Allogeneic Hematopoietic Cell Transplantation Improves Outcome in Myelodysplastic Syndrome Across High-Risk Genetic Subgroups: Genetic Analysis of the Blood and Marrow Transplant Clinical Trials Network 1102 Study

Jurjen Versluis, MD, PhD[1,2]; Wael Saber, MD, MS[3]; Harrison K. Tsai, MD, PhD[1]; Christopher J. Gibson, MD[1]; Laura W. Dillon, PhD, FACMG[4]; Asmita Mishra, MD[5]; Joseph McGuirk, DO[6]; Richard T. Maziarz, MD[7]; Peter Westervelt, MD, PhD[8]; Pranay Hegde, BA[4]; Devdeep Mukherjee, PhD[4]; Michael J. Martens, PhD[3]; Brent Logan, PhD[3]; Mary Horowitz, MD, MS[3]; Christopher S. Hourigan, MD, PhD[4,9]; Ryotaro Nakamura, MD[10]; Corey Cutler, MD, MPH[1]; and R. Coleman Lindsley, MD, PhD[1]; on behalf of the Blood and Marrow Transplant Clinical Trials Network

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ABSTRACT

PURPOSE Allogeneic hematopoietic cell transplantation (HCT) in patients with myelodysplastic syndrome (MDS) improves overall survival (OS). We evaluated the impact of MDS genetics on the benefit of HCT in a biological assignment (donor *v* no donor) study.

METHODS We performed targeted sequencing in 309 patients age 50-75 years with International Prognostic Scoring System (IPSS) intermediate-2 or high-risk MDS, enrolled in the Blood and Marrow Transplant Clinical Trials Network 1102 study and assessed the association of gene mutations with OS. Patients with *TP53* mutations were classified as $TP53^{multihit}$ if two alleles were altered (via point mutation, deletion, or copy-neutral loss of heterozygosity).

RESULTS The distribution of gene mutations was similar in the donor and no donor arms, with *TP53* (28% *v* 29%; $P = .89$), *ASXL1* (23% *v* 29%; $P = .37$), and *SRSF2* (16% *v* 16%; $P = .99$) being most common. OS in patients with a *TP53* mutation was worse compared with patients without *TP53* mutation (21% ± 5% [SE] *v* 52% ± 4% at 3 years; $P < .001$). Among those with a *TP53* mutation, OS was similar between $TP53^{single}$ versus $TP53^{multihit}$ (22% ± 8% *v* 20% ± 6% at 3 years; $P = .31$). Considering HCT as a time-dependent covariate, patients with a *TP53* mutation who underwent HCT had improved OS compared with non-HCT treatment (OS at 3 years: 23% ± 7% *v* 11% ± 7%; $P = .04$), associated with a hazard ratio of 3.89; 95% CI, 1.87 to 8.12; $P < .001$ after adjustment for covariates. OS among patients with molecular IPSS (IPSS-M) very high risk without a *TP53* mutation was significantly improved if they had a donor (68% ± 10% *v* 0% ± 12% at 3 years; $P = .001$).

CONCLUSION HCT improved OS compared with non-HCT treatment in patients with *TP53* mutations irrespective of *TP53* allelic status. Patients with IPSS-M very high risk without a *TP53* mutation had favorable outcomes when a donor was available.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment for patients with myelodysplastic syndrome (MDS). Two biological assignment studies demonstrated improved overall survival (OS) for older patients with high-risk MDS and an available donor compared with those without a donor.[1,2] Although the survival benefit of HCT was observed across different clinical parameters, these studies did not assess somatic or germline gene mutations, which have been shown to predict outcomes after allogeneic HCT in retrospective cohorts.[3-7]

Mutations in *TP53* are unequivocally associated with dismal outcomes after HCT because of high rates of disease relapse or progression to AML.[3-5] Consequently, the role of HCT for patients with *TP53*-mutated MDS or AML is debated.[8] Retrospective analyses have evaluated the potential impact of disease-, patient-, and transplant-related variables, but

CONTEXT

Key Objective

To determine whether the improved survival of allogeneic hematopoietic cell transplantation (HCT) in a high-risk myelodysplastic syndrome (MDS) biological assignment trial of HCT was independent of gene mutations.

Knowledge Generated

Overall survival was significantly improved by HCT in high-risk genetic subgroups including *TP53*-mutated MDS and International Prognostic Scoring System-Molecular very high risk. The improvement by HCT was independent of baseline clinical or genetic characteristics including *TP53* mutational clearance.

Relevance *(C.F. Craddock)*

This pivotal prospective study demonstrates that allogeneic HCT represents an important, potentially curative, therapeutic strategy in patients with high-risk genetic sub-groups of MDS, including patients with *TP53* mutated MDS.*

*Relevance section written by *JCO* Associate Editor Charles F. Craddock, MD.

results are conflicting, and conclusions are fundamentally limited by the lack of a comparative non-HCT group.[3,7,9,10]

We performed a genetic analysis of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1102 study of older patients with advanced MDS to identify whether the survival benefit observed in patients biologically assigned to HCT compared with non-HCT approaches was independent of gene mutations. We specifically focused on mutations associated with outcome in this high-risk MDS cohort, including *TP53*.

METHODS

Clinical Cohort

Samples were obtained from the BMT CTN 1102 study (ClinicalTrials.gov identifier: NCT02016781), a multicenter trial comparing reduced intensity conditioning (RIC) HCT with hypomethylating therapy or best supportive care in patients age 50-75 years with International Prognostic Scoring System (IPSS) intermediate-2 or high-risk de novo MDS.[1] Frozen whole blood collected at the time of enrollment was available from 309 of 384 enrolled patients in the Center for International Blood and Marrow Transplant Research (CIBMTR) Research Sample Repository or the NMDP Repository (Fig 1). Sample availability was higher in patients assigned to the donor arm compared with the no donor arm (n = 229, 88.1% *v* n = 80, 64.5%; $P < .001$). Patient characteristics and clinical outcomes were aligned with those previously reported for this trial. Baseline characteristics were not significantly different between patients with an available sample compared with those without (Data Supplement [Table S1], online only) and, among patients with samples, were similar in the donor and no donor group. The median follow-up in survivors was 32 months (range, 6-38). All patients provided written informed consent to participate in both the BMT CTN 1102 trial and the CIBMTR research database. This study was approved by the BMT CTN and CIBMTR and conducted with approval of the Dana-Farber Cancer Institute institutional review board.

Genetic Analysis

Targeted DNA sequencing on samples at the time of enrollment was performed on 113 genes known to be recurrently mutated in myeloid malignancies or associated with germline predisposition to develop myeloid malignancies (Data Supplement [Table S2]), using a variant allele fraction (VAF) cutoff of 0.02 (Custom SureSelect, Agilent Technologies, Santa Clara, CA). *TP53* mutation allele abundance was quantified just before transplantation in DNA extracted from preconditioning blood samples using a custom targeted error-corrected DNA sequencing panel covering the entire coding sequence of the *TP53* gene (VariantPlex, ArcherDx, Boulder, CO).[11] Detailed sequencing information is provided in the Data Supplement (Appendix). MDS with *TP53* mutations was further categorized on the basis of the number of *TP53* mutations (single-nucleotide variants or small indels) and the presence of *TP53* deletion or copy-neutral loss of heterozygosity (CN-LOH). Those with ≥2 *TP53* mutations or ≥1 point mutation in combination with *TP53* CN-LOH, *TP53* deletion, or chromosome 17/17p deletion by karyotype were classified as $TP53^{multihit}$, whereas those with a single *TP53* point mutation without LOH were classified as $TP53^{single}$.[12,13] *FLT3* internal tandem duplications and *KMT2A* partial tandem duplications were identified as described.[14,15] The genetic analysis was locked before merging with clinical data.

