haematologica
Journal of the Ferrata Storti Foundation

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

by Mahmood Aldapt, Yu-Hung Wang, Kashish J. Shah, Mobachir El Kettani, James Foran, Mohamed Kharfan-Dabaja, Hemant Murthy, Aref Al-Kali, Mithun V. Shah, Hassan Alkhateeb, Antoine N. Saliba, William Hogan, Cecilia Arana Yi, Lisa Sproat, Nathan Punwani, Nandita Khera, Jeanne Palmer, Mark Litzow, Ayalew Tefferi, Naseema Gangat, Mrinal M. Patnaik and Talha Badar

Received: September 25, 2025.
Accepted: December 23, 2025.

Citation: Mahmood Aldapt, Yu-Hung Wang, Kashish J. Shah, Mobachir El Kettani, James Foran, Mohamed Kharfan-Dabaja, Hemant Murthy, Aref Al-Kali, Mithun V. Shah, Hassan Alkhateeb, Antoine N. Saliba, William Hogan, Cecilia Arana Yi, Lisa Sproat, Nathan Punwani, Nandita Khera, Jeanne Palmer, Mark Litzow, Ayalew Tefferi, Naseema Gangat, Mrinal M. Patnaik and Talha Badar.
Clinical outcomes of venetoclax combined with hypomethylating agents versus hypomethylating agents alone in TP53-mutated myelodysplastic syndromes.
Haematologica. 2026 Jan 8. doi: 10.3324/haematol.2025.289268 [Epub ahead of print]

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

Mahmood Aldapt[1], Yu-Hung Wang[2], Kashish J. Shah[1], Mobachir El Kettani[1], James Foran[1], Mohamed Kharfan-Dabaja[1], Hemant Murthy[1], Aref Al-Kali[3], Mithun V Shah[3], Hassan Alkhateeb[3], Antoine N. Saliba[3], William Hogan[3], Cecilia Arana Yi[4], Lisa Sproat[4], Nathan Punwani[4], Nandita Khera[4], Jeanne Palmer[4], Mark Litzow[3], Ayalew Tefferi[3], Naseema Gangat[3], *Mrinal M Patnaik[3], *Talha Badar[1]

[1] Division of Hematology and Medical Oncology, Mayo Clinic, Jacksonville, Florida.
[2] National Taiwan University Cancer Center, Taipei, Taiwan.
[3] Division of Hematology, Mayo Clinic, Rochester, Minnesota.
[4] Division of Hematology, Mayo Clinic, Phoenix, Arizona, USA.

Authors contributions: M.A. contributed to data collection, data analysis, manuscript drafting, and revision. Y.H.W. contributed to data analysis, manuscript drafting, and revision. K.J.S., M.E.K., J.F., M.K.D., H.M., A.A.K., M.V.S., H.A., A.N.S., W.H., C.A.Y., L.S., J.P., M.L., A.T., N.P., N.K., and N.G. contributed to critical review and revision of the manuscript. M.M.P. contributed to manuscript drafting and critical revision. T.B. contributed to data collection, data analysis, manuscript drafting and revision, and provided overall study supervision. All authors reviewed and approved the final version of the manuscript.

Acknowledgement: The authors thank Mrs. Batool Hamzeh for her professional support in figures preparation and graphic design.

***Corresponding Author: Talha Badar, MD**, Division of Hematology and Medical Oncology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224. Email: badar.talha@mayo.edu **Mrinal M Patnaik, MD,** Professor of Medicine, Division of Hematology, Mayo Clinic, Rochester, MN 55905, USA. Email: patnaik.mrinal@mayo.edu

Running title: Outcome of *TP53*-mt MDS with HMA+/- Ven

Key words: *TP53*-mutation, Higher-risk MDS, Venetoclax, HMA

Data Sharing Statement: For original data, please contact badar.talha@mayo.edu

Competing Interests statement: T.B. received research funding from Takeda and Amgen. Served advisory board for Takeda, Amgen, Syndax and Morphosys. NG served in advisory board for Agios and DISC medicine. MKD received research/grant from BMS, Novartis and Pharmacyclics; Lecture/honoraria from Kite Pharma. No COI to disclose for other authors.

