knowledge Generated

Overall survival and leukemia-free survival were statistically significantly and clinically meaningfully prolonged in individuals who had donors in comparison with those who did not. Quality of life was not impaired with transplantation.

Relevance

MDS is common among older individuals, and allogeneic stem-cell transplantation is underutilized in this age group. This study demonstrates that having a suitable donor for allogeneic stem-cell transplantation is associated with improved survival. Consultation for allogeneic stem-cell transplantation should occur early in the disease course for older individuals with higher-risk MDS to identify donors. Allogeneic transplantation should be used in this older age-group with MDS.

therapies would be optimal, this design was considered impractical.[19-21] We, therefore, conducted a multicenter, biologic assignment trial in subjects 50-75 years of age with advanced de novo MDS (defined as intermediate-2 or high-risk MDS risk score per the International Prognostic Scoring System [IPSS])[22] considered eligible for a reduced-intensity conditioning (RIC)[23] allogeneic HCT, comparing outcomes of those with a suitable donor to those without a suitable donor.

METHODS

Study Design

The study was an open-label, multicenter, biologic assignment trial conducted by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 1102).[19] Biologic assignment was to a Donor or No-Donor arm based on high-resolution HLA typing of eligible family members and a 90-day search of the unrelated donor registry through the National Marrow Donor Program. Subjects assigned to the Donor arm were expected to undergo RIC HCT within 6 months of enrollment, whereas those assigned to the No-Donor arm were expected to receive non-HCT therapy or best supportive care. The target enrollment was 338-400 subjects, dependent on the ratio of Donor vs. No-Donor assignment, where 60%-70% of subjects were expected to have a donor identified within 90 days. The primary end point was 3-year OS from registration in an intention-to-treat analysis. Prespecified secondary end points included 3-year leukemia-free survival (LFS), quality-of-life (QOL) measures, and cost effectiveness. Enrollment began in January 2014 and ended in November 2018. In February 2020, an independent Data and Safety Monitoring Board released the study data for analysis. Information regarding Study Oversight can be found in the Data Supplement (online only).

Subjects and Treatment

Eligible subjects were between 50 and 75 years of age and were considered to be candidates for RIC HCT from an HLA-matched related or 8/8 HLA-matched unrelated donor (HLA-A, B, C, and DR using high-resolution typing) by the treating hematologist. All subjects were required to have been diagnosed with de novo intermediate-2 or high-risk MDS by IPSS criteria. Individuals for whom a myeloablative transplant or an alternative donor transplant (mismatched unrelated, haploidentical, or umbilical cord blood) was planned were ineligible. The definition of RIC HCT regimens was based on the Center for International Blood and Marrow Transplant Research criteria.[23] All subjects provided written informed consent before enrollment. Subjects received RIC HCT or non-HCT therapy according to institutional standards. Subjects not undergoing transplantation were eligible to receive HMA therapy or supportive care at referring institutions, whereas HCT was performed at the enrolling site. More details are available in the full Protocol (online only), available on the BMT CTN website.[24]

Statistical Analysis

The primary analysis was an intention-to-treat analysis of all enrolled subjects. Subjects were initially assigned to the No-Donor arm at the time of consent; subjects were immediately reassigned to the Donor arm when a suitable donor was identified, whereas those whose 90-day donor search ended without a donor identified or who died before the search ended remained in the No-Donor arm. Subjects who died or withdrew without finding a donor during the search period could potentially bias this analysis, but this was expected to occur infrequently and additional sensitivity analyses removed these cases to examine their impact. The primary analysis compared 3-year OS between arms using adjusted survival estimates[25] to account for the potential bias resulting from biologic assignment,[26] adjusting for prespecified characteristics: age, race or ethnicity, performance status, disease status, comorbidity index, IPSS score, MDS disease duration, and response to HMA therapy. Deaths from any cause were considered failures for OS; subjects followed for < 3 years were censored at their last contact date. A point-wise comparison

of three-year survival was used rather than the Cox proportional hazards model because of the potential for non–proportional hazards because of early mortality after HCT.

The targeted sample size was selected to provide at least 80% power to detect a 15% difference in the 3-year OS rate between the two study groups, assuming survival of 35%-40% in the Donor arm and 20%-25% in the No-Donor arm and 10% loss to follow-up. Since the required sample size depended also on the true, unknown proportion of donor availability, treatment assignment was monitored during the study. This study used a group sequential design with a maximum of four efficacy analyses planned, three interim and one final, the first occurring at study enrollment closure and yearly thereafter. A Bonferroni correction was used to control the overall type I error rate for multiplicity, with a Haybittle-Peto boundary of 3.00 used for interim analyses and 2.03 for the final analysis. Confidence intervals and *P* values for the OS primary analysis are adjusted for multiple interim analyses.

A prespecified, as-treated analyses was also performed for OS and LFS at 3 years, adjusting for the above-mentioned variables, with death and transformation to AML considered LFS failures. QOL was measured by the Functional Assessment of Cancer Therapy—General, the Medical Outcomes Study 36-Item Short Form Survey Physical Component Score and Mental Component Score, and the EuroQol-5D utility score,[27-29] and changes in scores from enrollment were compared between arms using analysis of covariance models adjusted for enrollment score. *P* values $< .05$ were considered statistically significant and QOL score differences greater than half a standard deviation were considered clinically meaningful. Prespecified subgroup analyses by response to HMA, age, disease duration, and IPSS were conducted using treatment interaction terms in pseudovalue regression models for 3-year OS and LFS.[30]

In Donor arm subjects who underwent HCT within 6 months of biologic assignment, post-transplant outcomes of OS, disease-free survival (DFS, defined as freedom from death, MDS recurrence, and AML transformation), relapse, treatment-related mortality (TRM), and acute and chronic graft-versus-host disease (GVHD) were described using the Kaplan-Meier and Aalen-Johansen estimators. These outcomes are described through 27 months post-HCT to coincide with the primary end point's 3-year time point and the 9-month window during which Donor arm subjects are expected to undergo transplant. For these outcomes, multivariable models were constructed using stepwise variable selection to assess the potential influence of response to HMA, age, disease duration, IPSS, and Revised International Prognostic Scoring System.

