TO THE EDITOR:

Validation of the international working group proposal for *SF3B1* mutant myelodysplastic syndromes

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We recently participated in an international effort proposing *SF3B1* mutant (MT) myelodysplastic syndromes (MDS) as a unique disease subtype under the auspice of the international working group (IWG) for the prognosis of MDS.[1] We hereby validate those findings among an independent large cohort that was not included in the original proposal.

Among 1729 MDS patients with known *SF3B1* mutation status at our institution, 320 patients (19%) harbored *SF3B1* MT (Table 1). Similar to the IWG cohort, patients with *SF3B1* MT were slightly older, had predominantly lower-risk disease, ring sideroblast phenotype, lower myeloblast percentage, and preserved neutrophil/platelet counts. No gender difference was observed in our cohort. The landscape of concomitant somatic mutations was similar to the IWG cohort, with notable distinct comutation rates in *SF3B1* MT vs wild-type (WT) populations (Table 1).

The median overall survival (OS) for *SF3B1* MT MDS patients was 84 months (95% confidence interval [CI], 68-100) compared with 31 months for WT patients (95% CI, 28-34; $P < .005$). The rate of acute myeloid leukemia (AML) transformation was 12.5% for *SF3B1* MT patients compared with 38% for *SF3B1* WT ($P < .005$). There was no difference in OS among *SF3B1* MT and WT in patients with >5% myeloblasts (median OS, 24 vs 20 months; $P = .17$).

Data on variant allele frequency (VAF) were reported in 234 *SF3B1* MT patients. The mean VAF was 32.3%. The hazard ratio (HR) for OS was 0.66 (95% CI, 0.43-0.1; $P = .065$) for *SF3B1* VAF >30% compared with ≤30%, although this was not independently associated with favorable OS after adjusting for the revised international prognostic scoring system (IPSS-R) (HR, 0.74; 95% CI, 0.47-1.16; $P = .2$). There was no difference in the rate of AML transformation in patients with high vs low VAF (9% vs 13%; $P = .3$). There was no difference in mean *SF3B1* VAF between MDS–single lineage dysplasia (SLD)/multilineage dysplasia (MLD), MDS–ring sideroblasts (RS), and MDS–excess blasts (EB) (29, 32, and 30, respectively; $P = .2$).

Confirming the IWG proposal among patients with *SF3B1* MT, presence of >5% myeloblasts (median OS, 24 vs 94 months; $P < .005$), complex karyotype (median OS, 13 vs 89 months; $P < .005$), presence of del(5q)/−5 isolated or complex (median OS, 24 vs 92 months; $P < .005$), presence of del7/−7 (median OS, 51 vs 86 mo; $P = .026$), and chromosome 3 abnormalities (median OS, 37 vs 89 months; $P = .01$) was associated with worse outcome. In our cohort, *SF3B1* MT was associated with worse

outcome among patients with isolated del5q MDS. Among 63 isolated del(5q) MDS classified by the World Health Organization 2016 criteria in patients with molecular data available, 6 patients (10%) harbored *SF3B1* MT (median VAF 38.9%) with no concomitant *TP53* MT. *SF3B1* MT patients had a significantly shorter median OS compared with WT (23.9 vs 83.5 months; $P = .001$).

RUNX1 MT was associated with worse OS and higher AML transformation among *SF3B1* MT patients. The median OS for concomitant *RUNX1/SF3B1* MT patients was 40 months (95% CI, 33-47 months) compared with 94 months (95% CI, 73-115 months) for *RUNX1* WT/*SF3B1* MT ($P < .001$), and the rate of AML transformation was 33% vs 10.5% ($P = .001$) (Figure 1A-B). The HR for mortality was 1.96 (95% CI, 1.1-3.4) in the presence of *RUNX-1* MT after adjusting for IPSS-R ($P = .019$). *EZH-2* MT was associated with a trend for worse OS (median OS, 55 months; 95% CI, 23-88 months) for *EZH-2/SF3B1* MT compared with 84 months for *EZH-2WT/SF3B1* MT (95% CI, 66-109 months; $P = .06$). In our database, only 15 patients (4%) had *TP53* concomitant MT, and no difference in median OS was observed, although a higher AML transformation was identified (33% vs 11%; $P = .039$).

SF3B1 MT retained favorable prognostic value in the context of therapy-related MDS (t-MDS). Of the 272 t-MDS patients in our database with known *SF3B1* mutation status, 31 were *SF3B1*-MT (11%). Of those with *SF3B1*-MT, 60% were classified as MDS-RS compared with 4.1% of those with *SF3B1*-WT t-MDS. Complex cytogenetics were seen in 37.4% vs 10.3% of patients with *SF3B1*-WT vs SF3B1-MT ($P = .009$). *TP53* mutation was seen in 36.1% of *SF3B1*-WT patients vs 10% of *SF3B1*-MT patients ($P = .004$). The AML transformation rate was 34.4% in *SF3B1*-WT t-MDS compared with 12.9% t-MDS *SF3B1*-MT ($P = .016$). Median OS was 17 months in *SF3B1*-WT t-MDS vs 43 months in *SF3B1*-MT t-MDS ($P = .004$).