Statistical Analysis

To identify mutations associated with OS in the whole study cohort, we evaluated 17 genes that were mutated in ≥10 patients in the study cohort (Data Supplement [Fig S1 and Table S3]). Genes that were mutated less frequently were

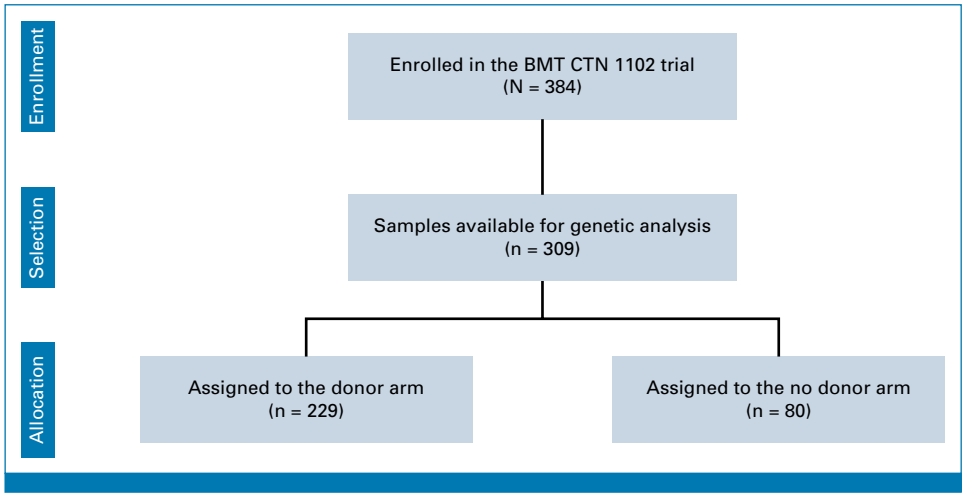

FIG 1. Patients included in this study. BMT CTN, Blood and Marrow Transplant Clinical Trials Network.

subject to descriptive analysis. OS was considered as the time from consent until death from any cause or until censoring at the date of last contact being alive. OS curves were estimated using the Kaplan-Meier method, and cumulative incidences of relapse or progression to leukemia were estimated with the Aalen-Johansen method, with death without relapse or disease progression being treated as competing events. Outcomes were compared in univariate analysis of survival and competing risks using log-rank and Gray's test, respectively. Comparisons between the two groups were performed using the Mann-Whitney U test for continuous variables, whereas the Fisher's exact test was used for categorical variables.

The impact of allogeneic HCT was assessed using two methods: (1) a time-dependent analysis allowing the HCT covariate to change at the time of HCT, where OS curves were shown using Simon-Makuch plots[16] and (2) a dynamic landmarking analysis at 3, 6, and 9 months from consent by treatment arm in which patients were assigned to no HCT group if they were not transplanted at the landmark time.[17,18]

Multivariable analysis was performed using a Cox proportional hazards model with adjustment for prespecified variables, which included age at enrollment (older than 65 *v* 65 years and younger), performance status (Karnofsky <90 *v* 90-100 or Eastern Cooperative Oncology Group 1 *v* 0), IPSS risk status (high *v* intermediate-2), and MDS disease duration (≥3 *v* <3 months). Stepwise selection of variables with an univariate of $P < .2$ for OS was used to generate a multivariable model integrating the remaining clinical and genetic features, with $P < .1$ as the threshold for variable inclusion in the model.

RESULTS

Genetic Characteristics

We identified ≥1 mutation in 272 of 309 (88%) patients. The overall distribution of somatic gene mutations was similar in the donor and no donor arms, with *TP53* (28% *v* 29%; $P = .89$), *ASXL1* (23% *v* 29%; $P = .37$), *SRSF2* (16% *v* 16%; $P = .99$), and *DNMT3A* (17% *v* 10%; $P = .20$) being the most common (Fig 2). Inferred germline mutations in *DDX41* were found in 7% (n = 23) of patients, and rare variants affecting core telomerase components *TERT* (n = 9) or *TERC* (n = 1) were observed in 3% of patients, consistent with a recent report.[6] The frequency and distribution of gene mutations in the BMT CTN 1102 cohort were similar to those from a retrospective registry-level MDS transplant cohort (n = 227) matched for age, IPSS risk group, and primary versus therapy-related MDS status (Fig 2).[3]

Clinical and Genetic Characteristics of *TP53* Mutations

Among 87 patients with a *TP53* mutation, 48 (55%) were classified as $TP53^{multihit}$, including 27 with ≥2 *TP53* mutations, 15 with one *TP53* mutation and *TP53* LOH identified by NGS, and six with one *TP53* mutation and deletion of chromosome 17/17p by karyotype (Data Supplement [Fig S2]). The presence of a *TP53* mutation, but not *TP53* allelic state, was significantly associated with clinical and molecular characteristics, including a higher frequency of complex karyotype ($TP53^{multihit}$ = 67% and $TP53^{single}$ = 62% *v* $TP53^{WT}$ = 10%; $P < .001$ and $P < .001$, respectively) and lower platelet count at enrollment ($TP53^{multihit} = 42 \times 10^9$/L and $TP53^{single} = 62 \times 10^9$/L *v* $TP53^{WT} = 90 \times 10^9$/L; $P = .002$ and $P = .032$, respectively; Data Supplement [Table S4]). Consistent with these differences, patients with a *TP53* mutation were significantly more likely to have IPSS high-risk disease than those without a *TP53* mutation (52% *v* 26%; $P < .001$). Other clinical and transplant characteristics were not different between patients with and without a *TP53* mutation (Data Supplement [Table S4]).

Genetic Determinants of Outcomes

In univariate analysis, the presences of a *TP53* mutation and $KMT2A^{PTD}$ were significantly associated with shorter OS compared with patients without those mutations (*TP53*:

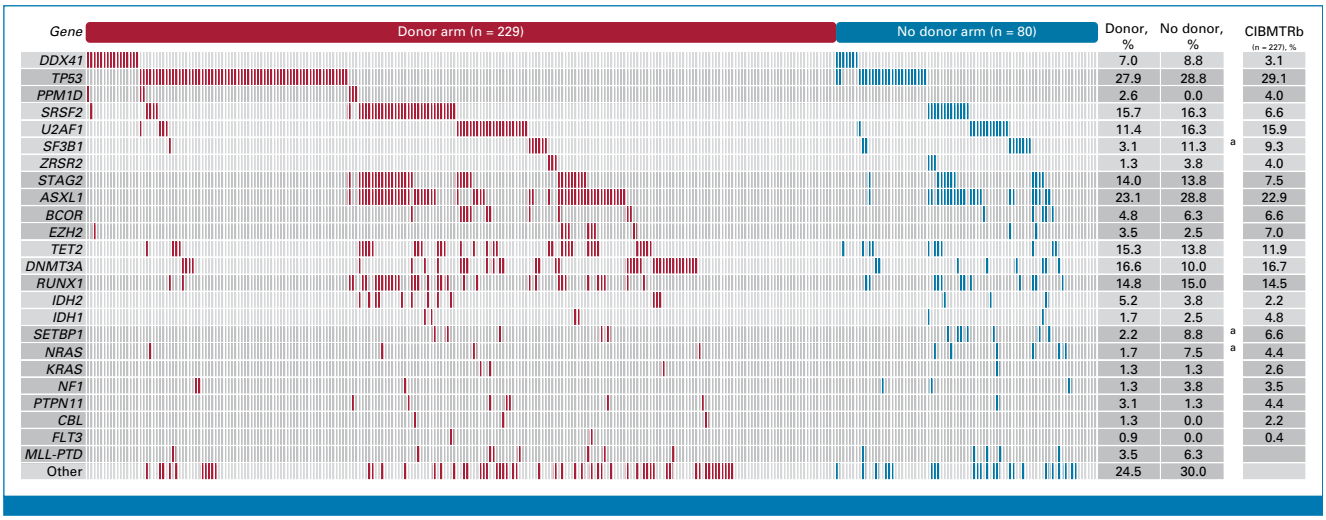

FIG 2. Spectrum of myeloid driver mutations in the BMT CTN 1102 study. A comutation plot shows mutations in individual genes per study arm as labeled on the top. Mutations are depicted by colored bars and each column represents one of the 309 patients. [a]Significant with $P < .05$ (Fisher's exact test). [b]Selection of patients with de novo MDS with IPSS intermediate-2 or high risk age 50-75 years from a matched retrospective cohort.[3] BMT CTN, Blood and Marrow Transplant Clinical Trials Network; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome.