RESULTS

Enrollment and Subject Characteristics

Enrollment occurred between January 2014 and November 2018, with 384 subjects (median age 66.7 years; 235 [62.1%] > 65) registered at 34 transplantation centers and biologically assigned to the Donor (n = 260) or No-Donor (n = 124) arms (Fig 1). Subject and donor characteristics are shown in Table 1. The Donor and No-Donor arms were well balanced with respect to age, sex, Karnofsky performance status, IPSS disease risk, MDS disease duration, and in their use of, and responsiveness to, HMA. The Data and Safety Monitoring Board permitted early release of the study data for publication following an efficacy finding at the second interim analysis. At the time of analysis, 287 (74.7%) subjects had complete 3-year data for analysis, with an additional 47 (12.2%) followed for at least 2 years from registration. Follow-up was similar between study arms (completeness index: 94.4% in the Donor arm and 93.9% in the No-Donor arm).[31] Three subjects (1%) withdrew consent. Seven subjects died during the 90-day search period without finding a donor and were analyzed in the No-Donor arm. Five subjects died in the Donor arm before the 90-day search window ended and were analyzed in the Donor arm.

Overall Survival

At the time of the analysis, 211 subjects had died (125 Donor and 86 No-Donor). The median follow-up time for surviving subjects was 34.2 months (range: 2.3-38 months) in the Donor arm and 26.9 months (range: 2.4-37.2 months) in the No-Donor arm. Adjusted OS at 3 years was significantly higher in the Donor arm when compared with the No-Donor arm: 47.9% (95% CI, 41.3 to 54.1) versus 26.6% (95% CI, 18.4 to 35.6, absolute improvement 21.3% [95% CI, 10.2 to 31.8]; $P = .0001$; Fig 2A, Data Supplement). High IPSS risk score significantly affected OS outcomes (reference: intermediate-2 risk: hazard ratio [HR] 1.75; $P < .0001$), as did no response to HMA before HCT (reference: no exposure to HMA, HR 1.64, $P = .0097$; Data Supplement). In a sensitivity analysis, excluding the eight subjects assigned to the No-Donor arm who died (n = 7) or withdrew (n = 1) before the end of the 90-day search window had no effect on outcomes (adjusted OS: 48.0% *v* 28.1%; $P = .0004$). Subgroup analyses of OS found no evidence of interactions between treatment assignment and age group (older than or younger than 65 years, $P = .73$), HMA response type ($P = .33$), or other factors considered (Fig 2B).

Leukemia-Free Survival

LFS was significantly higher in the Donor arm when compared with the No-Donor arm at 3 years: 35.8% (95% CI, 29.8 to 41.8) versus 20.6% (95% CI, 13.3 to 29.1, absolute improvement: 15.2% [95% CI, 13.3 to 29.1], $P = .003$; Fig 2C, Data Supplement). Significant predictors of LFS included high-risk IPSS score (HR 1.541, $P = .0011$) and unresponsiveness to HMA (HR 1.643, $P = .0037$; Data Supplement). Excluding subjects in the No-Donor arm who died or withdrew during the 90-day donor search window had no effect on outcomes (35.9% *v*

