Clinical outcomes of venetoclax combined with hypomethylating agents *versus* hypomethylating agents alone in *TP53*-mutated myelodysplastic syndromes

TP53-mutated (*TP53*-mt) myelodysplastic syndromes (MDS) are aggressive myeloid neoplasms associated with inferior responses to conventional chemotherapy and a high risk of progression to acute myeloid leukemia (AML).[1-3] Although multiple targeted and immunotherapeutic strategies have been evaluated in clinical trials with limited success, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only intervention shown to modestly improve survival.[4-7]

Following the success of azacitidine (AZA) and venetoclax (VEN) in improving survival outcomes for adults with AML ineligible for intensive chemotherapy, the AZA+VEN combination has been investigated in patients with higher-risk MDS. In a phase Ib study, AZA+VEN demonstrated encouraging safety, along with preliminary efficacy (the combination resulted in complete remission [CR] in 30% and marrow CR in 50%).[8] However, the phase III VERONA trial, which randomized newly diagnosed patients with higher-risk MDS to AZA+VEN *versus* (*vs*.) AZA alone, did not meet its primary endpoint of improved overall survival (OS) (hazard ratio [HR]=0.908; *P*=0.3772), without significant new safety concerns.[9] An important distinction of this study is the exclusion of patients with therapy-related MDS, a subgroup in which approximately 30-50% harbor *TP53*-mt. Retrospective studies in *TP53*-mt AML suggest that the combination of AZA+VEN improves response rates compared with AZA alone, which may be particularly relevant for patients eligible for allo-HCT, but with no impact on OS (median OS 9.23 months for patients receiving a hypomethylating agent [HMA] *vs*. 7.3 months for those treated with HMA+VEN; *P*=0.8).[10] Real-world data on clinical outcomes in patients with *TP53*-mt MDS receiving a HMA (azacitidine or decitabine) plus VEN are limited.

To address this gap, we conducted a retrospective study comparing first-line HMA+VEN with HMA alone in patients with *TP53*-mt MDS treated at Mayo Clinic Comprehensive Cancer Center off clinical trials between June 2016 and April 2024 (starting from April 2018 for patients treated with HMA+VEN). Data were obtained from Mayo Clinic electronic medical records, after Institutional Review Board approval. Patients were diagnosed according to the fifth edition of the World Health Organization classification,[11] and responses were assessed using 2023 International Working Group MDS response criteria; measurable residual disease was not assessed in this cohort.[12] Multi-hit *TP53* was defined as per International Consensus Classification criteria.[13] To minimize selection bias, we performed propensity score matching analysis between the two groups (HMA