21% ± 5% [SE] *v* 52% ± 4% at 3 years; hazard ratio [HR], 2.55; 95% CI, 1.86 to 3.50; $P < .001$; *KMT2A*^{PTD}: 8% ± 7% *v* 45% ± 3% at 3 years; HR, 2.21; 95% CI, 1.22 to 3.99; $P = .009$), whereas the presence of a germline *DDX41* mutation (74% ± 9% *v* 41% ± 3% at 3 years; HR, 0.39; 95% CI, 0.17 to 0.87; $P = .022$) and somatic mutations in *STAG2* (HR, 0.57; 95% CI, 0.34 to 0.96; $P = .034$) was associated with favorable OS (Data Supplement [Table S3]). OS at 3 years was similar in patients with *TP53*^{single} and *TP53*^{multihit} allelic states (22% ± 8% *v* 20% ± 6%; HR, 1.29; 95% CI, 0.79 to 2.11; $P = .31$; Fig 3A). The cumulative incidence of MDS relapse or progression to AML was significantly higher in patients with a *TP53* mutation compared with those without a *TP53* mutation (68% ± 5% *v* 42% ± 4% at 3 years; $P < .001$), and among patients with a *TP53* mutation, the incidence was significantly higher in those with *TP53*^{multihit} compared with *TP53*^{single} (74% ± 6% *v* 62% ± 8% at 3 years; $P = .03$; Fig 3B). Similarly, OS and cumulative incidence of MDS relapse or progression to AML were not different comparing *TP53* with or without complex karyotype or deletion 17/17p (Data Supplement [Fig S3]).

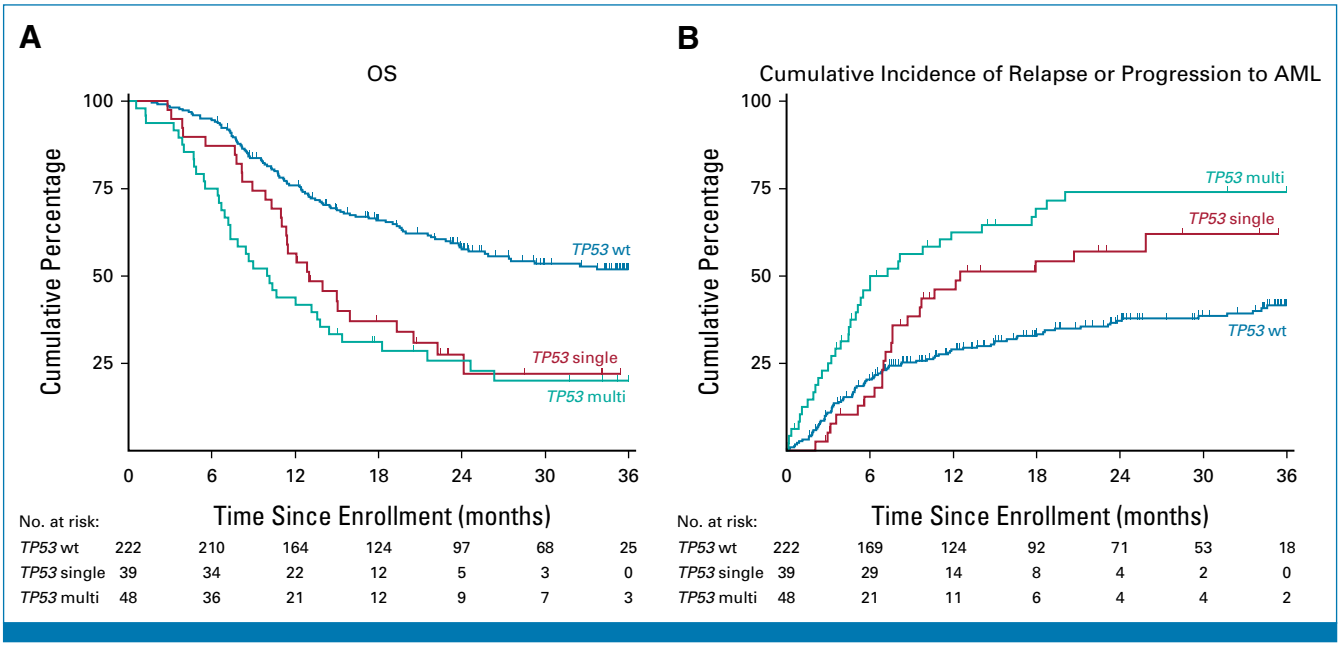

FIG 3. Clinical outcomes by *TP53* allelic state. (A) OS by *TP53* allelic state. (B) Cumulative incidence of MDS relapse or progression to AML by *TP53* allelic state, with death considered as a competing event. Time is measured from consent. MDS, myelodysplastic syndrome; OS, overall survival.