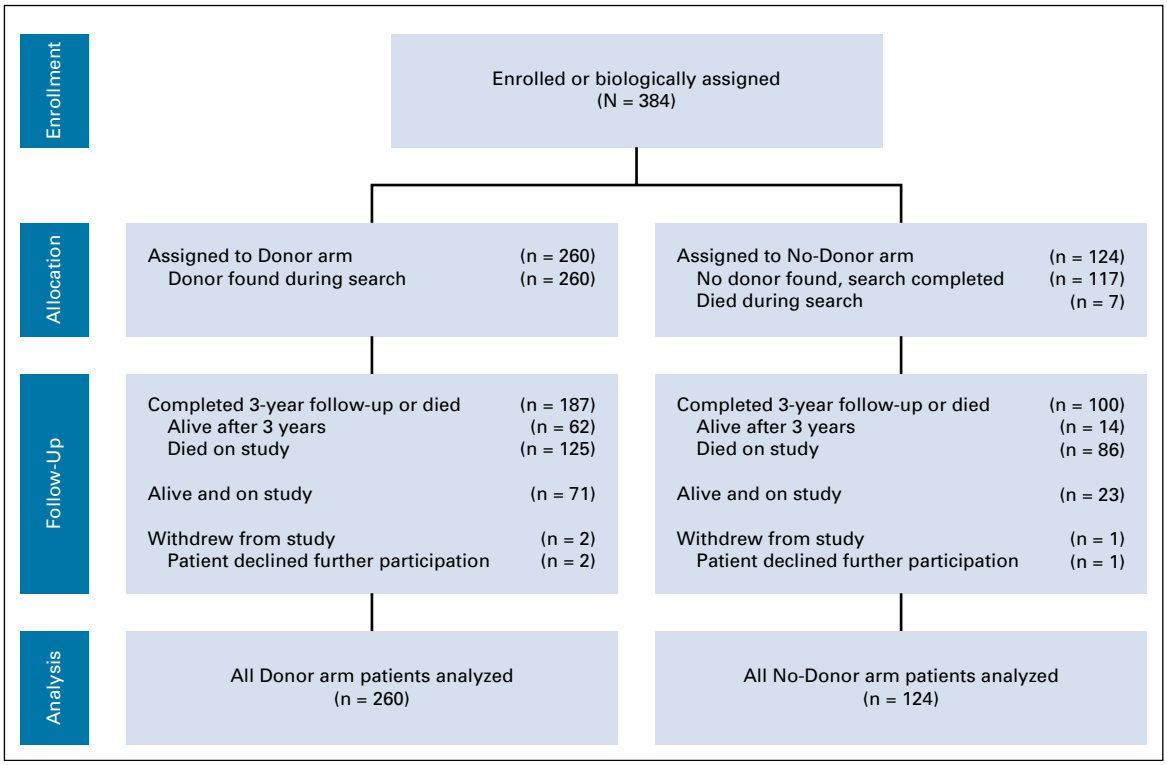

FIG 1. CONSORT diagram for BMT CTN 1102. Two hundred sixty (67.7%) of the enrolled subjects were biologically assigned to the Donor arm and 124 (32.3%) assigned to the No-Donor arm. On the Donor arm, 187 (71.9%) of the participants have completed the 3-year follow-up period, with 62 surviving until 3 years and 125 dying. Of the No-Donor arm participants, 100 (80.6%) have completed the follow-up period, 14 surviving until the 3 years and 86 dying. Three subjects withdrew from study, two on the Donor arm and one on the Non-Donor arm, each declining to participate further in completing study visits and quality-of-life assessments. The remaining 71 subjects on the Donor arm and 23 on the Non-Donor arm are still being followed until the 3-year mark.

21.8%, $P = .0074$). Subgroup analysis of LFS detected no interactions of treatment assignment with age group (older than or younger than 65 years, $P = .90$), HMA response type ($P = .99$), or any other factor (Fig 2D).

Treatment Compliance and As-Treated Analysis

The overall noncompliance rate for the trial was 26.3% (Data Supplement). Overall, 44 subjects (16.7%) in the Donor arm did not undergo HCT because of disease progression to AML (18), subject preference (16), progressive comorbidity (7), donor or insurance issues (2), and death (1). In addition, 26 subjects (10%) in the Donor arm received a myeloablative HCT because of physician or subject preference (14), or disease-related issues (12). In the No-Donor arm, 31 subjects (25%) underwent HCT, including nine who found a matched donor after the 90-day search period (one related and eight unrelated). All others received alternative donor transplant, including six who received myeloablative conditioning.

In the as-treated analysis, OS comparing the HCT and No HCT arms demonstrated a significant advantage in 3-year OS (47.4% *v* 16.4%, $P < .0001$) and LFS (39.3% *v* 10.9%, $P < .0001$) for subjects who underwent HCT (Figs 3A and 3B). Among subjects in the No-Donor arm who underwent alternative donor HCT within 6 months of assignment in the absence of disease progression to AML (n = 25), 3-year OS and LFS were both 58.5%.

Transplantation Outcomes

Among the 216 Donor arm subjects who underwent HCT within 6 months of biologic assignment, OS was 55.7% (95% CI, 48.4 to 62.4) and DFS was 49.7% (95% CI, 42.6 to 56.5) at 27 months post-HCT. The estimated median DFS is 26.1 months; median OS has not been reached, with a median follow-up post-HCT among survivors of 28.4 months (interquartile range: 18.0-32.0 months). One hundred-day and 1-year TRM were 7.4% and 15.5%, respectively. In multivariable models, higher IPSS risk score was a significant predictor of both OS (HR 1.85; 95% CI, 1.21 to 2.83; $P = .004$) and DFS (HR 2.17; 95% CI, 1.47 to 3.20; $P < .0001$), whereas response to HMA only predicted OS (baseline: no treatment, HR 2.42 for any response, 2.17 for no response, $P = .005$ and .01, respectively; Data Supplement). At 27 months post-HCT, the cumulative incidence of relapse following HCT was 29.6% (95% CI, 23.5 to 35.9), and TRM was 20.6% (95% CI, 15.3 to 26.5).

TABLE 1. Baseline Clinical Characteristics of Enrolled Subjects

Subject Characteristic	Donor Arm (n = 260)	No-Donor Arm (n = 124)	Total (N = 384)
Age, years			
Mean (SD), No. (%)	65.6 (5.6)	66.0 (5.9)	65.7 (5.7)
Median (range)	66.3 (50.1-75.3)	67.3 (50.7-75.1)	66.7 (50.1-75.3)
65 or older, No. (%)	155 (59.6)	80 (64.5)	235 (61.2)
Sex, No. (%)			
Female	95 (36.5)	48 (38.7)	143 (37.2)
Male	165 (63.5)	76 (61.3)	241 (62.8)
Ethnicity, No. (%)			
Hispanic or Latino	11 (4.2)	9 (7.3)	20 (5.2)
Not Hispanic or Latino	233 (89.6)	108 (87.1)	341 (88.8)
Unknown	9 (3.5)	7 (5.6)	16 (4.2)
NA	7 (2.7)	0 (0.0)	7 (1.8)
Race, No. (%)			
American Indian or Alaskan	1 (0.4)	1 (0.8)	2 (0.5)
Asian	8 (3.1)	2 (1.6)	10 (2.6)
Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	6 (2.3)	9 (7.3)	15 (3.9)
White	234 (90.0)	105 (84.7)	339 (88.3)
More than one race	0 (0.0)	0 (0.0)	0 (0.0)
Other, specify	1 (0.4)	0 (0.0)	1 (0.3)
Unknown	6 (2.3)	4 (3.2)	10 (2.6)
NA	4 (1.5)	3 (2.4)	7 (1.8)
KPS,[a] No. (%)			
90–100	99 (55.0)	35 (41.7)	134 (50.8)
< 90	81 (45.0)	49 (58.3)	130 (49.2)
ECOG performance status,[a] No. (%)			
0	24 (30.0)	16 (40.0)	40 (33.3)
> 0	56 (70.0)	24 (60.0)	80 (66.7)
MDS subtype, No. (%)			
RCUD	5 (1.9)	1 (0.8)	6 (1.6)
RARS	5 (1.9)	2 (1.6)	7 (1.8)
RAEB-1	61 (23.5)	31 (25.0)	92 (24.0)
RAEB-2	132 (50.8)	63 (50.8)	195 (50.8)
RCMD	36 (13.8)	14 (11.3)	50 (13.0)
Isolated del(5q)	6 (2.3)	7 (5.6)	13 (3.4)
Unclassifiable	15 (5.8)	6 (4.8)	21 (5.5)
MDS duration from diagnosis to enrollment, months			
Mean (SD), No. (%)	8.4 (21.6)	11.0 (27.1)	9.2 (23.5)
Median (range)	2.5 (0.2-182.3)	2.2 (0.3-211.6)	2.3 (0.2-211.6)
Highest IPSS score, No. (%)			
Intermediate-2 (1.5-2.0)	173 (66.5)	81 (65.3)	254 (66.1)
High risk (≥ 2.5)	87 (33.5)	43 (34.7)	130 (33.9)