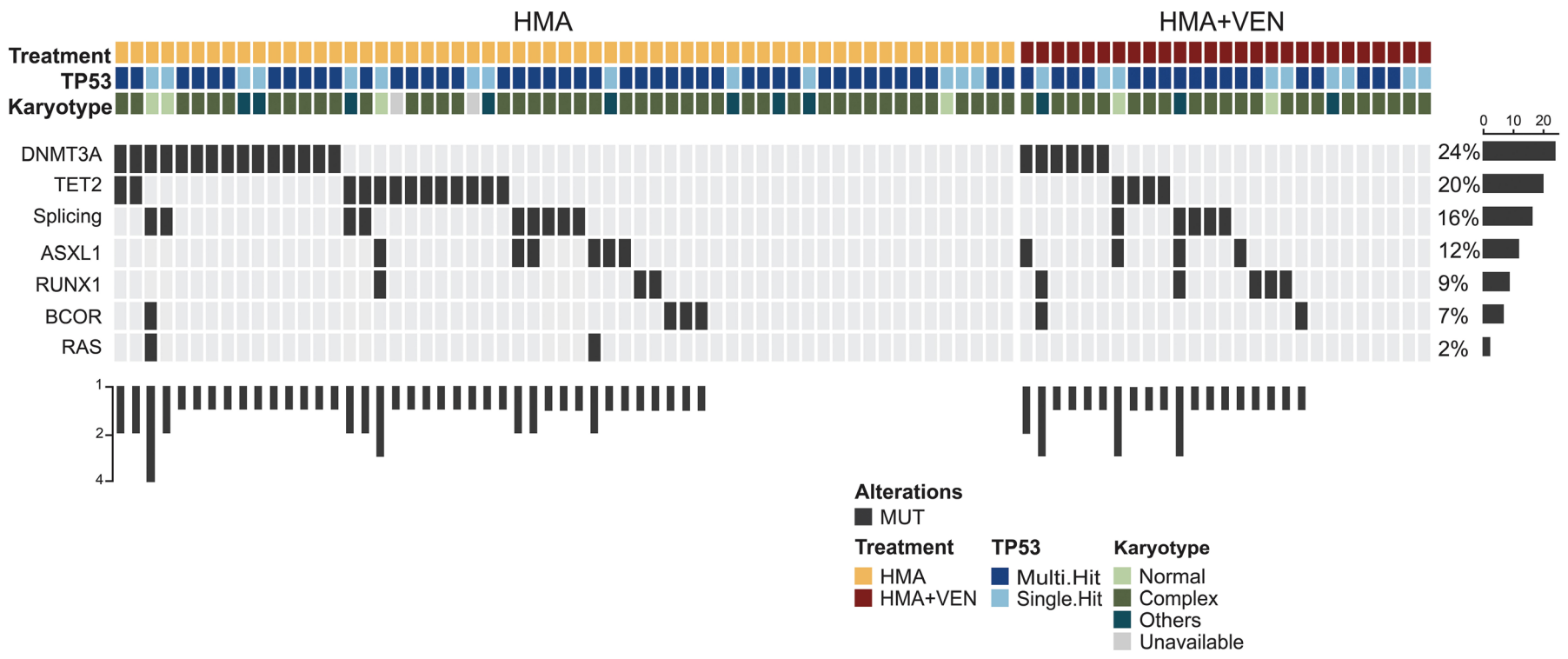

Figure 1. Baseline genomic and cytogenetic features by treatment cohort. Oncoprint of *TP53*-mutated myelodysplastic syndromes at diagnosis, stratified by initial therapy: hypomethylating agent (HMA) *versus* HMA plus venetoclax (HMA+VEN). Common co-mutations (*DNMT3A, TET2*, spliceosome genes, *ASXL1, RUNX1, BCOR, RAS*) are included. Bars at the right display mutation frequencies; the histogram below shows the number of co-mutations per patient.

vs. HMA+VEN) incorporating patient- and disease-related variables predictive of outcomes, including age at diagnosis, sex, therapy-related MDS, bone marrow blast percentage, complex cytogenetics, *TP53* variant allele frequency, *TP53* multi-hit status, and concurrent somatic mutations.

Among 140 patients (102 treated with HMA; 38 treated with HMA+VEN) included in the study, the median age was 70 years (range, 19–87) for the HMA group and 65 years (range, 37–80) for the HMA+VEN group. Patients in the HMA+VEN group presented with a higher median bone marrow blast percentage (9.5% [range, 0–19]) in comparison to those receiving HMA alone (5% [range, 0–16]; *P*=0.02), as well as a higher *TP53* variant allele frequency (42% [range, 6–96] *vs*. 36.5% [range, 2–94]; *P*=0.03). Frequency rates for multi-hit *TP53*-mt (76% *vs*. 77%), complex cytogenetics (86.5% *vs*. 81%), and common somatic co-mutations (including *ASXL1, TET2, DNMT3A, RAS, BCOR*, and splicing factor mutations) were comparable between the two groups (Figure 1). Likewise, the Molecular International Prognostic Scoring System risk categories did not differ significantly. The median number of treatment cycles was 3 (range, 1-8) in the HMA+VEN group and 3.5 (range, 1–42) in the HMA group (*P*=0.34). Among patients who subsequently underwent allo-HCT, the median number of cycles was 4 (range, 1–6) in the HMA+VEN group and 4 (range, 1–8) in the HMA group. Venetoclax was most commonly administered on a 14-day schedule in 51.6% of cases. However, a substantial proportion of patients received 28-day (22.6%), 21-day (16.1%), or 7-day (9.7%) schedules at the discretion of the treating physician (*Online Supplementary Table S1*)

The ORR, i.e., complete remission (CR), CR with limited count recovery, CR with uni- or bilineage recovery, partial remission, and hematologic improvement was significantly higher with HMA+VEN (75%) than with HMA alone (40.2%; P<0.001). The composite CR rate was 63% in the HMA+VEN group compared with 37% among patients treated with HMA alone (*P*=0.004), although CR rates were statistically not different (36.4% *vs*. 25%; *P*=0.26). A larger proportion of patients proceeded to allo-HCT following HMA+VEN than after HMA alone (42% *vs*. 19%; *P*=0.008) (*Online Supplementary Tables S1* and *S2*). Rates of progression to AML (29% *vs*. 31%; *P*>0.99) and early post-transplant, non-relapsed mortality rates at day 60 (3% *vs*. 3%; *P*=0.96) and day 90 (3% *vs*. 4%; *P*=0.75) were comparable between groups.