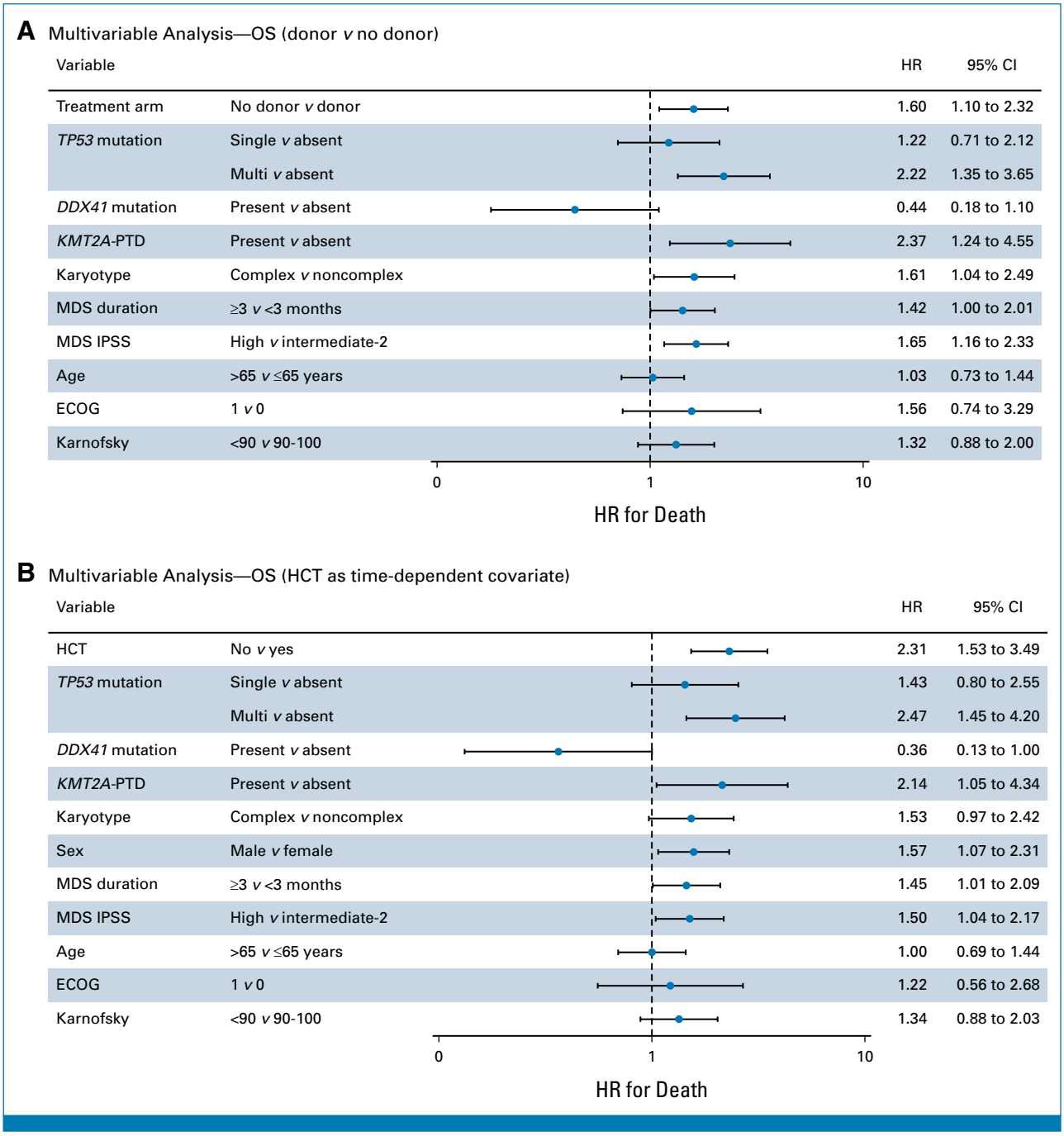

FIG 4. Forest plots of the multivariable analysis. Forest plot of subgroup analyses showing the HR for death and 95% CI in (A) the multivariable analysis of the donor versus no donor comparison and (B) the multivariable time-dependent analysis where HCT was considered as a time-dependent variable. Multivariable Cox regression analysis was used, with adjustment for treatment arm (A) or HCT (B), *TP53* allelic state, *DDX41* mutation, *KMT2A*^{PTD}, complex karyotype, duration of disease, IPSS score, sex, age, and performance score. ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; HR, hazard ratio; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; OS, overall survival.

Outcome Analysis Adjusted for Clinical and Genetic Variables

To identify the impact of (1) donor availability and (2) the actual application of HCT in this high-risk MDS cohort, we constructed two multivariable models adjusted for pre-specified clinical variables including age at enrollment, performance status, IPSS risk status, MDS disease duration, and clinical and genetic variables identified with stepwise selection. The first model is based on the random assignment on the basis of donor availability, whereas the second model addresses the HCT versus no HCT comparison, where HCT was treated as a time-dependent covariate.

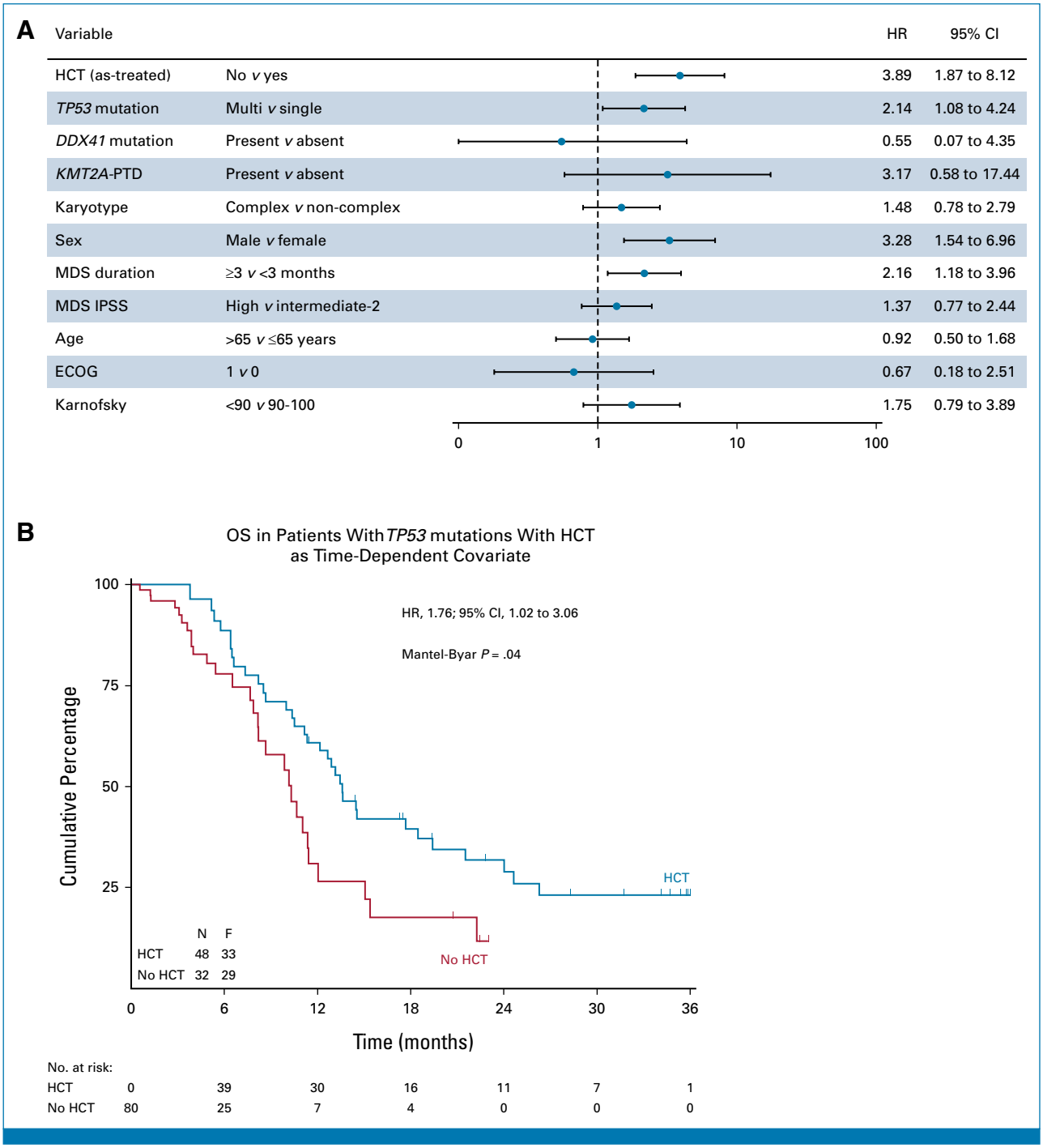

FIG 5. Forest plot of the multivariable analysis in patients with mutated *TP53*. (A) Forest plot of subgroup analyses in patients with mutated *TP53* showing the HR for death and 95% CI in the multivariable time-dependent analysis where HCT was considered as a time-dependent variable. Multivariable Cox regression analysis was used, with adjustment for HCT, *TP53* allelic state, *DDX41* mutation, *KMT2A*^{PTD}, complex karyotype, duration of disease, IPSS score, sex, age, and performance score. (B) OS in patients with *TP53* mutations in which HCT is considered as a time-dependent covariate according to a Simon-Makuch plot. Time is measured from consent and patients switch from the no HCT to the HCT at the time of HCT if they received HCT. (C) Serial analysis of enrollment and pre-HCT *TP53* samples (n = 35). Patients with pre-HCT *TP53* VAF ≥5% (left) and pre-HCT *TP53* VAF <5% (right) are shown. (D) OS in patients with *TP53* mutations by pre-HCT *TP53* VAF cutoff of 5%. Time is measured from transplantation. ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; HR, hazard ratio; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; OS, overall survival; VAF, variant allele fraction. (continued on following page)