(continued on following page)

TABLE 1. Baseline Clinical Characteristics of Enrolled Subjects (continued)

Subject Characteristic	Donor Arm (n = 260)	No-Donor Arm (n = 124)	Total (N = 384)
Highest IPSS-R score, No. (%)			
Very low	4 (1.5)	0 (0.0)	4 (1.0)
Low	2 (0.8)	0 (0.0)	2 (0.5)
Intermediate	79 (30.4)	34 (27.4)	113 (29.4)
High	82 (31.5)	51 (41.1)	133 (34.6)
Very high	93 (35.8)	39 (31.5)	132 (34.4)
Response to hypomethylating therapy, No. (%)			
Complete response	10 (3.8)	7 (5.6)	17 (4.4)
Partial response	46 (17.7)	23 (18.5)	69 (18.0)
No response	79 (30.4)	42 (33.9)	121 (31.5)
Never had therapy	88 (33.8)	33 (26.6)	121 (31.5)
Unknown	37 (14.2)	19 (15.3)	56 (14.6)
Results of cytogenetics test, No. (%)			
Abnormalities identified	151 (58.1)	81 (65.3)	232 (60.4)
No evaluable metaphases	4 (1.5)	0 (0.0)	4 (1.0)
No abnormalities	84 (32.3)	31 (25.0)	115 (3.0)
Not done or missing	21 (8.1)	12 (9.7)	33 (8.6)
No. of distinct cytogenetic abnormalities, No. (%)			
1	43 (28.5)	28 (34.6)	71 (30.6)
2	31 (20.5)	19 (23.5)	50 (21.6)
3	20 (13.2)	14 (17.3)	34 (14.7)
≥ 4	52 (34.4)	20 (24.7)	72 (31.0)
Missing	5 (3.3)	0 (0.0)	5 (2.2)
Donor type, No. (%)			
Matched related	80 (30.8)	NA	80 (30.8)
Matched unrelated	180 (69.2)	NA	180 (69.2)
HCT-CI, No. (%)			
0	41 (15.8)	NA	41 (15.8)
1	31 (11.9)	NA	31 (11.9)
2	35 (13.5)	NA	35 (13.5)
3+	98 (37.7)	NA	98 (37.7)
Missing	55 (21.2)	NA	55 (21.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; HCT-CI, Hematopoietic Cell Transplant-Comorbidity Index; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; KPS, Karnofsky performance score; MDS, myelodysplastic syndrome; NA, no answer; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCUD, refractory cytopenia with unilineage dysplasia; SD, standard deviation.

[a]Either KPS or ECOG was collected from participants at enrollment.

Only high IPSS score predicted relapse in multivariable models (HR 2.85; 95% CI, 1.74 to 4.68; $P < .0001$). Grades II-IV and III-IV acute GVHD occurred in 43.1% (95% CI, 36.1 to 49.9) and 17.1% (95% CI, 12.2 to 22.7) by day 100, respectively, whereas chronic GVHD was reported in 55.5% (95% CI, 47.8 to 62.5) of subjects by 27 months post-HCT. Among 63 subjects with chronic GVHD severity scores, 40 were classified as moderate and 23 had severe chronic GVHD. Conditioning regimens used before HCT are listed in the Data Supplement.

Quality of Life

Preliminary analyses of patient-reported QOL outcomes demonstrated no differences between Donor and No-Donor arms in any of the QOL scores at any time points evaluated (enrollment, 6, 12, 18, 24, and 36 months) that