To the Editor

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 (HR-MDS). In a phase 1b study, AZA+VEN demonstrated encouraging safety, along with preliminary efficacy (the combination resulted in complete remission [CR] in 30% and marrow complete remission [mCR] in 50%). (8) However, the phase III VERONA trial, which randomized newly diagnosed patients with HR-MDS to AZA+VEN versus (vs.) AZA alone, did not meet its primary endpoint of 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 (tMDS), 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 [mOS] 9.23 months for HMA vs. 7.3 months for HMA+VEN; p=0.8)(10). Real-world data on clinical outcomes in patients with *TP53*-mt MDS receiving hypomethylating agent (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 HMA+VEN

patients). Data was obtained from Mayo Clinic electronic medical records, after Institutional Review Board approval. Diagnosis was made according to the 5th edition of the World Health Organization (WHO) classification,(11) and responses were assessed per 2023 International Working Group (IWG) MDS response criteria, and measurable residual disease (MRD) assessment was not performed in this cohort.(12) Multi-hit (MH) *TP53* was defined as per International Consensus Classification (ICC) criteria.(13) To minimize selection bias, we performed propensity score matching (PSM) analysis between the two groups (HMA vs. HMA+VEN) incorporating patient- and disease-related variables predictive of outcomes, including age at diagnosis, sex, t-MDS, bone marrow blast percentage (BM blast %), complex cytogenetics (CG), *TP53* VAF, *TP53* MH status, and concurrent somatic mutations.

Among 140 patients (HMA 102; HMA+VEN 38) included in the study, the median age was 70 years (yrs) (19–87) for the HMA group and 65 yrs (37–80) for the HMA+VEN group. Patients in the HMA+VEN group presented with a higher median BM blast % (9.5% [0–19]) in comparison to those receiving HMA alone (5% [0–16]; p=0.02), as well as a higher *TP53* VAF (42% [6–96] vs. 36.5% [2–94]; p=0.03). Frequency rates for MH *TP53*-mt (76% vs. 77%), complex CG (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, IPSS-M risk categories did not differ significantly. The median number of treatment cycles was 3.0 (1–8) for the HMA+VEN group and 3.5 (1–42) for the HMA group (p=0.34). Among patients who subsequently underwent allo-HCT, the median number of cycles was 4 (1–6) in the HMA+VEN group and 4 (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. (Supplementary Table1)

The ORR: complete remission (CR), CR with limited count recovery (CRh), CR with uni- or bilineage (CR_L), and hematological improvement (HI) was significantly higher with HMA+VEN (75%) compared with HMA alone (40.2%; p=<0.001). Composite CR (cCR) was 63% for HMA+VEN compared with 37% for HMA alone (p=0.004), although CR rates were statistically non-different (36.4% vs. 25%; p=0.26). A higher proportion of patients proceeded to allo-HCT following HMA+VEN (42% vs. 19%; p=0.008) in comparison to HMA alone. (Supplementary tables 1 and 2) Rates of AML progression (29% vs. 31%; p>0.99) and early post allo-HCT, non-relapsed mortality 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: median RFS (mRFS) was 9.9 months for HMA+VEN vs. 8.87 months for HMA alone (p=0.43), and median OS (mOS) was 13.73 months vs. 16.4 months, respectively (p=0.43). When censoring at allo-HCT, mRFS was 7.9 months for HMA+VEN vs. 7.8 months for HMA alone (p=0.85) and mOS was 9.3 months for HMA+VEN vs. 15.6 months for HMA alone (p=0.19). All differences remained statistically non-significant (Figure2). We evaluated OS among patients with SH vs. MH *TP53*-mt treated with HMA alone vs. HMA+VEN. No significant differences were observed in mOS in either subgroup: SH *TP53* (18.37 vs. 13.70 months, p=0.26) or MH *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 BM blast ≥10% and observed no significant differences in mOS between HMA alone and HMA+VEN (16.40 vs. 13.73 months, p=0.84), respectively. Contrary to prior belief, we did not observe statistically significant differences in mRFS (9.70 vs 9.57 months, p=0.45) or mOS (14.20 vs. 14.57 months, p=0.67) between decitabine- and azacitidine-based therapy, respectively.

In multivariable analyses for RFS censored at allo-HCT, ORR was independently associated with longer RFS (HR 0.24; 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 CG (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. (Supplementary Figure 1A). For OS censored at allo-HCT, ORR 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 CG (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 (Supplementary Figure 1B).

To address baseline imbalances, a 1:1 propensity score–matched cohort (n=38 vs. 38) with balanced characteristics was analyzed (Supplementary Table 1). In this matched analysis, the ORR was numerically higher in the HMA+VEN group compared to the HMA alone group (60.5% vs. 47%; p=0.08), as was the cCR rate (55% vs. 44.7%; p=0.35), with neither 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: mRFS was 9.30 vs. 11.53 months (p=0.52), and mOS was 13.37 vs. 18.37 months (p=0.13) for the HMA+VEN and HMA alone groups, respectively. (Figure 3).

In this real-world cohort of patients with *TP53*-mt MDS, treatment with HMA+VEN was associated with higher ORR 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 CG was associated with inferior OS. The ORR was not an independent predictor of OS. For RFS, ORR 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, where 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 confer 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) Venetoclax-based chemotherapy may have a role in patients with MDS who progress on HMA based therapy.(16, 17)

HR-MDS, particularly those with *TP53*-mt, continue to represent a major therapeutic challenge. Despite the introduction of HMAs such as azacitidine and decitabine, outcomes in this subgroup remain poor, with limited response durability and short overall survival. 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) had shown encouraging response rates in early-phase trials.(3) However, these combination therapies failed to achieve regulatory end points 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.