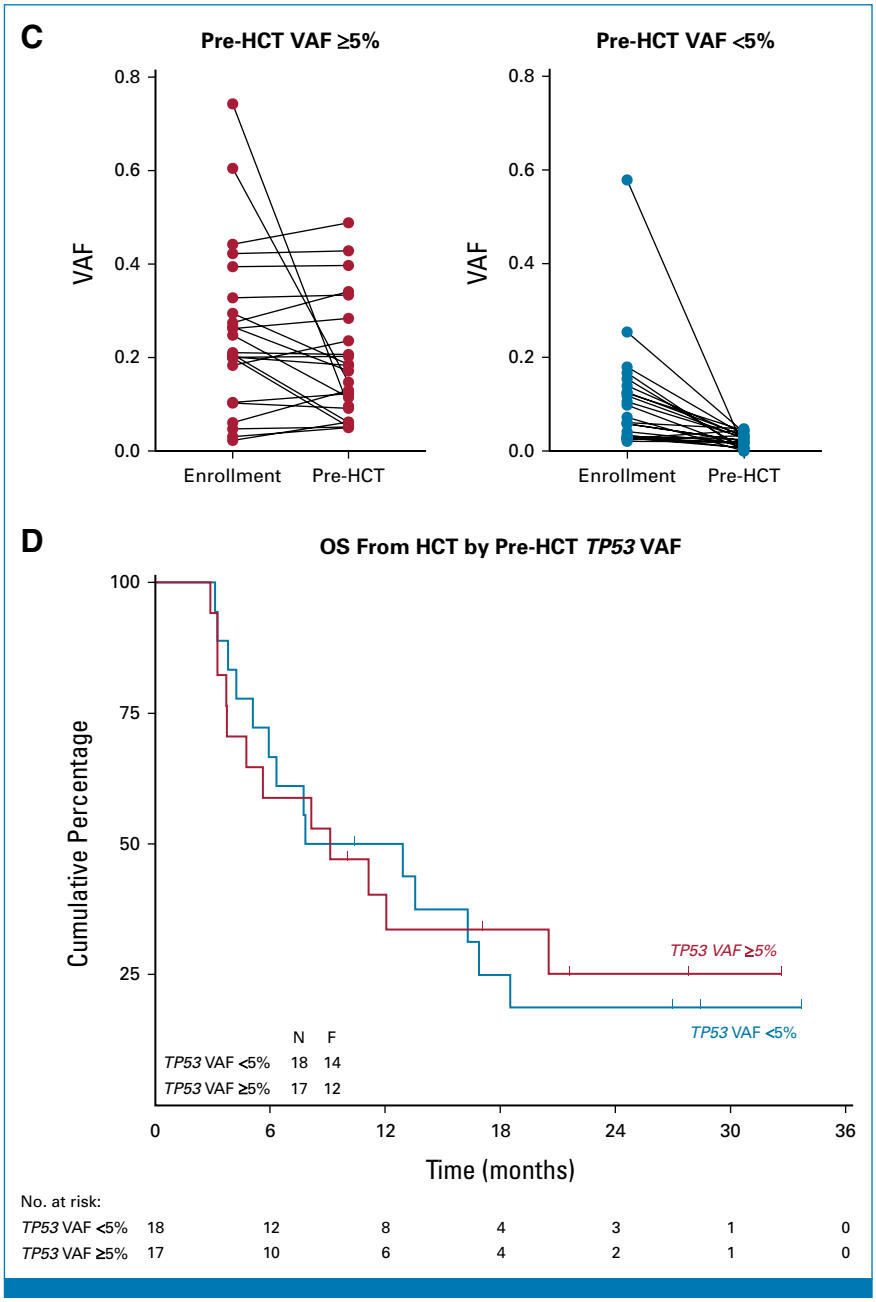

FIG 5. (Continued).

In the donor versus no donor analysis, *TP53*, *KMT2A*^{PTD}, and *DDX41* mutations were associated with OS after adjustment for covariates (Fig 4A). Patients who were assigned to the donor arm had improved OS compared with patients in the no donor arm (HR, 1.60; 95% CI, 1.10 to 2.32; P = .013; Fig 4A). *TP53* allelic state was associated with worse outcome, particularly patients with *TP53*^{multihit} compared with those without *TP53* mutations (HR, 2.22; 95% CI, 1.35 to 3.65; P = .002; Fig 4A). Applying that multivariable model to patients with a *TP53* mutation, we found that patients in the donor arm had a nonsignificant improved OS compared with those in the no donor arm (HR, 1.76; 95% CI, 0.95 to 3.26; P = .073; Data Supplement [Fig S4]). No interactions were found between treatment arms and mutations in both multivariable models.

In the time-dependent analysis of HCT, we included 197 patients who actually received HCT after RIC and 78 patients who did not receive HCT (Data Supplement [Fig S5]). Using a multivariable model in which HCT was considered as time-dependent covariate, adjusted for age, sex, performance status, IPSS, MDS duration, and complex karyotype, *TP53* and *KMT2A*^{PTD} were associated with differential survival (Fig 4B). HCT was associated with a 2-fold lower instantaneous risk of death compared with patients not receiving HCT after adjustment for covariates (HR, 2.31; 95% CI, 1.53 to