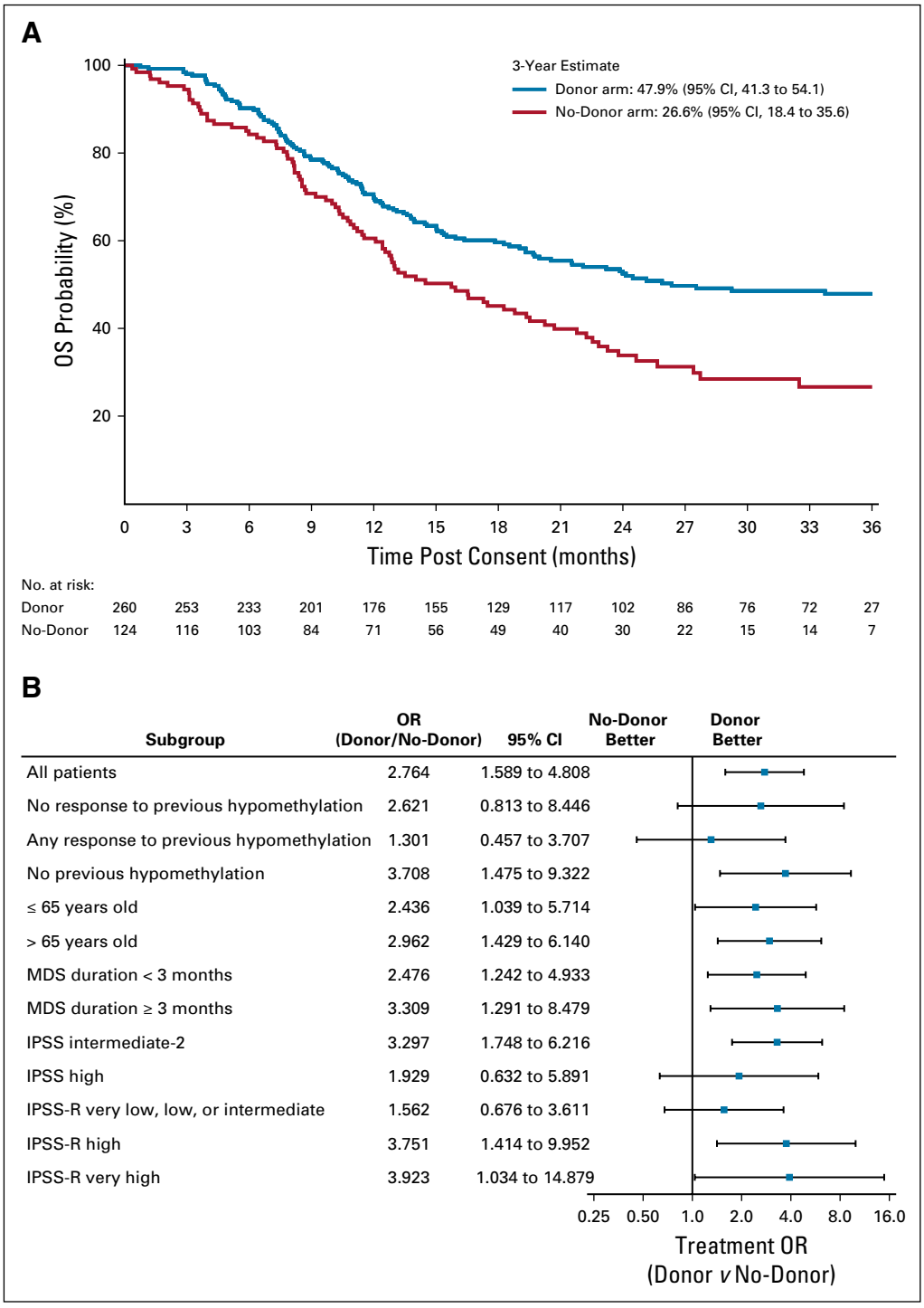

FIG 2. (A) Estimates of OS after registration. OS curves are adjusted for age, race or ethnicity, performance status, IPSS score, duration of disease, and response to HMA in an intention-to-treat analysis. (B) Forest plot of subgroup analyses for OS. The forest plot shows the OR of OS at 3 years for Donor versus No-Donor arm subjects in subgroups determined by age, race or ethnicity, performance status, IPSS score, duration of disease, and response to HMA. NOTE. x-axis has a logarithmic scale. (C) Estimates of LFS after registration. LFS curves are adjusted for age, race or ethnicity, performance status, IPSS score, duration of disease, and response to HMA in an intention-to-treat analysis. (D) Forest plot of subgroup analyses for LFS. The forest plot shows the OR for LFS at 3 years after consent for Donor versus No-Donor arm subjects in subgroups determined by age, race or ethnicity, performance status, IPSS score, duration of disease, and response to HMA. NOTE. x-axis has a logarithmic scale. HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; OR, odds ratio; OS, overall survival. (continued on following page)