References

1. Tefferi A, Fleti F, Chan O, et al. TP53 variant allele frequency and therapy-related setting independently predict survival in myelodysplastic syndromes with del(5q). Br J Haematol. 2024;204(4):1243-1248.
2. Shah MV, Hung K, Baranwal A, et al. Evidence-based risk stratification of myeloid neoplasms harboring TP53 mutations. Blood Adv. 2025;9(13):3370-3380.
3. Ramanathan R, Xie Y, Badar T, Zeidan AM, Patel SA. Contemporary management paradigms and emerging therapeutics for myelodysplastic syndromes/neoplasms. Br J Haematol. 2025;206(6):1571-1581.
4. Versluis J, Saber W, Tsai HK, et al. 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. J Clin Oncol. 2023;41(28):4497-4510.
5. Fernández HF, Mishra A. Transplant options and outcomes for TP53 myeloid disease. Hematology. 2024;2024(1):335-339.
6. Shah MV, Arber DA, Hiwase DK. TP53 -Mutated Myeloid Neoplasms: 2024 Update on Diagnosis, Risk-Stratification, and Management. Am J Hematol. 2025;100 Suppl 4(Suppl 4):88-115.
7. Nakamura R, Saber W, Martens MJ, et al. Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome. J Clin Oncol. 2021;39(30):3328-3339.
8. Garcia JS, Platzbecker U, Odenike O, et al. Efficacy and safety of venetoclax plus azacitidine for patients with treatment-naive high-risk myelodysplastic syndromes. Blood. 2025;145(11):1126-1135.
9. AbbVie. AbbVie Provides Update on VERONA Trial for Newly Diagnosed Higher-Risk Myelodysplastic Syndromes [updated 6/16/2025. Available from: https://news.abbvie.com/2025-06-16-AbbVie-Provides-Update-on-VERONA-Trial-for-Newly-Diagnosed-Higher-Risk-Myelodysplastic-Syndromes. Accessed on 2025, June 16.
10. Badar T, Nanaa A, Atallah E, et al. Comparing venetoclax in combination with hypomethylating agents to hypomethylating agent-based therapies for treatment naive TP53-mutated acute myeloid leukemia: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND). Blood Cancer J. 2024;14(1):32.
11. Loghavi S, Kanagal-Shamanna R, Khoury JD, et al. Fifth Edition of the World Health Classification of Tumors of the Hematopoietic and Lymphoid Tissue: Myeloid Neoplasms. Mod Pathol. 2024;37(2):100397.
12. Zeidan AM, Platzbecker U, Bewersdorf JP, et al. Consensus proposal for revised International Working Group 2023 response criteria for higher-risk myelodysplastic syndromes. Blood. 2023;141(17):2047-2061.
13. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
14. Gangat N, Karrar O, Iftikhar M, et al. Venetoclax and hypomethylating agent combination therapy in newly diagnosed acute myeloid leukemia: Genotype signatures

for response and survival among 301 consecutive patients. Am J Hematol. 2024;99(2):193-202.
15. Döhner H, Pratz KW, DiNardo CD, et al. Genetic risk stratification and outcomes among treatment-naive patients with AML treated with venetoclax and azacitidine. Blood. 2024;144(21):2211-2222.
16. Zeidan AM, Borate U, Pollyea DA, et al. A phase 1b study of venetoclax and azacitidine combination in patients with relapsed or refractory myelodysplastic syndromes. Am J Hematol. 2023;98(2):272-281.
17. Ghorab A, Al-Kali A, Elliot M, et al. Clinical outcome of myelodysplastic syndrome progressing on hypomethylating agents with evolving frontline therapies: continued challenges and unmet needs. Blood Cancer J. 2022;12(6):93.

Figure legend

Figure 1. Baseline genomic and cytogenetic features by treatment cohort

Oncoprint of *TP53*-mutated MDS at diagnosis, stratified by initial therapy (HMA vs HMA+VEN). Common co-mutations (*DNMT3A, TET2*, spliceosome genes, *ASXL1, RUNX1, BCOR, RAS*) are included. Bars at right display mutation frequencies; the histogram below shows the number of co-mutations per patient.

Figure 2. Unmatched cohort Kaplan-Meier curves

Kaplan–Meier RFS estimates from therapy initiation (A), OS estimates from therapy initiation (B), RFS censored at allo-HCT estimates (C), and OS censored at allo-HCT estimates (C). Tick marks indicate censored data.

Figure 3. PSM cohort Kaplan–Meier curves

Kaplan–Meier RFS estimates from therapy initiation (A) and OS estimates from therapy initiation (B). Tick marks indicate censored data.

