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, MD1; Wael Saber, MD, MS2; Michael J. Martens, PhD2; Alyssa Ramirez, BS3; Bart Scott, MD4; Betul Oran, MD5; Eric Leifer, PhD6; Roni Tamari, MD7; Asmita Mishra, MD8; Richard T. Maziarz, MD9; Joseph McGuirk, DO10; Peter Westervelt, MD, PhD11; Sumithira Vasu, MBBS12; Mrinal Patnaik, MBBS13; Rammurti Kamble, MD14; Stephen J. Forman, MD1; Mikkael A. Sekeres, MD, MS15; Frederick Appelbaum, MD4; Adam Mendizabal, PhD3; Brent Logan, PhD2; Mary Horowitz, MD, MS2; and Corey Cutler, MD, MPH16; on behalf of the Blood and Marrow Transplant Clinical Trials Network

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.

J Clin Oncol 39:3328-3339. © 2021 by American Society of Clinical Oncology

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.2,3 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.4,5 Allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy for MDS and an established therapy for younger patients with MDS.6-10 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...
THE JOURNAL OF CLINICAL ONCOLOGY

Survival of Older Adults With MDS Based on Donor Availability

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.

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). 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. 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.

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 to account for the potential bias resulting from biologic assignment, 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, 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.

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). 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]; $P = .0001$; 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, 90-day search window had no effect on outcomes (35.9% v
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% vs 16.4%, $P < .0001$) and LFS (39.3% vs 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).
| 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,* 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,* 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)
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)
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, retrospective comparative analyses, and confirmed the findings from similarly designed...
prospective studies conducted in Europe. 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). The German cooperative group also conducted a trial comparing continued azacytidine versus HCT in patients with higher-risk MDS (age, 55-70

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.
years) after azacitidine induction (four to six cycles). This trial showed an improved 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 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. 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. Our approach to conduct a biologic assignment trial has been successfully used to evaluate the role of HCT in multiple scenarios. Although selection bias can still arise with biologic assignment, this design was considered the most feasible for this research question. To reduce bias, we enrolled subjects without knowledge of donor status and adjusted survival estimates. 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% ± 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.
REFERENCES

1. Giralt SA, Horowitz M, Weisdorf D, et al: Review of stem-cell transplantation for myelodysplastic syndromes in older patients in the context of the decision memo for allogeneic hematopoietic stem cell transplantation for myelodysplastic syndrome emanating from the Centers for Medicare and Medicaid Services. J Clin Oncol 29:566-572, 2011

2. Silverman LR, Demakos EP, Peterson BL, et al: Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the cancer and leukemia group B. J Clin Oncol 20:2429-2440, 2002

3. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al: Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study. Lancet Oncol 10:223-232, 2009

4. Kantarjian H, Issa JP, Rosenfeld CS, et al: Decitabine improves patient outcomes in myelodysplastic syndromes: Results of a phase III randomized study. Cancer 106:1794-1803, 2006

5. Lubbert M, Suciu S, Baila L, et al: Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: Final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. J Clin Oncol 29:1987-1996, 2011

6. Itzykson R, Thiépont S, Querol B, et al: Long-term outcome of higher-risk MDS patients treated with azacitidine: An update of the GFM compassionate program cohort. Blood 119:6172-6173, 2012

7. Prebet T, Gore SD, Esterni B, et al: Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol 29:3322-3327, 2011

8. Cutler CS, Lee SJ, Greenberg P, et al: A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low-risk myelodysplastic syndrome is associated with improved outcome. Blood 104:579-585, 2004

9. Oliansky DM, Larson RA, Weisdorf D, et al: The role of cytoxic therapy with hematopoietic stem cell transplantation in the treatment of adult acute lymphoblastic leukemia: Update of the 2006 evidence-based review. Biol Blood Marrow Transplant 18:18-36.e6, 2012

10. de Witte T, Bowen D, Robin M, et al: Allogeneic hematopoietic stem cell transplantation for MDS and CMML: Recommendations from an international expert panel. Blood 129:1753-1762, 2017

11. Allalith E, Logan B, Chen M, et al: Comparison of patient age groups in transplantation for myelodysplastic syndrome: The Medicare coverage with evidence development study. JAMA Oncol 5:485-493, 2019

12. McClure BL, Weisdorf DJ, Pedersen TL, et al: Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol 28:1878-1887, 2010

13. Koreth J, Pidala J, Perez WS, et al: Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: An international collaborative decision analysis. J Clin Oncol 31:2662-2670, 2013

14. Platzbecker U, Schetelig J, Finke J, et al: Allogeneic hematopoietic cell transplantation in patients age 60-70 years with de novo high-risk myelodysplastic syndrome or secondary acute myelogenous leukemia: Comparison with patients lacking donors who received azacitidine. Biol Blood Marrow Transplant 18:1415-1421, 2012

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.03380.