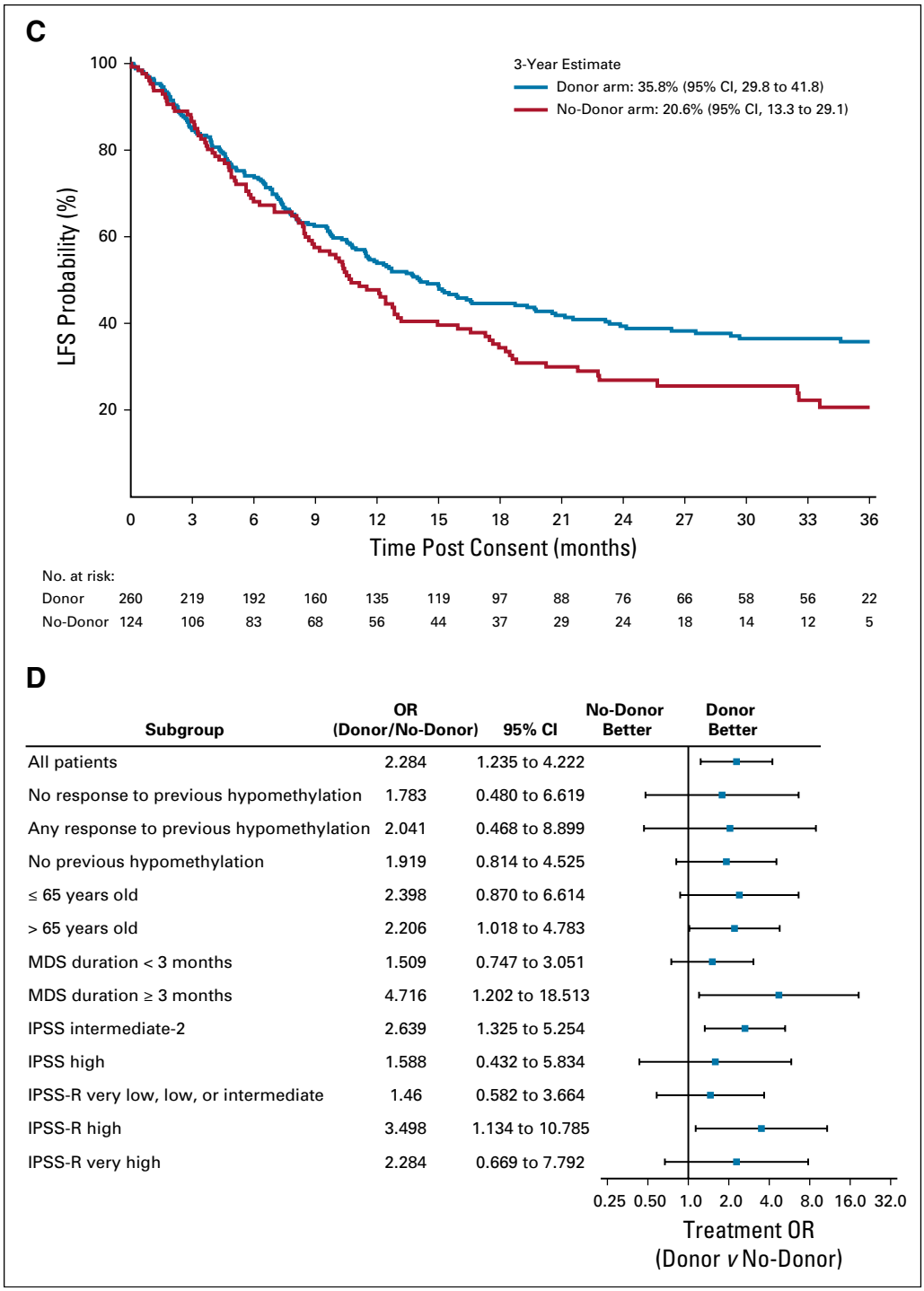

FIG 2. (Continued).

were both statistically significant and clinically meaningful (Data Supplement).

DISCUSSION

This large, multicenter, biologic assignment trial demonstrated a significant 3-year OS and LFS advantage in older MDS subjects who were RIC HCT candidates with matched donors identified when compared with those without a donor. The benefit of having a matched donor was seen across subgroups, including those who were of Medicare age (> 65 years) and younger. Our prospective data are consistent with the survival outcomes observed in cohort studies,[6,16,32,33] retrospective comparative analyses,[13,14] and confirmed the findings from similarly designed

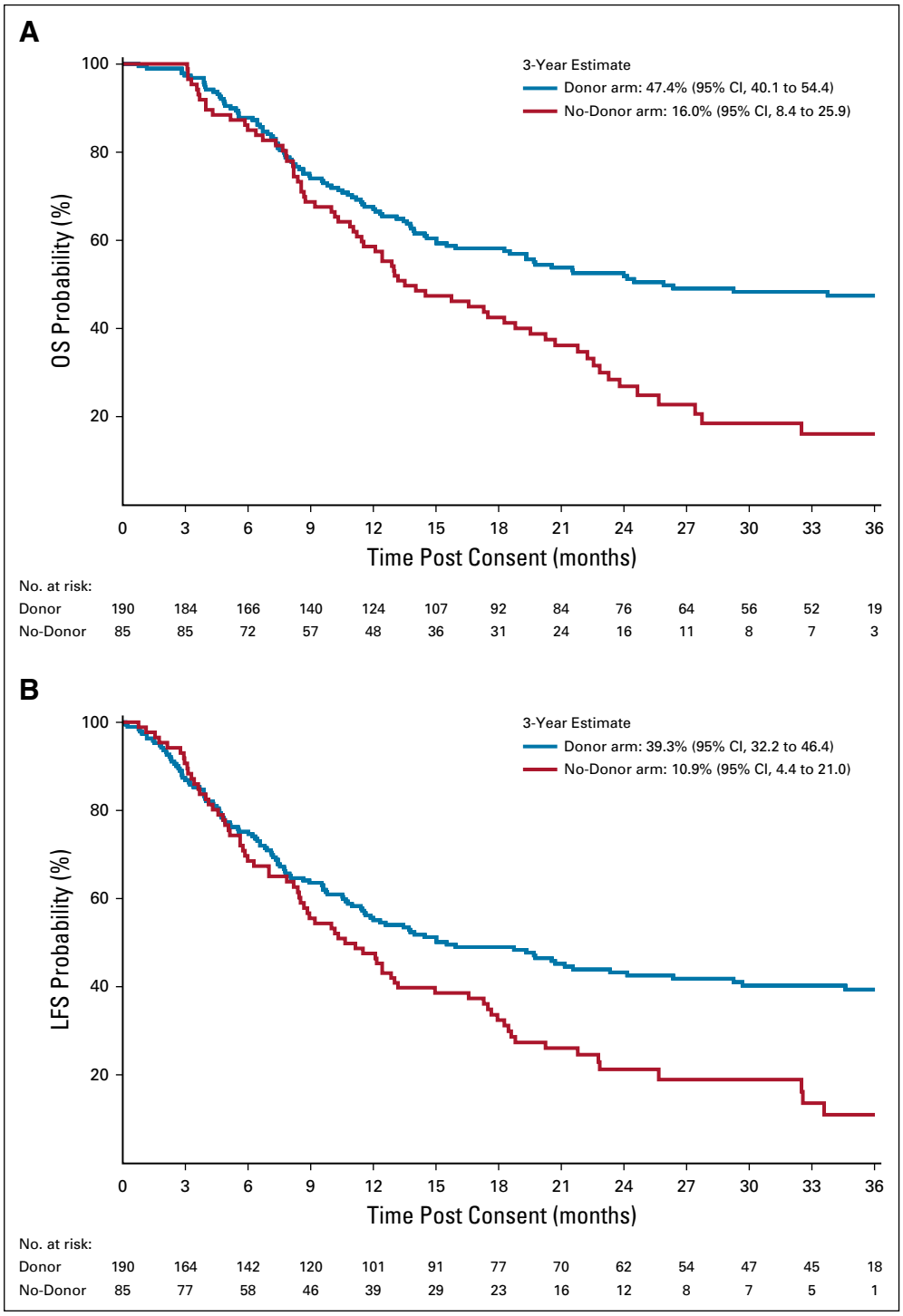

FIG 3. (A) Estimates of OS after registration, as-treated analysis. OS curves are adjusted for age, race or ethnicity, performance status, IPSS score, duration of disease, and response to HMA in an as-treated analysis. (B) Estimates of LFS after registration, as-treated analysis. LFS curves are adjusted for age, race or ethnicity, performance status, IPSS score, duration of disease, and response to HMA in an as-treated analysis. HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; LFS, leukemia-free survival; OS, overall survival.

prospective studies conducted in Europe.[15,16] The French HCT-MDS study group reported trial results on 162 patients with MDS (age: 50-70 years; Donor: n = 112, No-Donor: n = 50) demonstrating better 4-year OS in patients with an HLA-matched donor (37%) compared with those without a donor (15%, $P = .002$).[15] The German cooperative group also conducted a trial comparing continued azacytidine versus HCT in patients with higher-risk MDS (age, 55-70

years) after azacytidine induction (four to six cycles).[18] This trial showed an improved the 3-year OS of 49% versus 22% (95% CI, 36 to 61, 6 to 44) with HCT (n = 83) versus continuous treatment with 5-Aza (n = 26; $P = .027$).