Figure 1

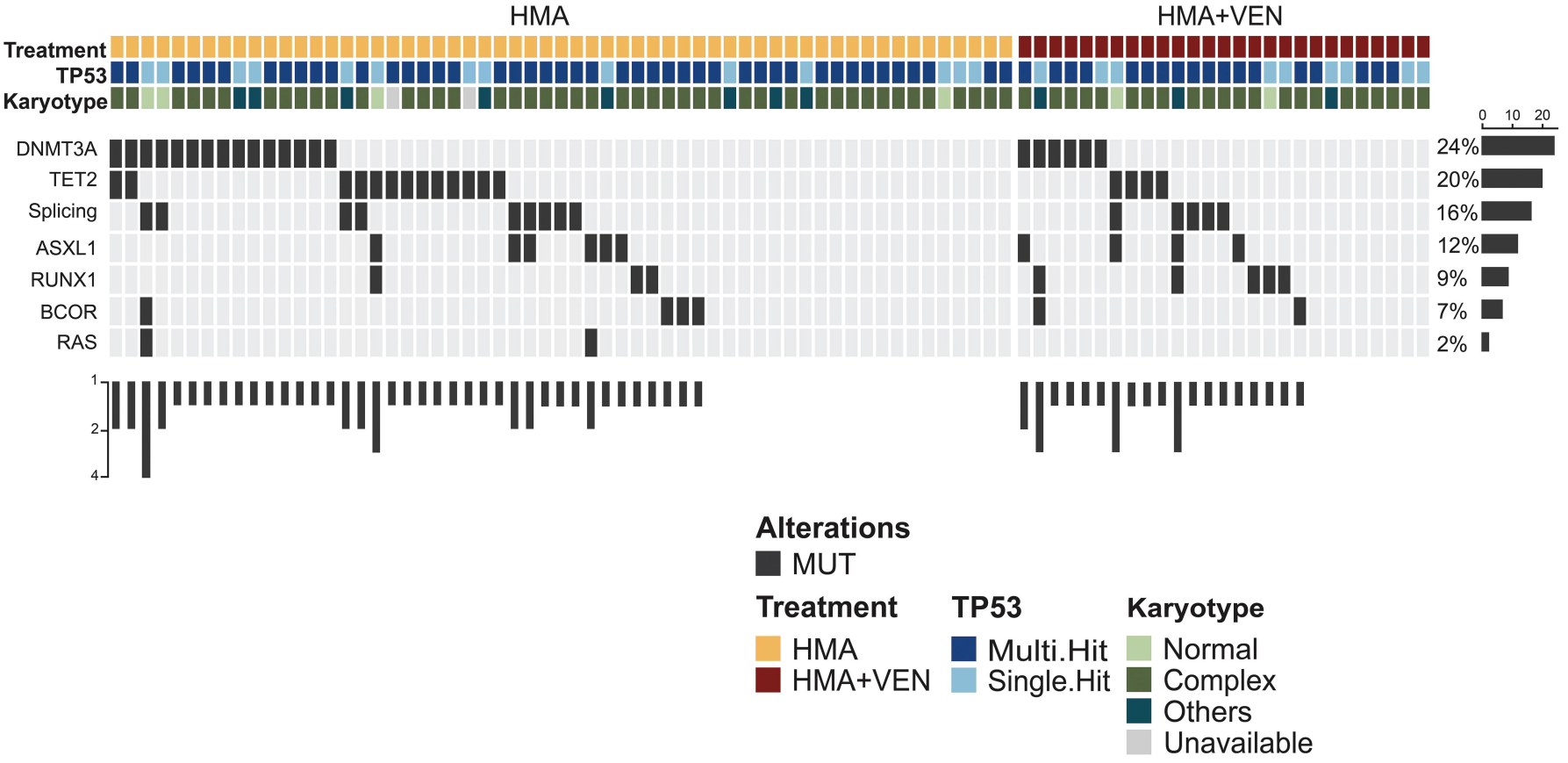
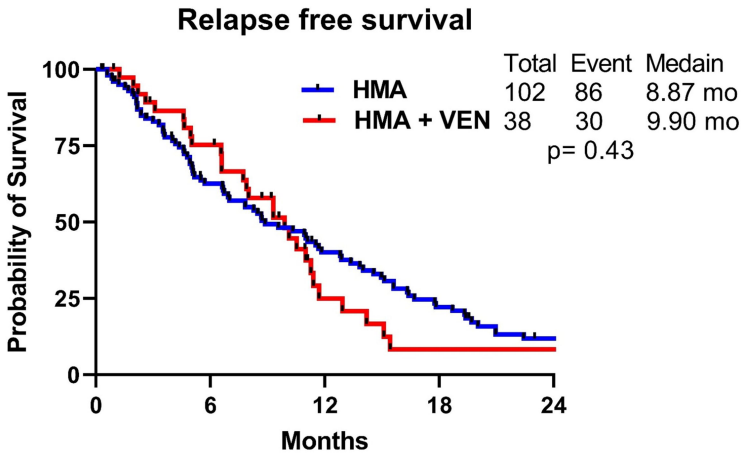
