LETTER TO THE EDITOR

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

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

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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

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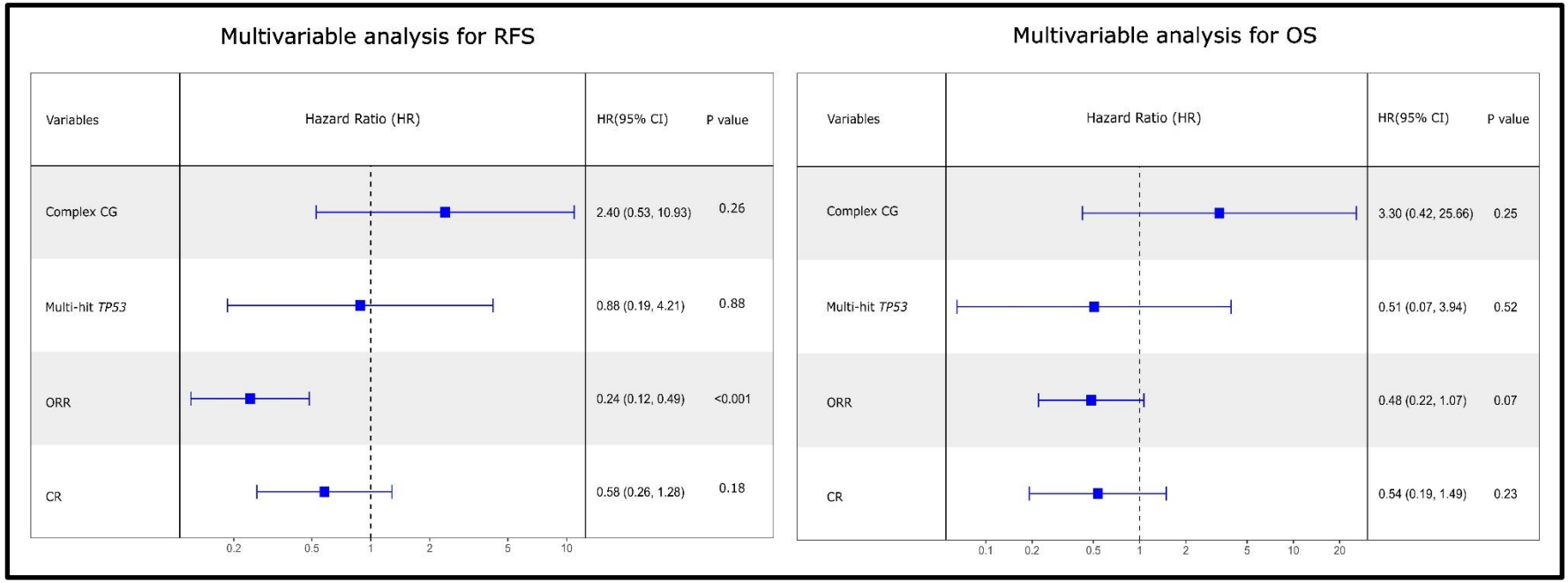
Supplementary Table 1: Baseline characteristics and treatment outcomes, including patient characteristics for variables involved in propensity score matching.

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.