Our trial was approved by the CMS to prospectively address their question posed in 2010: compare(d) to Medicare beneficiaries with MDS who do not receive hematopoietic stem-cell transplantation, do Medicare beneficiaries with MDS who receive hematopoietic stem-cell transplantation have improved outcomes as indicated by relapse-free mortality, progression-free survival, relapse, and OS? A recently reported prospective CIBMTR study (NCT01166009) compared outcomes from 688 patients with MDS (age ≥ 65 years) with 592 patients 55-64 years of age. The study demonstrated no significant difference in 3-year OS.[11] Together, the data from these two trials provide strong evidence that the use of HCT improves health outcomes in Medicare beneficiaries with MDS. Furthermore, the QOL measures between the two groups in our trial were similar, indicating that the observed survival benefit with RIC HCT was achieved without an early decrement in QOL.

Although randomized controlled trials represent the gold-standard design to compare two therapies, a study that randomly assigns subjects to transplantation is difficult to perform and poses ethical challenges, particularly when one therapy has curative potential.[26] Our approach to conduct a biologic assignment trial has been successfully used to evaluate the role of HCT in multiple scenarios.[34-36] Although selection bias can still arise with biologic assignment, this design was considered the most feasible for this research question.[19] To reduce bias, we enrolled subjects without knowledge of donor status and adjusted survival estimates.[25,26] Excessive early deaths before the end of the 90-day search period could have potentially biased the study in favor of the Donor arm, but there were few early deaths and excluding those subjects had no effect on outcomes. Noncompliance with prescribed therapy occurred at the predicted rate (26.3% *v* 25% anticipated). Noncompliance is expected in a real-world scenario, where the timing and conditioning regimen for HCT may differ from original intent because of disease progression, donor availability, and evolving comorbidity. Noncompliance in this trial was clinically appropriate, reflected best clinical care, and did not favor the Donor arm. Donor arm subjects who did not undergo HCT had worse outcomes than those who did, and subjects on the No-Donor arm who underwent HCT had better outcomes than those who did not.

Our trial excluded subjects who were considered for alternative donor HCT. No prospective study has been done to compare outcomes of alternative donor transplant to HLA-matched transplantation in MDS, although registry analyses suggest that alternative donor outcomes are either similar or only minimally inferior to HLA-matched transplantation,[37-39] particularly with the adoption of post-transplant cyclophosphamide as GVHD prophylaxis.[40] Although not designed to specifically evaluate this end point, the favorable outcomes seen with alternative donor transplantation in the No-Donor arm support these assertions.

We designed this trial with a focus on RIC HCT candidates to ensure enrollment of the intended age group (median of 66.7 years). The RIC regimen was left to participating centers according to their institutional guidelines; however, the two most commonly used regimens were fludarabine combined with busulfan or melphalan. Although recent registry studies suggested superior outcomes with fludarabine or melphalan in AML or MDS,[41,42] our study was not designed to address this question. Similarly, our study was not designed to address the issue of the optimal pre-transplant therapeutic strategy, as the majority of subjects received HMA before the registration, reflecting current practice.

Next-generation sequencing–based mutation analysis was not initially performed as part of this trial, despite accumulating evidence that specific somatic mutations in MDS are associated with prognosis and HCT outcomes.[43-46] Future studies are warranted to better define the benefit of HCT according to molecularly informed prognosis toward personalized medicine. Additionally, better assessment tools for older patients with MDS incorporating frailty and resiliency may enhance risk-stratification for HCT (NCT03992352).[47]

Despite the safety of RIC HCT, older patients with hematologic malignant diseases are not routinely offered HCT. In a large trial for older patients with high-risk MDS, only 13% of patients proceeded to HCT,[48] and in a cross-sectional survey of 101 physicians responsible for 4,154 patients with MDS, fewer than 5% of patients were evaluated for HCT.[49] Our study demonstrated a significant survival advantage in older patients with MDS who are RIC HCT candidates and have a matched donor identified when compared with those without a donor. Based on these data, HCT should be included as an integral part of MDS management plans in fit older adults with higher-risk MDS. Early referral to a transplant center and coverage of HCT by CMS are strongly recommended.

AFFILIATIONS

[1]City of Hope National Medical Center, Duarte, CA
[2]Medical College of Wisconsin, Milwaukee, WI
[3]The Emmes Company, Rockville, MD
[4]Fred Hutchinson Cancer Research Center, Seattle, WA
[5]University of Texas MD Anderson Cancer Center, Houston, TX
[6]National Heart, Lung, and Blood Institute, Bethesda, MD
[7]Memorial Sloan Kettering Cancer Center, New York, NY
[8]Moffitt Cancer Center, Tampa, FL
[9]Oregon Health and Science University, Portland, OR
[10]University of Kansas Medical Center, Kansas City, KS

[11]Washington University in Saint Louis, Saint Louis, MO
[12]The Ohio State University Comprehensive Cancer Center, Columbus, OH
[13]Mayo Clinic, Rochester, MN
[14]Baylor College of Medicine, Houston, TX
[15]Cleveland Clinic, Cleveland, OH
[16]Dana Farber Cancer Institute, Boston, MA

CORRESPONDING AUTHOR

Corey Cutler, MD, MPH, Dana Farber Cancer Institute 450 Brookline Ave, D2-031, Boston, MA 02115; e-mail: corey_cutler@dfci.harvard.edu.