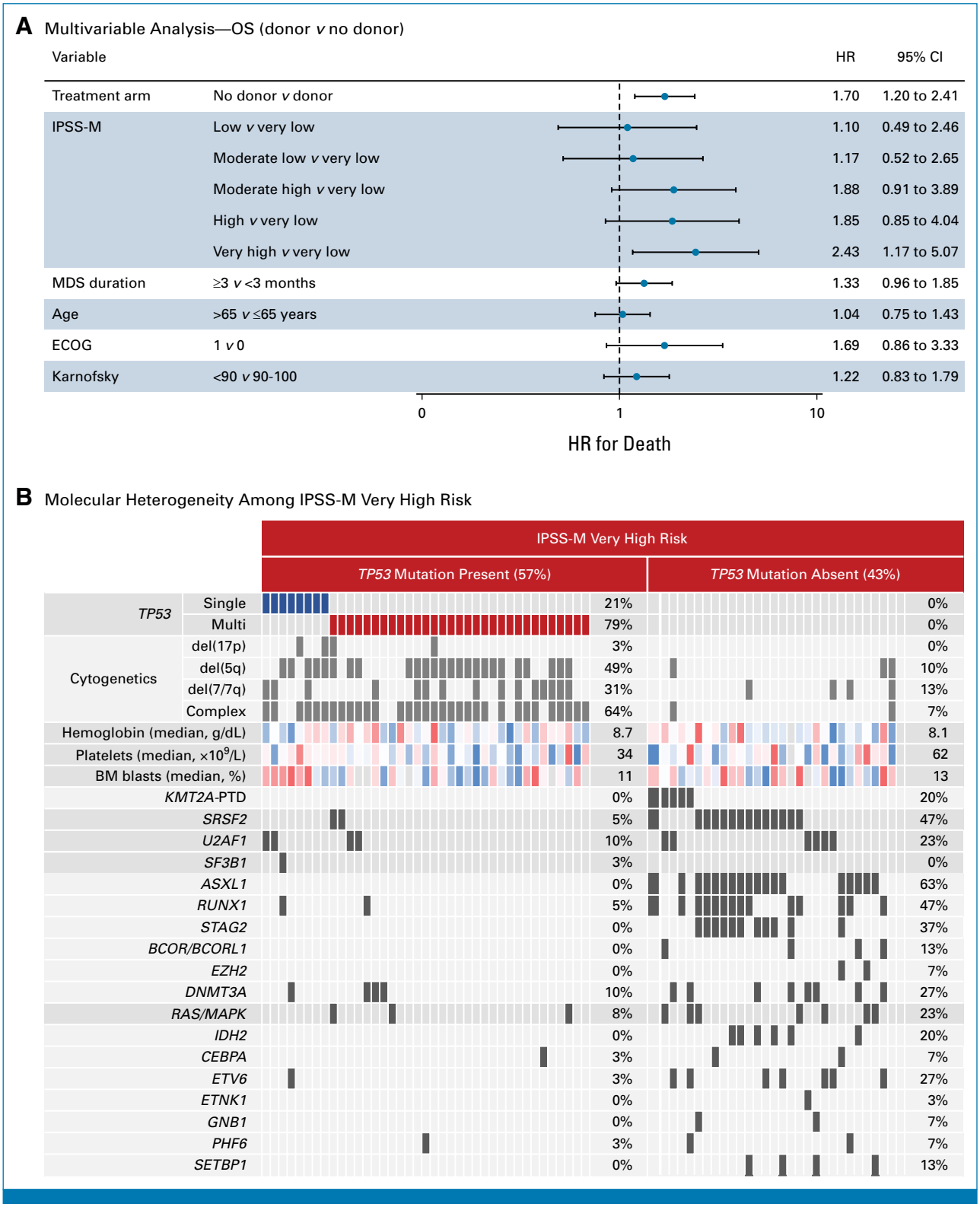

FIG 6. Outcome based on IPSS-M risk classification. (A) Forest plot of subgroup analyses showing the hazard ratio for death and 95% CI in the intention-to-treat analysis of donor versus no donor. Multivariable Cox regression analysis was used, with adjustment for treatment arm, IPSS-M score, duration of disease, age, and performance score. (B) A comutation plot shows mutations in individual genes in patients with IPSS-M very high risk per *TP53* mutation status as labeled on the top. Mutations, cytogenetic abnormalities, hemoglobin, platelet count, and bone marrow blasts are depicted by colored bars and each column represents one of the 69 patients. For hemoglobin, platelet count, and bone marrow blast, the color scheme ranges from red (high-risk value) to blue (low-risk value). (C) OS (left) and cumulative incidence of MDS relapse or progression to AML (right) by donor versus no donor comparison in patients with IPSS-M very high risk (continued on following page)

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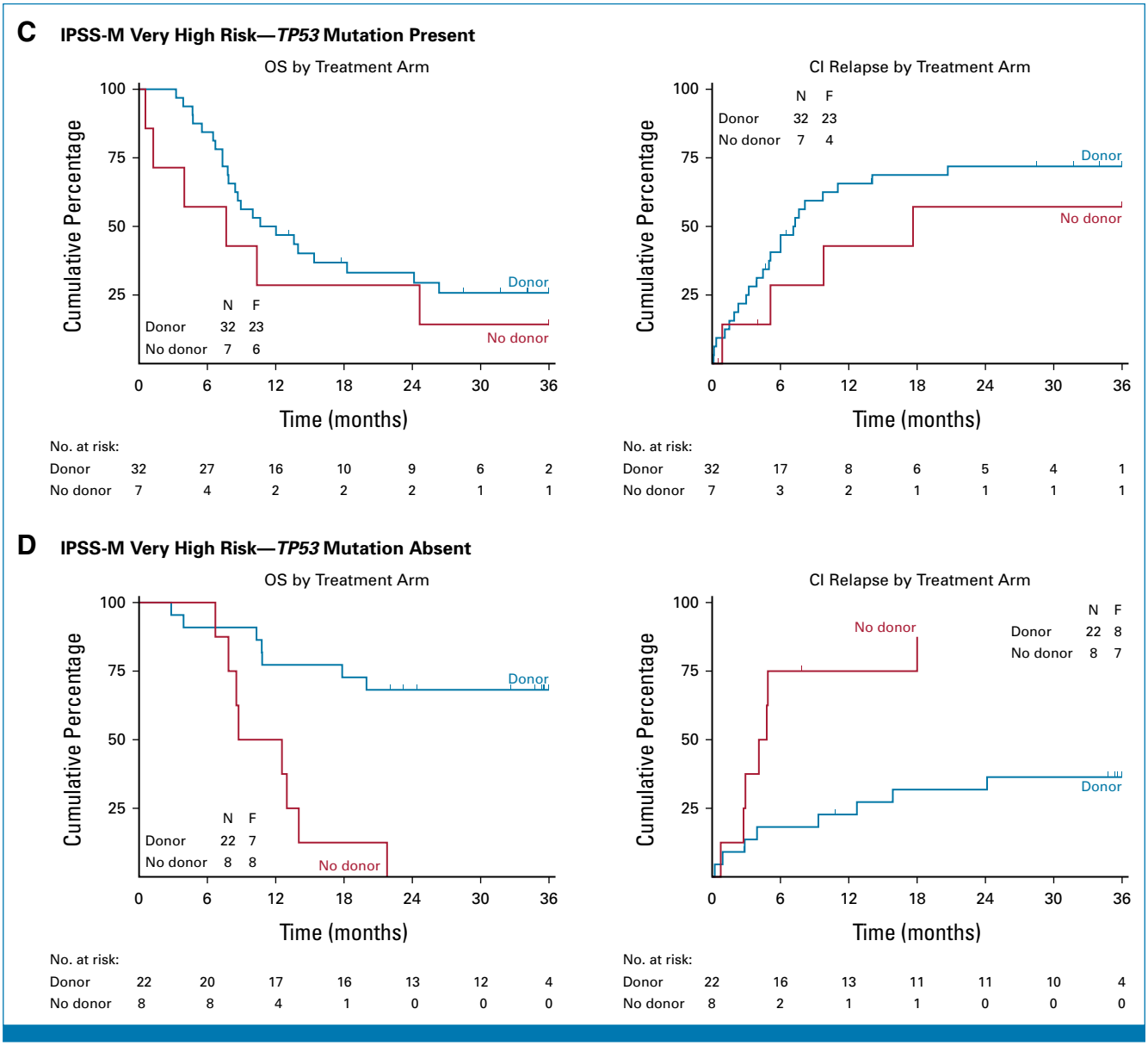

FIG 6. (Continued). with a *TP53* mutation. (D) OS (left) and cumulative incidence of MDS relapse or progression to AML (right) by donor versus no donor comparison in patients with IPSS-M very high risk without a *TP53* mutation. Time is measured from consent. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPSS-M, molecular International Prognostic Scoring System; MDS, myelodysplastic syndrome; OS, overall survival.

3.49; $P < .001$). To assess the impact of HCT in the subset of patients with the highest risk of death, we specifically applied this multivariable time-dependent model to patients with a *TP53* mutation (Fig 5A). We found that patients with a *TP53* mutation who were not transplanted had reduced OS compared with patients who received HCT (HR, 3.89; 95% CI, 1.87 to 8.12; $P < .001$; Fig 5A), indicating that HCT might improve long-term survival in patients with mutated *TP53*, independent of other risk factors. No interactions were found between HCT and mutations in both multivariable models. OS in patients with *TP53* mutations who actually received RIC HCT estimated 23% ± 7% at 3 years which was significantly improved compared with no HCT in a time-dependent survival analysis (Fig 5B). These observations were also consistently found at multiple landmark time points, although only significant at the 9-month landmark (Data Supplement [Fig S6]).

Molecular Clearance of *TP53* Mutation Before HCT Does Not Predict Long-Term Survival

It has been proposed that long-term survival after HCT of patients with *TP53*-mutated MDS is limited to those whose mutation burden can be reduced below a VAF of 5%.[19]

Therefore, we obtained samples from all patients who received HCT and had an available sample in the CIBMTR Research Sample Repository (n = 35 of n = 55 total) and then performed targeted, error-corrected sequencing of the *TP53* coding sequence. We determined whether *TP53* variants present at the time of enrollment were persistent in the preconditioning blood sample, quantified the allele abundance, and analyzed the association between quantitative molecular responses and clinical outcome. Using a high-sensitivity analysis, we found that 33 of 35 patients (94%) had persistent *TP53* mutations (median VAF, 0.045; range, 0.0049-0.489; Fig 5C). Using a 5% VAF cutoff per previous published analyses, 17 of 35 (48.6%) had persistent mutations. To test the hypothesis that pre-HCT molecular clearance explained the observed long-term survival among patients with *TP53*-mutated MDS, we analyzed the association between pre-HCT molecular positivity (at either 2% or 5% VAF cutoffs) with OS after transplantation. OS at 3 years was similar for patients with a pre-HCT *TP53* VAF cutoff of ≥5% versus <5% (22% ± 12% *v* 18% ± 10%; *P* = .95; Fig 5D) and also not different for a cutoff of ≥2% versus <2% (24% ± 9% *v* 11% ± 11%; *P* = .26; Data Supplement [Fig S7]).