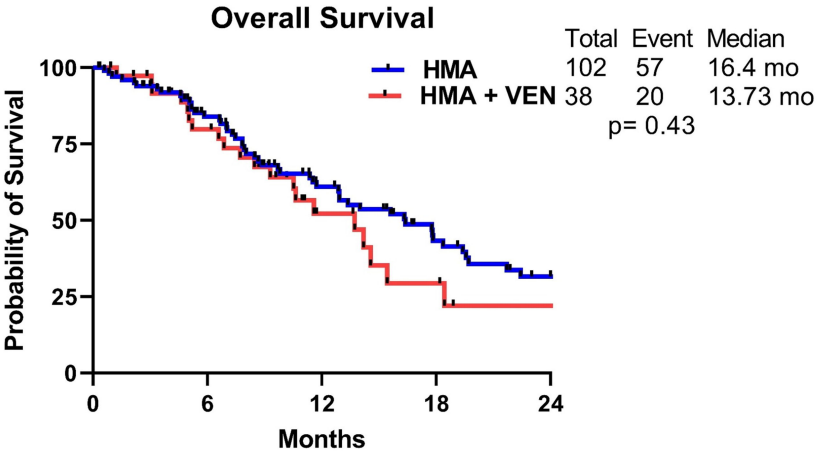
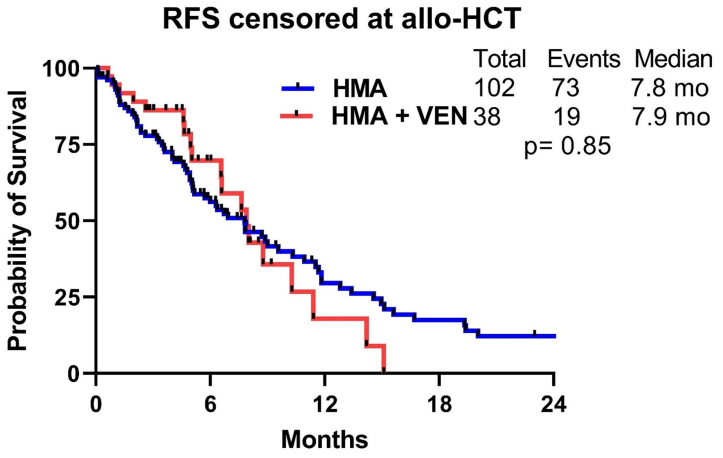
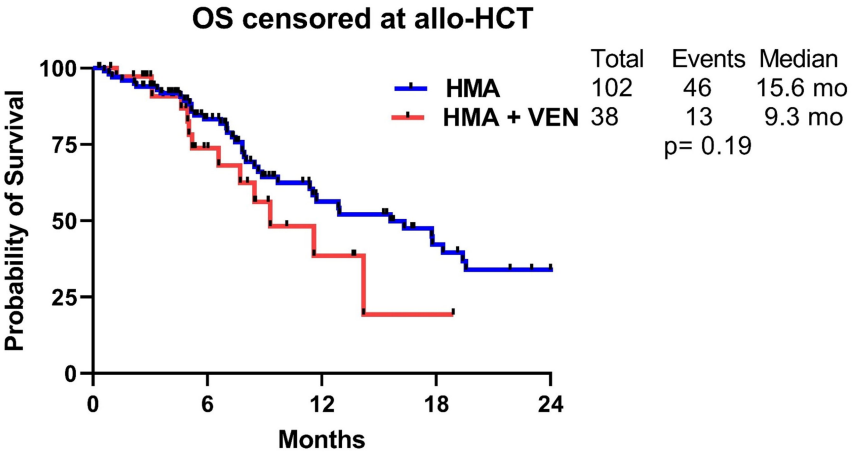