The relapse-free survival (RFS) and OS from the time of therapy initiation were not significantly different between the groups: the median RFS was 9.9 months for the group treated with HMA+VEN and 8.87 months for the group given

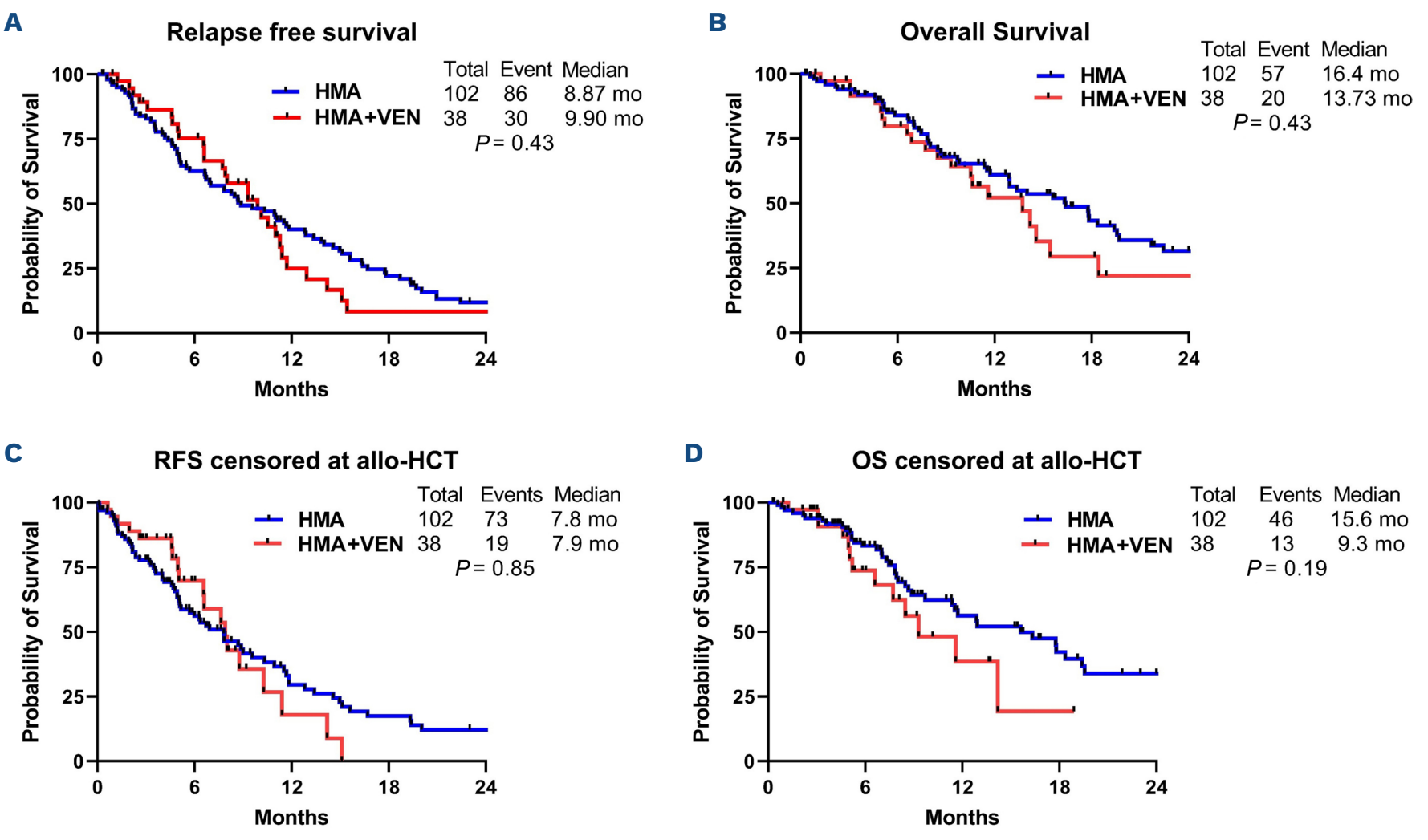

Figure 2. Unmatched cohort Kaplan-Meier curves. Kaplan-Meier survival estimates for patients divided according to whether they received a hypomethylating agent alone or with venetoclax. (A) Relapse-free survival estimates from therapy initiation. (B) Overall survival estimates from therapy initiation. (C) Relapse-free survival estimates with censoring at allogeneic hematopoietic cell transplantation. (D) Overall survival estimates with censoring at allogeneic hematopoietic cell transplantation. Tick marks indicate censored data. HMA: hypomethylating agent; HMA+VEN: hypomethylating agent plus venetoclax; mo: months; RFS: relapse-free survival; allo-HCT: allogeneic hematopoietic cell transplantation; OS: overall survival.