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, Minal 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

ACKNOWLEDGMENT

The authors thank the transplantation-center teams for enrolling patients in this trial (Data Supplement).

CLINICAL TRIAL INFORMATION

NCT021016781

STUDY GROUPS

Written on behalf of the Blood and Marrow Transplant Clinical Trials Network.

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.

PRIOR PRESENTATION

Presented as abstract at the Annual Meeting of the American Society of Hematology, San Diego, CA, December 2020.

SUPPORT

Supported by Grant Nos. U10HL069294 and U24HL138660 to the Blood and Marrow Transplant Clinical Trials Network from the National Heart, Lung, and Blood Institute and the National Cancer Institute.

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.

Nakamura et al
15. Robin M, Porcher R, Ades L, et al: HLA-matched allogeneic stem cell transplantation improves outcome of higher risk myelodysplastic syndrome A prospective study on behalf of SFGM-TC and GFM. Leukemia 29:1496-1501, 2015

16. German MDS Study Group and Cooperative German Transplant Study Group University Medical Center-Hamburg-Eppendorf, Hamburg, Germany: 5-Azacytidine (5-Aza) Induction Followed by Allogeneic Stem Cell Transplantation Versus Continuous 5-Aza in Elderly MDS Patients (55-70 Years). A Prospective Randomized Study (VidazaAllo Study). Frankfurt, Germany. EBMT, 2019

17. Decision memo for allogeneic hematopoietic stem cell transplantation (HSCT) for myelodysplastic syndrome (CAG-00415N) 2010. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=238

18. Krogner N, Sockel K, Wolchicke C, et al: Prospective multicenter phase 3 study comparing 5-azacytidine (5-Aza) induction followed by allogeneic stem cell transplantation versus continuous 5-Aza according to donor availability in elderly MDS patients (55-70 years) (VidazaAllo study). Blood 132:208, 2018

19. Saber W, Le Rademacher J, Sekeres M, et al: Multicenter biologic assignment trial comparing reduced-intensity allogeneic hematopoietic cell transplant to hypomethylating therapy or best supportive care in patients aged 50 to 75 with intermediate-2 and high-risk myelodysplastic syndrome: Blood and Marrow Transplant Clinical Trials Network #1102 study rationale, design, and methods. Biol Blood Marrow Transplant 20:1566-1572, 2014

20. Wheatley K, Gray R: Commentary—Mendelian randomization—An update on its use to evaluate allogeneic stem cell transplantation in leukaemia. Int J Epidemiol 33:15-17, 2004

21. Burnett AK, Hills RK, Milligan DW, et al: Attempts to optimize induction and consolidation treatment in acute myeloid leukemia: Results of the MRC AML12 trial. J Clin Oncol 28:586-595, 2010

22. Greenberg P, Cox C, LeBeau MM, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 89:2079-2088, 1997

23. Baccigalupo A, Ballen K, Rizzo D, et al: Defining the intensity of conditioning regimens: Working definitions. Biol Blood Marrow Transplant 15:1628-1633, 2009

24. BMT CTN website. www.bmtctn.net

25. Zhang X, Lobezria FR, Klein JP, et al: A SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. Comput Methods Programs Biomed 88:95-101, 2007

26. Logan B, Leifer E, Bredeson C, et al: Use of biological assignment in hematopoietic stem cell transplantation clinical trials. Clin Trials 5:607-616, 2008

27. McQuelon RP, Russell GB, Cella DF, et al: Quality of life measurement in bone marrow transplantation: Development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. Bone Marrow Transpl 19:357-368, 1997

28. McHorney CA, Ware JE Jr, Raczek AE: The MOS 36-item short-form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31:247-263, 1993

29. Shaw JW, Johnson JA, Coons SJ: US valuation of the EQ-5D health states: Development and testing of the D1 valuation model. Med Care 43:203-220, 2005