HMA
HMA+VEN
Treatment
TP53
Karyotype
0
10
20
DNMT3A
TET2
Splicing
ASXL1
RUNX1
BCOR
RAS
24%
20%
16%
12%
9%
7%
2%
1
2
4
Alterations
MUT
Treatment
HMA
HMA+VEN
TP53
Multi.Hit
Single.Hit
Karyotype
Normal
Complex
Others
Unavailable

Figure 2

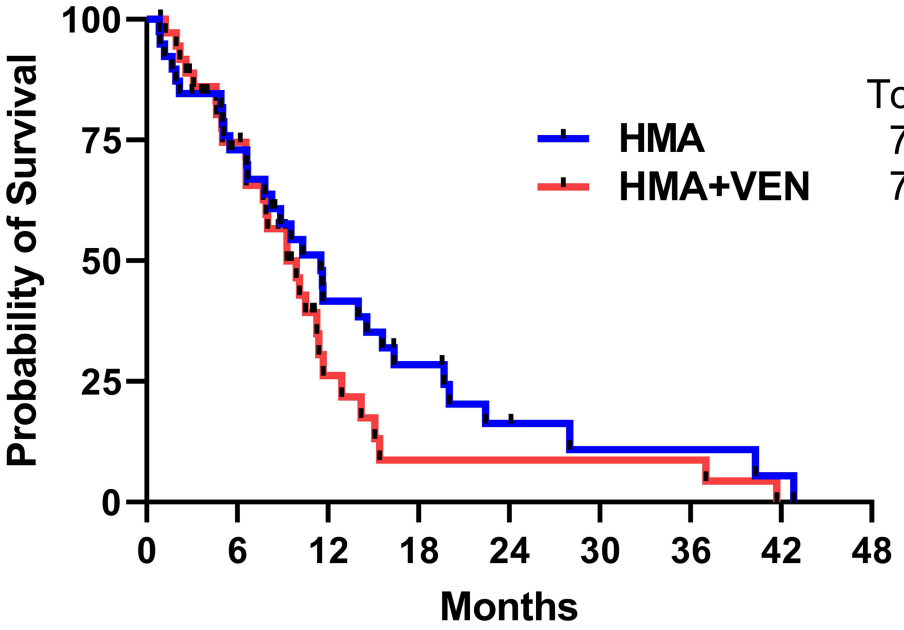

Relapse free survival
Total Event Medain
HMA 102 86 8.87 mo
HMA + VEN 38 30 9.90 mo
p= 0.43
Probability of Survival
100
75
50
25
0
0
6
12
18
24
Months


Overall Survival
Total Event Median
HMA 102 57 16.4 mo
HMA + VEN 38 20 13.73 mo
p= 0.43
Probability of Survival
100
75
50
25
0
0
6
12
18
24
Months


RFS censored at allo-HCT
Total Events Median
HMA 102 73 7.8 mo
HMA + VEN 38 19 7.9 mo
p= 0.85
Probability of Survival
100
75
50
25
0
0
6
12
18
24
Months


OS censored at allo-HCT
Total Events Median
HMA 102 46 15.6 mo
HMA + VEN 38 13 9.3 mo
p= 0.19
Probability of Survival
100
75
50
25
0
0
6
12
18
24
Months

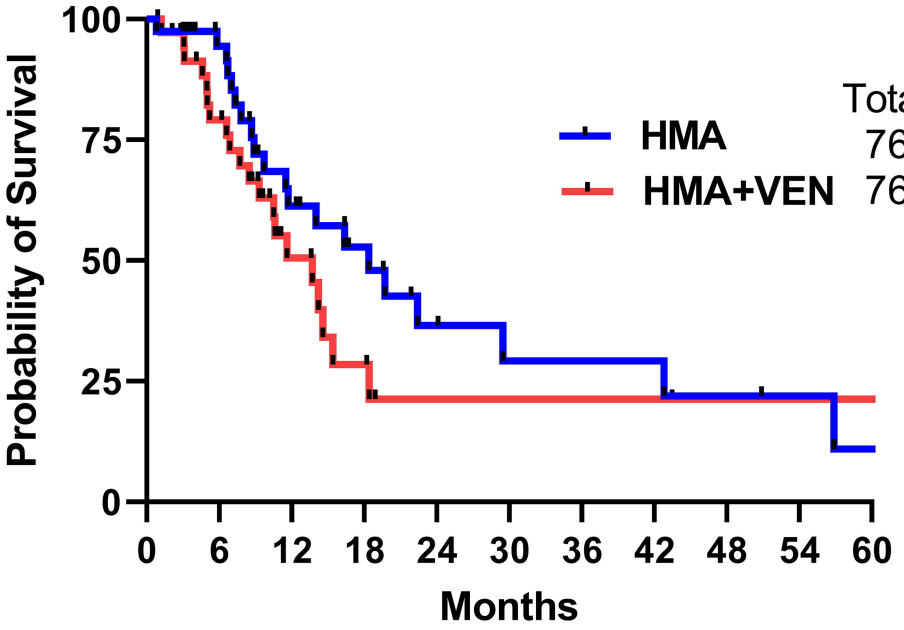
PSM: Relapse free survival



	Total	Events	Median
HMA	76	30	11.53 mo
HMA+VEN	76	29	9.30 mo

p= 0.52

PSM: Overall survival



	Total	Events	Median
HMA	76	20	18.37 mo
HMA+VEN	76	20	13.37 mo

p= 0.13

Clinical Outcomes of Venetoclax Combined with Hypomethylating Agents Versus Hypomethylating Agents Alone in *TP53*-mutated Myelodysplastic Syndromes

Mahmood Aldapt[1], Yu-Hung Wang[2], Kashish J. Shah[1], Mobachir El Kettani[1], James Foran[1], Mohamed Kharfan-Dabaja[1], Hemant Murthy[1], Aref Al-Kali[3], Mithun V Shah[3], Hassan Alkhateeb[3], Antoine N. Saliba[3], William Hogan[3], Cecilia Arana Yi[4], Lisa Sproat[4], Nathan Punwani[4], Nandita Khera[4], Jeanne Palmer[4], Mark Litzow[3], Ayalew Tefferi[3], Naseema Gangat[3], *Mrinal M Patnaik[3], *Talha Badar[1]

[1]Division of Hematology and Medical Oncology, Mayo Clinic, Jacksonville, Florida.
[2]National Taiwan University Cancer Center, Taipei, Taiwan.
[3]Division of Hematology, Mayo Clinic, Rochester, Minnesota.
[4]Division of Hematology, Mayo Clinic, Phoenix, Arizona, USA.