Outcome on the Basis of Molecular IPSS Risk Classification

The molecular IPSS (IPSS-M) is a six-tiered MDS risk classification that was developed by combining hematologic parameters, cytogenetic risk, and somatic mutations in 31 genes.[13] Since the relative weights of selected variables in the IPSS-M were determined in an unselected cohort that spanned IPSS low- and high-risk disease and in which <10% received allogeneic transplantation, we sought to determine whether IPSS-M risk model was predictive of transplantation outcomes. In the donor versus no donor analysis, only the IPSS-M very high-risk subgroup was associated with inferior survival compared with very low-risk patients after adjustment for clinical- and transplant-related covariates (HR, 2.43; 95% CI, 1.17 to 5.07; *P* = .018; Fig 6A). Patients in the IPSS-M very high-risk subgroup had a heterogeneous molecular profile, with 57% having a *TP53* mutation (of which 79% were $TP53^{multihit}$), and the remaining 43% with *TP53* wild-type disease most commonly had *ASXL1*, *RUNX1*, and *SRSF2* mutations (Fig 6B). Although patients with IPSS-M very high risk with a *TP53* mutation had poor outcome irrespective of donor availability (26% ± 8% *v* 14% ± 13% at 3 years; *P* = .28; Fig 6C), IPSS-M very high risk without a *TP53* mutation had significantly improved survival in those with a donor compared with those in the no donor arm (68% ± 10% *v* 0% ± 12% at 3 years; *P* = .001; Fig 6D). No interactions were found between treatment arms and IPSS-M risk groups.

Outcomes in Patients With Germline *DDX41* Mutations

Inferred germline *DDX41* mutations were present in 7% (n = 23) of patients with MDS in this study. Patients with mutated *DDX41* had higher hemoglobin levels at enrollment (11.6 *v* 9.1 g/dL; *P* < .001) and higher bone marrow blast count (12% *v* 8%; *P* = .040) compared with patients without *DDX41* mutations (Data Supplement [Table S5]). Other clinical and transplantation characteristics were not significantly different among patients with a germline *DDX41* mutation versus those without.

The presence of a germline *DDX41* mutation was associated with favorable outcomes, consistent with previous studies.[13,20] Twenty of 23 patients proceeded to HCT (Table 1). Only one patient, who also had somatic biallelic *TP53* mutations, experienced MDS relapse after HCT. Non-relapse mortality (NRM) was observed in five patients, including one patient who received myeloablative conditioning, three of seven who received melphalan, and one patient who received fludarabine, cyclosphamide, and total body irradiation who had HCT-CI score ≥3. There was no NRM among *DDX41* patients receiving fludarabine with 2 days of busulfan or fludarabine and total body irradiation.

DISCUSSION

Allogeneic HCT confers superior survival in transplant eligible patients with high-risk MDS and an available donor.[1,2,21] Analyses of retrospective, registry-level transplant cohorts have suggested that the benefit of transplantation may not extend across MDS molecular subtypes,[3-5,13,22] but these studies all lacked direct comparison with non-HCT treatment. To determine directly whether HCT improves MDS outcomes independent of gene mutations, we performed genetic analysis of the prospective BMT CTN 1102 biologic assignment trial. Even after adjustment for genetic variables, survival after allogeneic HCT remained superior compared with non-HCT treatment with no interaction between genetic subtype and treatment effect.

Previous retrospective studies have found that the presence of a *TP53* mutation is the most powerful predictor of poor survival of patients with MDS after transplantation, with long-term survival varying from 0% to 25% across studies.[3-5,7,23] The absence of a non-HCT control group in such retrospective analyses has thus called into question whether the long-term survival observed in these studies was reasonably attributable to the transplantation intervention. In this study, we directly addressed this question and now conclude definitively that reduced intensity transplantation mediates long-term survival for patients with *TP53*-mutated MDS compared with non-HCT treatment. Moreover, we show that the benefit of HCT over non-HCT treatment was independent of *TP53* allelic state and not restricted to specific subgroups of *TP53* mutated MDS, including VAF, complex karyotype, or mutation clearance after pre-HCT hypomethylating agent treatment.

Together, these data indicate that no patient with *TP53*-mutated MDS should be excluded from consideration for HCT a priori on the basis of *TP53* status alone. Despite the

TABLE 1. Characteristics of Patients With *DDX41* Mutations

Age (years)	*TP53* Mutation Type	HCT	Conditioning	Donor	HCT-CI	OS From Enrollment (months)	Survival Status	Cause of Death
72	Multi	Yes	RIC: Flu + Mel	Unrelated	1	5.2	Death	NRM: organ failure
69		Yes	RIC: Flu + Mel	Unrelated	1	7.7	Death	NRM: infection
56		Yes	MAC: Flu + Bu	Missing	Missing	8.1	Death	NRM: organ failure
69		Yes	RIC: Flu + Cy + TBI	Missing	Missing	10.3	Death	Relapse
68		Yes	RIC: Flu + Cy + TBI	Unrelated	≥3	13.8	Death	NRM: ARDS
71		Yes	RIC: Flu + Mel	Unrelated	≥3	15.0	Death	NRM: pneumonia
64		Yes	RIC: Flu + Mel	Related	2	17.1	Alive	
65		Yes	RIC: Flu + Bu	Unrelated	≥3	17.8	Alive	
66		Yes	RIC: Flu + Mel	Related	≥3	24.2	Alive	
64		Yes	RIC: Flu + Bu	Missing	Missing	26.4	Alive	
66		Yes	RIC: Flu + Cy + TBI	Missing	Missing	29.7	Alive	
67		Yes	RIC: Flu + Bu	Unrelated	≥3	34.3	Alive	
68		Yes	RIC: Flu + Mel	Unrelated	≥3	34.8	Alive	
67		Yes	MAC: Flu + Bu	Unrelated	≥3	35.2	Alive	
69		Yes	RIC: Flu + Bu	Unrelated	0	35.6	Alive	
69		Yes	RIC: Flu + Mel	Unrelated	≥3	35.7	Alive	
73		Yes	RIC: Flu + Bu	Unrelated	2	37.9	Alive	
69		Yes	RIC: Flu + Mel	Related	0	38.0	Alive	
62		Yes	RIC: Flu + TBI	Unrelated	2	38.0	Alive	
73		Yes	RIC: Flu + TBI	Unrelated	≥3	38.1	Alive	
68		No				17.9	Alive	
67	Single	No				22.5	Alive	
67		No				24.2	Alive	

Abbreviations: ARDS, acute respiratory distress syndrome; Bu, busulfan; Cy, cyclophosphamide; HCT, hematopoietic cell transplantation; HCT-CI, hematopoietic cell transplantation comorbidity index; MAC, myeloablative conditioning; Mel, melphalan; NRM, nonrelapse mortality; OS, overall survival; RIC, reduced intensity conditioning; TBI, total body irradiation.

relative benefit of HCT over non-HCT treatment, however, the absolute survival benefit remains modest, meriting value-based discussions between physicians and patients on the appropriateness of transplantation. Recent data have indicated that *TP53*-mutated disease consists of an immune-privileged, evasive phenotype in the bone marrow microenvironment, which might result in reduced sensitivity to alloreactive T cells.[24] Strategies to exploit alloreactivity and restore the microenvironment might improve outcomes after HCT. Several other approaches could be considered to improve long-term outcomes, including early allogeneic HCT in patients with *TP53*-mutated MDS[25] or pre-, peri-, and post-HCT interventions aimed at mitigating the risk of relapse. Pretransplant treatment with hypomethylating agents has been associated with clinical responses in patients with mutated *TP53*, which has also been shown feasible to bridge time to HCT during a donor search period.[19,26,27] Combination of hypomethylating treatment with novel agents, for example eprenetapopt or magrolimab, yielded promising results with high rates of complete remission, mutational clearance, and prolonged survival in patients with *TP53*-mutated myeloid disease.[28-31] Data on efficacy and especially tolerability of these combinations for disease reduction before HCT are needed.