STUDY GROUPS

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DISCLAIMER

The views expressed in this article are those of the authors and do not reflect the views or the official policy or position of the National Heart, Lung, and Blood Institute, the National Cancer Institute, or the National Marrow Donor Program.

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AUTHOR CONTRIBUTIONS

Conception and design: Ryotaro Nakamura, Wael Saber, Bart Scott, Betul Oran, Peter Westervelt, Stephen J. Forman, Mikkael A. Sekeres, Frederick Appelbaum, Adam Mendizabal, Brent Logan, Mary Horowitz, Corey Cutler
Administrative support: Alyssa Ramirez, Joseph McGuirk, Sumithira Vasu, Stephen J. Forman
Provision of study materials or patients: Richard T. Maziarz, Joseph McGuirk, Sumithira Vasu
Collection and assembly of data: Ryotaro Nakamura, Wael Saber, Michael J. Martens, Alyssa Ramirez, Bart Scott, Betul Oran, Roni Tamari, Asmita Mishra, Joseph McGuirk, Peter Westervelt, Sumithira Vasu, Mrinal Patnaik, Rammurti Kamble, Adam Mendizabal, Mary Horowitz, Corey Cutler
Data analysis and interpretation: Ryotaro Nakamura, Wael Saber, Michael J. Martens, Bart Scott, Betul Oran, Eric Leifer, Roni Tamari, Asmita Mishra, Richard T. Maziarz, Joseph McGuirk, Peter Westervelt, Sumithira Vasu, Rammurti Kamble, Stephen J. Forman, Mikkael A. Sekeres, Frederick Appelbaum, Adam Mendizabal, Brent Logan, Mary Horowitz, Corey Cutler
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome

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Ryotaro Nakamura
Consulting or Advisory Role: Viracor Eurofins, Magenta Therapeutics, Kadmon, Napajen Pharma
Research Funding: Helocyte, Miyarisan Pharmaceutical
Travel, Accommodations, Expenses: Kyowa Hakko Kirin, Alexion Pharmaceuticals

Bart Scott
Honoraria: Bristol Myers Squibb
Consulting or Advisory Role: Celgene, Acceleron Pharma, Astex Pharmaceuticals, Novartis
Speakers' Bureau: Alexion Pharmaceuticals, Celgene, Jazz Pharmaceuticals, Novartis
Research Funding: Celgene

Betul Oran
Research Funding: AROG Phamarceuticals, Astex Pharmaceuticals

Asmita Mishra
Research Funding: Novartis

Richard T. Maziarz
Honoraria: Novartis, Omeros, PACT Pharmaceuticals
Consulting or Advisory Role: Novartis, Incyte, Kite, a Gilead company, Bristol Myers Squibb, Intellia Therapeutics, Artiva
Patents, Royalties, Other Intellectual Property: Athersys Inc shared patent re: use of mesenchymal stromal cells for treatment of GVHD
Travel, Accommodations, Expenses: Novartis, Incyte, Kite, a Gilead company

Joseph McGuirk
Honoraria: Kite, a Gilead company, AlloVir, Juno Therapeutics, Magenta Therapeutics
Consulting or Advisory Role: Kite, a Gilead company, Juno Therapeutics, AlloVir, Magenta Therapeutics, EcoR1 Capital
Speakers' Bureau: Kite/Gilead
Research Funding: Novartis, Fresenius Biotech, Astellas Pharma, Bellicum Pharmaceuticals, Gamida Cell, Pluristem Therapeutics, Kite, a Gilead company, AlloVir
Travel, Accommodations, Expenses: Kite, a Gilead company

Peter Westervelt
Consulting or Advisory Role: Pfizer

Sumithira Vasu
Consulting or Advisory Role: Omeros, Johnson & Johnson
Patents, Royalties, Other Intellectual Property: The Ohio State University has entered into an exclusive licensing agreement with Kiadis Inc

Mrinal Patnaik
Honoraria: Kura Oncology
Consulting or Advisory Role: Kura Oncology
Research Funding: Stemline Therapeutics

Stephen J. Forman
Stock and Other Ownership Interests: MustangBio, Lixte Biotechnology
Consulting or Advisory Role: Alimera Sciences, Lixte Biotechnology, MustangBio
Research Funding: MustangBio
Patents, Royalties, Other Intellectual Property: MustangBio

Mikkael A. Sekeres
Consulting or Advisory Role: Celgene, Millennium, Pfizer, Novartis
Research Funding: Takeda, Pfizer, Bristol Myers Squibb

Frederick Appelbaum
Stock and Other Ownership Interests: Jasper Therapeutics

Brent Logan
Consulting or Advisory Role: Daiichi Sankyo, Enlivex Therapeutics Ltd, Gamida Cell

Mary Horowitz
Consulting or Advisory Role: Magenta Therapeutics, Janssen Research & Development, Medac
Research Funding: Biovitrum, Jazz Pharmaceuticals, Magenta Therapeutics, Novartis, Kite/Gilead, Actinium Pharmaceuticals, Amgen, Amneal Pharmaceuticals, Anthem, Bluebird Bio, Bristol Myers Squibb, Chimerix, CSL Behring, Cyto-Sen Therapeutics, Daiichi Sankyo, Gamida Cell, GlaxoSmithKline, Mesoblast, Miltenyi Biotec, Neovii, Oncoimmune, Pfizer, Pharmacyclics, Regeneron, Sanofi, Seattle Genetics, Shire

Corey Cutler
Stock and Other Ownership Interests: Bluebird Bio, Idera, Verastem, Northwest Biotherapeutics, Actinium Pharmaceuticals
Honoraria: Omeros, Pfizer
Consulting or Advisory Role: Incyte, Jazz Pharmaceuticals, CareDX, Mesoblast, Syndax, Medsenic

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