Authors contributions: M.A. contributed to data collection, data analysis, manuscript drafting, and revision. Y.H.W. contributed to data analysis, manuscript drafting, and revision. K.J.S., M.E.K., J.F., M.K.D., H.M., A.A.K., M.V.S., H.A., A.N.S., W.H., C.A.Y., L.S., J.P., M.L., A.T., N.P., N.K., and N.G. contributed to critical review and revision of the manuscript. M.M.P. contributed to manuscript drafting and critical revision. T.B. contributed to data collection, data analysis, manuscript drafting and revision, and provided overall study supervision. All authors reviewed and approved the final version of the manuscript.

Corresponding Author: Talha Badar, MD, Division of Hematology and Medical Oncology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224. Email: badar.talha@mayo.edu **Mrinal M Patnaik, MD,** Professor of Medicine, Division of Hematology, Mayo Clinic, Rochester, MN 55905, USA. Email: patnaik.mrinal@mayo.edu

Running title: Outcome of *TP53*-mt MDS with HMA+/- Ven

Key words: *TP53*-mutation, Higher-risk MDS, Venetoclax, HMA

Data Sharing Statement: For original data, please contact badar.talha@mayo.edu

Competing Interests statement: T.B. received research funding from Takeda and Amgen. Served on an advisory board for Syndax, Takeda, Amgen, Morphosys and Pfizer.

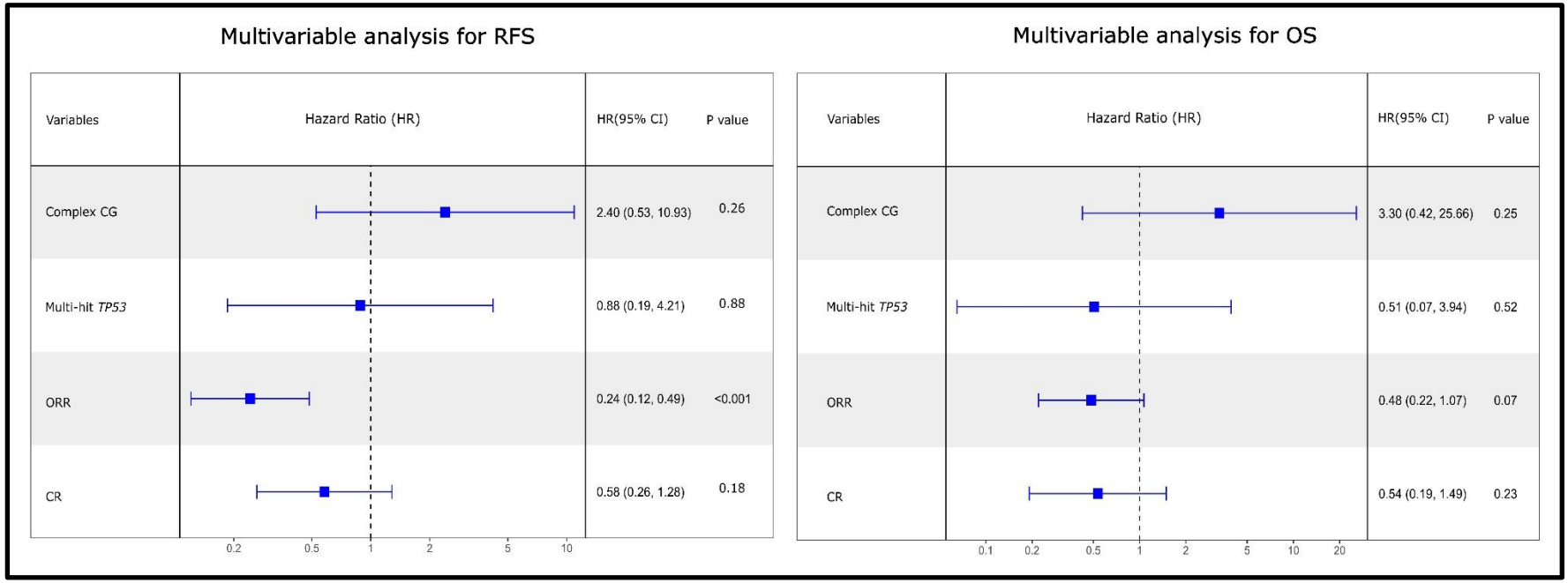
Supplementary Table 1: Baseline characteristics and treatment outcomes, including patient characteristics for variables involved in propensity score matching.