HMA alone (*P*=0.43), and the median OS was 13.73 months and 16.4 months, respectively (*P*=0.43). When censoring at allo-HCT, the median RFS was 7.9 months in the HMA+VEN group and 7.8 months for the patients treated with HMA alone (*P*=0.85) and the median OS was 9.3 months for the HMA+VEN group and 15.6 months for the group treated only with HMA (*P*=0.19). All differences remained statistically non-significant (Figure 2). We evaluated OS among patients with single-hit *versus* multi-hit *TP53*-mt treated with HMA alone or HMA+VEN. No significant differences were observed in median OS in either subgroup: single-hit *TP53* (18.37 *vs*. 13.70 months; *P*=0.26) or multi-hit *TP53* (16.30 *vs*. 15.43 months; *P*=0.85) receiving HMA and HMA+VEN respectively. Similarly, we examined the difference in OS in the subgroup with bone marrow blast percentage ≥10% and observed no significant differences in median OS between the groups treated with HMA alone or HMA+VEN (16.40 *vs*. 13.73 months; *P*=0.84). Contrary to prior belief, we did not observe statistically significant differences in median RFS (9.70 *vs*. 9.57 months; *P*=0.45) or median OS (14.20 *vs*. 14.57 months; *P*=0.67) between patients receiving decitabine- or azacitidine-based therapy, respectively.

In multivariable analyses for RFS censored at allo-HCT, the overall response rate was independently associated with longer RFS (HR=0.24; 95% confidence interval [95% CI]: 0.12–0.49; *P*<0.001), whereas CR (HR=0.58; 95% CI: 0.26–1.28; *P*=0.18) was not statistically significant. Complex cytogenetics (HR=2.40; 95% CI: 0.53–10.93; *P*=0.26) and multi-hit *TP53* (HR=0.88; 95% CI: 0.19–4.21; *P*=0.88) were also not significant (*Online Supplementary Figure S1A*). For OS censored at allo-HCT, overall response rate demonstrated a trend toward significance (HR=0.48; 95% CI: 0.22–1.07; *P*=0.07), whereas CR was not independently associated with survival (HR=0.54; 95% CI: 0.19–1.49; *P*=0.23). Complex cytogenetics (HR=3.30; 95% CI: 0.42–25.66; *P*=0.25) and multi-hit *TP53* (HR=0.51; 95% CI: 0.07–3.94; *P*=0.52) also did not show significant associations (*Online Supplementary Figure S1B*). To address baseline imbalances, a 1:1 propensity score–matched cohort (N=38 *vs*. N=38) with balanced characteristics was analyzed (*Online Supplementary Table S1*). In this matched analysis, the overall response rate was numerically higher in the group given HMA+VEN than in the group treated with HMA alone (60.5% *vs*. 47%; *P*=0.08), as was the composite CR rate (55% *vs*. 44.7%; *P*=0.35), with neither differences reaching statistical significance. Similarly, no significant difference was observed in the proportion of patients undergoing allo-HCT (42% *vs*. 34%; *P*=0.63). Survival outcomes also remained comparable between groups: the median RFS was 9.30 *vs*. 11.53 months (*P*=0.52), and median OS was 13.37 *vs*. 18.37 months (*P*=0.13) for the groups treated with HMA+VEN and HMA alone, respectively. (Figure 3).

In this real-world cohort of patients with *TP53*-mt MDS, treatment with HMA+VEN was associated with a higher overall response rate and enabled more patients to proceed to allo-HCT; however, given the limitations of retrospective data, this finding should be interpreted with caution and does not establish that treatment directly influenced transplant eligibility; moreover, these advantages did not translate into improved survival. In multivariable modeling after censoring at the time of allo-HCT, achieving CR was independently associated with longer OS, while the presence of complex cytogenetics was associated with inferior OS. The overall response rate was not an independent predictor of OS. For RFS, overall response rate was significantly associated with longer RFS, whereas CR did not retain statistical significance.