With the development of the IPSS-M, prognostic modeling in MDS now integrates clinical variables, cytogenetic risk, and molecular genetic profile to define six risk categories based on leukemia-free survival and OS outcomes.[13] However, in the IPSS-M cohort, fewer than 10% of patients received allogeneic HCT, raising the possibility that the relative weights of selected variables could differ in the context of transplantation. In the BMT CTN 1102 cohort, half of patients fell within the IPSS-M high-risk and very high-risk groups (28% and 22%, respectively), consistent with the clinical practice to prioritize higher-risk patients for transplantation. Although we found that patients in the IPSS-M very high-risk group had inferior transplant outcomes, we noted that this group was heterogeneous, including patients with biallelic *TP53* mutations and patients without *TP53* mutations who had a rather different clinical and genetic profile, including *ASXL1*, *RUNX1*, and splicing factor mutations in the context of relatively high blast counts. In the relatively small subgroup of IPSS-M very high-risk patients without *TP53* mutations who had no available donor, we observed poor outcomes, consistent with the non-HCT IPSS-M model. However, when a donor was available, outcomes of these IPSS-M very high-risk patients were favorable. These findings indicate that IPSS-M very high risk MDS without a *TP53* mutation may be very sensitive to allogeneic HCT and could be ideal candidates for early transplantation as a path to long-term survival.[32]

We found germline *DDX41* mutations in 7% of patients, and these were associated with favorable outcomes with a low risk of relapse, consistent with previous reports.[33,34] The only patient with germline *DDX41* mutation who experienced disease relapse had somatic biallelic *TP53* alterations. These data indicate that MDS with a *DDX41* mutation is highly curable with RIC-HCT, and treatment strategies should focus on minimizing toxicity to reduce the risk of NRM.

In conclusion, our data indicate that the benefit of HCT in patients with IPSS intermediate-2 and high-risk MDS extends to high-risk genetic subgroups. Moreover, patients with *TP53*-mutated MDS, irrespective of additional clinical or genetic variables, including allelic state, VAF, and pre-HCT mutation clearance, have superior survival with RIC allogeneic HCT compared with non-HCT treatment approaches, indicating that these patients should not be excluded for HCT on the basis of genetic findings alone, further reinforcing the conclusion that such patients should be offered transplantation when a donor is available. Patients with IPSS-M very high-risk MDS without a *TP53* mutation had favorable outcomes when a donor was available, suggesting that such patients see particular benefit from early transplantation.

AFFILIATIONS

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[2]Erasmus University Medical Center Cancer Institute, Rotterdam, the Netherlands
[3]Medical College of Wisconsin, Milwaukee, WI
[4]Laboratory of Myeloid Malignancies, Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD
[5]Moffitt Cancer Center, Tampa, FL
[6]University of Kansas Cancer Center, Kansas City, KS
[7]Oregon Health and Science University, Portland, OR
[8]Washington University in Saint Louis, Saint Louis, MO
[9]Myeloid Malignancies Program, National Institutes of Health, Bethesda, MD
[10]City of Hope National Medical Center, Duarte, CA

CORRESPONDING AUTHOR

R. Coleman Lindsley, MD, PhD, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215; Twitter: @ColemanLindsley; e-mail: coleman_lindsley@dfci.harvard.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Jurjen Versluis, Wael Saber, Brent Logan, Ryotaro Nakamura, Corey Cutler, R. Coleman Lindsley
Financial support: Ryotaro Nakamura, R. Coleman Lindsley
Administrative support: R. Coleman Lindsley
Provision of study materials or patients: Joseph McGuirk, Richard T. Maziarz, Peter Westervelt, Mary Horowitz, Corey Cutler
Collection and assembly of data: Jurjen Versluis, Wael Saber, Laura W. Dillon, Asmita Mishra, Pranay Hegde, Devdeep Mukherjee, Mary Horowitz, Ryotaro Nakamura, Corey Cutler, R. Coleman Lindsley
Data analysis and interpretation: Jurjen Versluis, Wael Saber, Harrison K. Tsai, Christopher J. Gibson, Laura W. Dillon, Asmita Mishra, Joseph McGuirk, Richard T. Maziarz, Peter Westervelt, Devdeep Mukherjee, Michael J. Martens, Brent Logan, Mary Horowitz, Christopher S. Hourigan, Ryotaro Nakamura, R. Coleman Lindsley
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Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Allogeneic Hematopoietic Cell Transplantation Improves Outcome in Myelodysplastic Syndrome Across High-Risk Genetic Subgroups: Genetic Analysis of the Blood and Marrow Transplant Clinical Trials Network 1102 Study

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Jurjen Versluis
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Joseph McGuirk
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Travel, Accommodations, Expenses: Kite, a Gilead company, Syncopation Life Sciences, SITC/ACCC

Richard T. Maziarz
Leadership: Artiva
Honoraria: Novartis
Consulting or Advisory Role: Novartis, Incyte, Kite/Gilead
Research Funding: Bristol Myers Squibb/Celgene/Juno, ORCA Therapeutics, Gamida Cell, Allovir, Novartis
Patents, Royalties, Other Intellectual Property: Athersys, Inc shared patent re: use of mesenchymal stromal cells for treatment of GVHD

Peter Westervelt
Travel, Accommodations, Expenses: Magenta Therapeutics

Mary Horowitz
Consulting or Advisory Role: Medac (Inst)
Research Funding: Jazz Pharmaceuticals (Inst), Novartis (Inst), Sanofi (Inst), Astellas Pharma (Inst), Xenikos (Inst), Gamida Cell (Inst)

Christopher S. Hourigan
Open Payments Link: https://openpaymentsdata.cms.gov/physician/1021742

Ryotaro Nakamura
Consulting or Advisory Role: Viracor Eurofins, Magenta Therapeutics, Kadmon, Napajen Pharma, Omeros, Bluebird Bio, Ono Pharmaceutical
Research Funding: Helocyte (Inst), Miyarisan pharmaceutical (Inst)
Travel, Accommodations, Expenses: Kyowa Hakko Kirin, Alexion Pharmaceuticals

Corey Cutler
Stock and Other Ownership Interests: Bluebird Bio, Verastem, Northwest Biotherapeutics, Actinium Pharmaceuticals, 2Seventy Bio, Alimera Sciences
Honoraria: Omeros, Janssen, Cimeio, Deciphera, Jazz Pharmaceuticals, Incyte, Sanofi, Bristol Myers Squibb, Mallinckrodt, CTI BioPharma Corp, Jasper Therapeutics, CSL Behring, InhibRx, Astellas Pharma, Rigel, Oxford Immune Algorithmics
Consulting or Advisory Role: Incyte, Jazz Pharmaceuticals, CareDX, Mallinckrodt/Therakos, Sanofi, CTI BioPharma Corp, Equillium, Bristol Myers Squibb, Cimeio, Editas Medicine
Uncompensated Relationships: Kadmon

R. Coleman Lindsley
Consulting or Advisory Role: Bluebird Bio, Takeda, Sarepta Therapeutics, Vertex, Verve Therapeutics, Qiagen, Jazz Pharmaceuticals
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