Variables	Total (N= 140)	HMA (N=102)	HMA+VEN (N=38)	P value
Age in year, range	69 (19-87)	70 (19-87)	65 (37-80)	0.34
Gender				
Male	93 (66%)	64 (63%)	29 (76%)	0.93
Female	47 (34%)	38 (37%)	9 (24%)	
Number of Cycles	3.5 (1-42)	3.5 (1-42)	3.0 (1-8)	0.34
Bone marrow blast %	6 (0-19)	5 (0-16)	9.5 (0-19)	0.02
IPSS-M				
Very low	2 (2%)	2 (2%)	0	0.18
Moderate low	4 (3%)	3 (3%)	1 (3%)	
Low	4 (3%)	4 (4%)	0	
High	48 (37.5%)	37 (41%)	11 (30%)	
Moderate high	5 (4%)	5 (5.5%)	0	
Very high	65 (51%)	40 (44%)	25 (68%)	
Data not available (N=12)				
Azacitidine	55 (39%)	43 (42%)	12 (32%)	0.4
Decitabine	85 (61%)	59 (58%)	26 (68%)	
TP53 VAF %, range	38 (2-96)	36.5 (2-94)	42 (6-96)	0.03
MH *TP53*	107 (77%)	78 (77%)	29 (76%)	0.53
Concurrent somatic mutation	81 (63%)	54 (59%)	27 (73%)	0.16
Commonly occurring mutations				
DNMT3A	21 (15%)	15 (17%)	6 (16%)	0.48
TET2	17 (12%)	13 (15%)	4 (10.5%)	0.31
ASXL1	10 (7%)	6 (7%)	4 (10.5%)	0.71
RAS	2 (1%)	2 (3%)	0	>0.99
Splicing function	14 (16%)	9 (9%)	5 (13%)	0.75
BCOR	6 (4%)	4 (4%)	2 (5%)	>0.99
Overall response rate (N= 124 evaluable)	59 (50%)	35 (40%)	24 (75%)	<0.001
CR	35 (28%)	23 (25%)	12 (36.4%)	0.26
CRh	7 (6%)	2 (2%)	5 (17%)	0.01
CR_L	12 (10%)	9 (10%)	3 (10%	1.00
HI	5 (4%)	3 (3%)	2 (7%)	0.59
mCR	14 (11%)	6 (7%)	8 (24%)	0.01
Allogeneic hematopoietic stem cell transplantation	35 (25%)	19 (19%)	16 (42%)	0.008
PSM cohort (variables)		**HMA (N=38)**	**HMA+VEN (N=38)**	**P value**
Age in year, range		70 (18-86)	65 (37-80)	0.35
Gender (Male)		29 (76%)	29 (76%)	0.79
t-MDS		23 (60.5%)	27 (71%)	0.23
Bone marrow blast %		8 (2-16)	9.5 (0-19)	0.20
Complex CG		34 (89%)	32 (86.5%)	>0.99
TP53 VAF %, range		39.5 (10-94)	42 (6-96)	0.80
MH *TP53*		28 (74%)	29 (76%)	>0.99
Concurrent somatic mutation		23 (60.5%)	27 (73%)	0.45
Overall response rate		18 (47%)	23 (60.5%)	0.08
cCR (CR/CRh/CR_L)		17 (44.7%)	21 (55%)	0.35
Allogeneic stem cell transplantation		13 (34%)	16 (42%)	0.63

HMA; hypomethylating agents, VEN; venetoclax, IPSS-M; molecular international prognostic scoring system, VAF; variant allele frequency, t; therapy related, CG; cytogenetics, MH; multi-hit, cCR; composite complete remission, CRh; CR with partial hematologic recovery, CR_L; CR with uni- or bilineage. P-values result from a Wilcoxon rank sum test (continuous variables) or Fisher's exact test (categorical variables).

Supplementary Table 2: Transplant outcomes		
Variables	**N=35**	**Median survival**
Conditioning regimen Myeloablative Reduced intensity	 12 (34%) 23 (66%)	
Median post-transplant relapse-free survival (RFS)		10.1 months
Median post-transplant overall survival (OS)		15.7 months
Post-transplant maintenance	18 (51%)	
Median OS by maintenance status Maintenance No maintenance	 	 24.5 months 14.5 months (p=0.25)

Survival outcomes were evaluated using Kaplan–Meier estimates



Supplementary Figure 1. Multivariable analyses of factors associated with outcomes (censored at allo-HCT). Forest plot showing adjusted HR with 95% CIs for complex cytogenetics, multi-hit TP53, ORR and CR for relapse free survival (A) and for overall survival (B)

Models include baseline variables with p<0.10 in univariate screens and are censored at transplant.