These observations are consistent with findings from the multi-institutional study conducted under the COMMAND consortium, in which no survival benefit was observed with HMA+VEN compared to HMA alone in patients with *TP53*-mt AML.[10] Similar outcomes have been reported in other analyses, suggesting that *TP53*-mt confers a chemo-resistant phenotype that does not derive meaningful benefit from venetoclax-based combinations, despite these regimens representing a paradigm shift in the management of AML.[14,15]

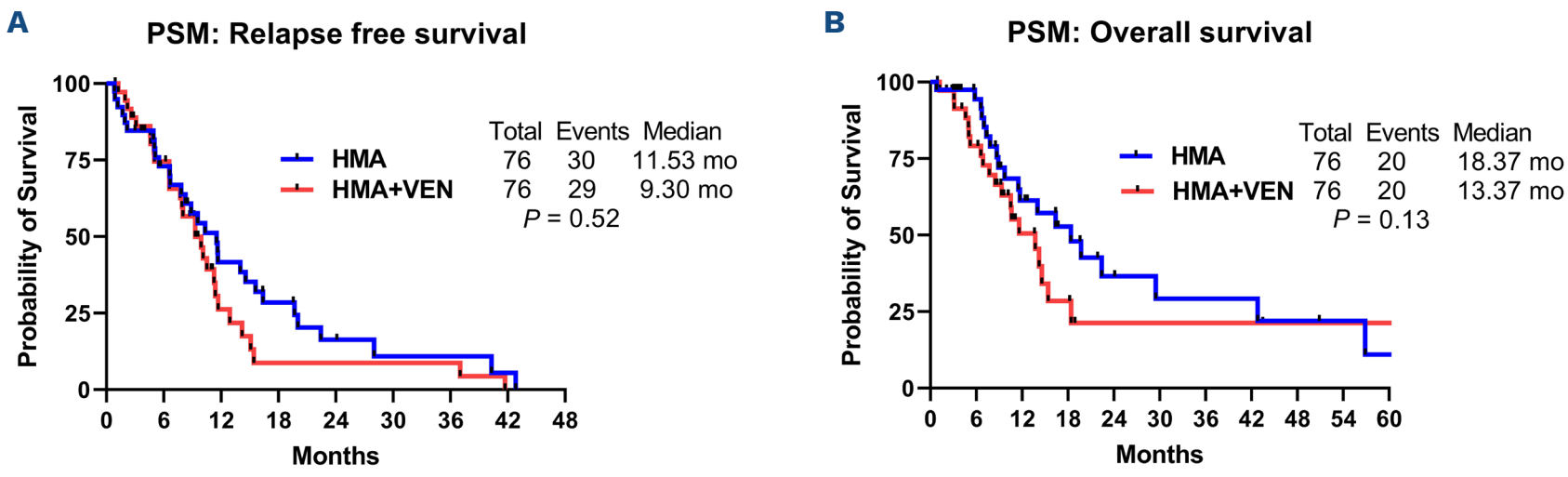

Figure 3. Kaplan–Meier curves for survival of the propensity score matched cohort. (A) Kaplan–Meier relapse-free survival estimates from therapy initiation. (B) Kaplan–Meier overall survival estimates from therapy initiation. Tick marks indicate censored data. PSM: propensity score matching: HMA: hypomethylating agent; HMA+VEN: hypomethylating agent plus venetoclax; mo: months.

Venetoclax-based chemotherapy may have a role in patients with MDS who progress on HMA-based therapy.[16,17]

Higher-risk MDS, particularly those with *TP53*-mt, continue to represent a major therapeutic challenge. Despite the introduction of HMA such as azacitidine and decitabine, outcomes in this subgroup remain poor, with limited response durability and short OS. Over the past two decades, numerous HMA-based combination strategies have been evaluated to improve outcomes. However, most have failed to demonstrate durable clinical benefit or survival advantage. More recently, several azacitidine-based combination therapies, including venetoclax, magrolimab (an anti-CD47 antibody), eprenetapopt (APR-246, a *TP53* reactivator), and sabatolimab (anti-TIM-3 antibody) showed encouraging response rates in early-phase trials.[3] However, these combination therapies failed to achieve regulatory endpoints in larger phase III clinical trials, especially in *TP53*-mt subgroups. Our institutional practice is to offer allo-HCT to all eligible patients once bone marrow blasts are cleared to optimize their long-term outcomes.

In conclusion, among patients with *TP53* mt MDS treated at our center, while HMA+VEN improved response rates and allowed for a greater proportion of patients to be bridged to allo-HCT, it did not improve either the RFS or OS, in comparison to HMA alone. These data underscore the highly refractory nature of *TP53*-mt myeloid neoplasms and the dire need for more effective therapies.

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Contributions

MA contributed to data collection and analysis, and drafting and revising the manuscript. Y-HW contributed to data analysis, and drafting and revising the manuscript. KJS, MEK, JF, MK-D, HM, AA-K, MVS, HA, ANS, WH, CAY, LS, JP, ML, AT, NP, NK and NG contributed to critical review and revision of the manuscript. MMP contributed to drafting and critically revising the manuscript. TB contributed to data collection and analysis, and drafting and revising the manuscript, and provided overall study supervision. All authors reviewed and approved the final version of the manuscript.

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Data-sharing statement

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