30. Klein JP, Logan B, Harhoff M, et al: Analyzing survival curves at a fixed point in time. Stat Med 26:4505-4519, 2007

31. Clark TG, Altman DG, De Stavola BL: Quantifying the completeness of follow-up. Lancet 359:1309-1310, 2002

32. Saber W, Cutler CS, Nakamura R, et al: Impact of donor source on hematopoietic cell transplantation outcomes for patients with myelodysplastic syndromes (MDS). Blood 122:1974-1982, 2013

33. Itzykson R, Thépot S, Quaesel B, et al: Prognostic factors for response and overall survival in 282 patients with higher-risk myelodysplastic syndromes treated with azacitidine. Blood 117:403-411, 2011

34. Cassileth PA, Harrington DP, Appelbaum FR, et al: Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. N Engl J Med 339:1649-1656, 1998

35. Oosterwert M, Suciu S, Verhoef G, et al: The presence of an HLA-identical sibling donor has no impact on outcome of patients with high-risk MDS or secondary AML (sAML) treated with intensive chemotherapy followed by transplantation: Results of a prospective study of the EORTC, EBMT, SAKK and GIMEMA Leukemia Groups (EORTC study 06921). Leukemia 17:859-968, 2003

36. Woods WG, Neudorf S, Gold S, et al: A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission: A report from the Children’s Cancer Group. Blood 97:56-62, 2001

37. Gerds AT, Woo Ahn K, Hu ZH, et al: Outcomes after umbilical cord blood transplantation for myelodysplastic syndromes. Biol Blood Marrow Transplant 23: 971-979, 2017

38. Robin M, Porcher R, Ruggeri A, et al: HLA-mismatched donors in patients with myelodysplastic syndrome: An EBMT registry analysis. Biol Blood Marrow Transplant 25:114-120, 2019

39. Ciurea SO, Shah MV, Saliba RM, et al: Haploidentical transplantation for older patients with acute myeloid leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant 24:1232-1236, 2018

40. Grunwald MR, Zhang M-J, Elmariah H, et al: Allogeneic transplantation for myelodysplastic syndrome in adults over 50 years old using reduced intensity/non-myeloablative conditioning: Haploidentical relative versus matched unrelated donor. Blood 134:3323, 2019

41. Oosterlund M, Brazauskas R, Hemmer M, et al: Hematopoietic cell transplant for acute myeloid leukemia and myelodysplastic syndrome: Conditioning regimen intensity. Blood Adv 2:2095-2103, 2018

42. Oran B, Pham A, Li SM, et al: Favorable impact of allogeneic stem cell transplantation in patients with therapy-related myelodysplasia regardless of TP53 mutational status. Biol Blood Marrow Transplant 20:2691-2698, 2014

43. Openshaw PJ, Darby S, Jones GT, et al: Prognostic factors in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med 376:536-547, 2017

44. Aldoss I, Pham A, Li SM, et al: Favorable impact of allogeneic stem cell transplantation in patients with therapy-related myelodysplasia regardless of TP53 mutational status. Haematologica 102:2030-2038, 2017

45. Derman BA, Kordas K, Ridgeway J, et al: Results from a multidisciplinary clinic guided by geriatric assessment before stem cell transplantation in older adults. Blood Adv 3:3488-3498, 2019

46. Sekeres MA, Schoonen WM, Kantarjian H, et al: Characteristics of US patients with myelodysplastic syndromes: Results of six cross-sectional physician surveys. J Natl Cancer Inst 100:1542-1551, 2008

47. Sekeres MA, Othus M, List AF, et al: Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia. North American Intergroup Study SWOG S1117. J Clin Oncol 35:2745-2753, 2017

48. Sekeres MA, Schoonen WM, Kantarjian H, et al: Characteristics of US patients with myelodysplastic syndromes: Results of six cross-sectional physician surveys. J Natl Cancer Inst 100:1542-1551, 2008
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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Ryotaro Nakamura
Consulting or Advisory Role: Viracor Eurofins, Magenta Therapeutics, Kadmon, Napajen Pharma
Research Funding: Helocyte, Myarisan 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: AROQ Pharmaceuticals, 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 Kadias Inc

Mikael 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

Mary Horowitz
Consulting or Advisory Role: Magenta Therapeutics, Janssen Research & Development, Medac
Research Funding: Biostrum, 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, Pharmaciesics, Regeneron, Sanofi, Seattle Genetics, Sine

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

No other potential conflicts of interest were reported.