We have previously reported that presence of ring sideroblasts with myeloblasts >5% was highly concordant with the presence of *TP53* mutation occurring in 80% of *SF3B1*-WT patients.[2]

In terms of response to treatment, patients with *SF3B1* MT had higher hematological improvement rate (HI) to erythroid stimulating agents; 92 out of 188 patients (49%) achieved HI compared with 105 out of 314 (33%) *SF3B1* WT patients ($P = .001$). There was a trend for lower response to hypomethylating agents; the HI rate was 49 out of 155 (32%) among *SF3B1* MT patients compared with 359 out of 915 (39%) among *SF3B1* WT patients ($P = .07$). There was no difference in response to lenalidomide, with

Table 1. Baseline characteristics based on *SF3B1* MT

	Comparing all *SF3B1* MT vs *SF3B1* WT (n = 1729)			Comparing *SF3B1* MT pts based on new IWG proposal criteria (n = 320)		
	SF3B1 MT n = 320	*SF3B1* WT n = 1409	*P*	*SF3B1* MT IWG (n = 175)	*SF3B1* MT non-IWG (n = 145)	*P*
Age (mean), y	70	68.5	.037	69	71	.2
Gender (male)	62%	64%	.55	67%	56%	.04
Race (white)	94%	90%	.13	96%	92%	.38
t-MDS	9%	17%	.001	10%	9%	.7
WHO 2016			<.005			<.005
MDS-SLD	3%	9%		5%	1%	
MDS-MLD	8%	26%		8%	8%	
MDS-SLD-RS	31%	1%		48%	11%	
MDS-MLD-RS	25%	3%		37%	9%	
MDS-EB-1	6%	17%		0	13%	
MDS-EB-2	6%	21%		0	12%	
MDS-U	1%	2%		1%	1%	
AML	2%	12%		0	5%	
MDS/MPN	3%	5%		0	8%	
del(5q)	2%	4%		0	4%	
MDS/MPN-RS-T	13%	0		0	28%	
IPSS-R			<.005			<.005
Very low	28%	10%		35%	18%	
Low	52%	25%		61%	43%	
Intermediate	10%	21%		4%	17%	
High	5%	19%		0	11%	
Very high	5%	25%		0	11%	
AML transformation	12.5%	38%	<.005	4.7%	22%	<.005
Myeloblasts	3.2%	8%	<.005	1.5%	5%	<.005
Hgb (g/dL)	11.3	9.7	.007	12.9	9.0	.2
ANC	3.5	2.4	.008	2.8	4.3	.01
Platelets	287	129	<.005	242	341	<.005
Mutation landscape						
TET-2	31%	21%	<.005	33%	28%	.5
DNMT3A	21%	13%	<.005	21%	21%	.96
ASXL-1	15%	22%	<.005	11%	19%	.15
IDH-1	1.9%	3.3%	.001	1%	3%	.5
IDH-2	2%	5%	<.005	2%	2%	.9
SRSF2	4%	13%	<.005	3%	6%	.3
U2AF1	1.6%	12%	<.005	1%	1%	.7
ZRSR2	5%	6%	.001	1%	1%	.6
EZH-2	5%	7.5%	<.005	0	11%	<.005

Number of somatic mutations tested using the standard Illumina platform, 70% included ≥54 gene panels with a minimum 13-gene panel.

ANC, absolute neutrophil count; Hgb, hemoglobin; MDS-U, MDS-unclassified; MPN, myeloproliferative neoplasm; pts, patients; RS-T, RS with thrombocytosis; WHO, World Health Organization.

Table 1. (continued)

| | Comparing all *SF3B1* MT vs *SF3B1* WT (n = 1729) | | | Comparing *SF3B1* MT pts based on new IWG proposal criteria (n = 320) | | |
	SF3B1 MT n = 320	*SF3B1* WT n = 1409	*P*	*SF3B1* MT IWG (n = 175)	*SF3B1* MT non-IWG (n = 145)	*P*
RUNX-1	12%	9%	.001	0	21%	<.005
ETV-6	1.6%	4%	.007	2%	1%	.9
TP53	4.7%	21%	<.005	0	10%	<.005
CBL	1.9%	3%	.007	2%	2%	.9
NRAS	1.9%	3.8%	<.005	1%	3.4%	.2
SETBP1	3.8%	4.3%	.1	3.5%	4%	.9
JAK-2	8.5%	3.4%	<.005	6%	12%	.16
MPL	2.2%	1.2%	.026	2%	1%	.8

Number of somatic mutations tested using the standard Illumina platform, 70% included ≥54 gene panels with a minimum 13-gene panel.

ANC, absolute neutrophil count; Hgb, hemoglobin; MDS-U, MDS-unclassified; MPN, myeloproliferative neoplasm; pts, patients; RS-T, RS with thrombocytosis; WHO, World Health Organization.

an HI rate of 22 out of 105 (23%) and 35 out of 145 (24%), respectively, for *SF3B1* MT and WT (*P* = .55). We previously reported *SF3B1* MT was a negative predictor of response to immunosuppressive therapy.[3] Luspatercept was recently approved for MDS-RS patients, a population highly enriched with *SF3B1* MT.[4] In the PACE-MDS study, the HI rate was 77% among
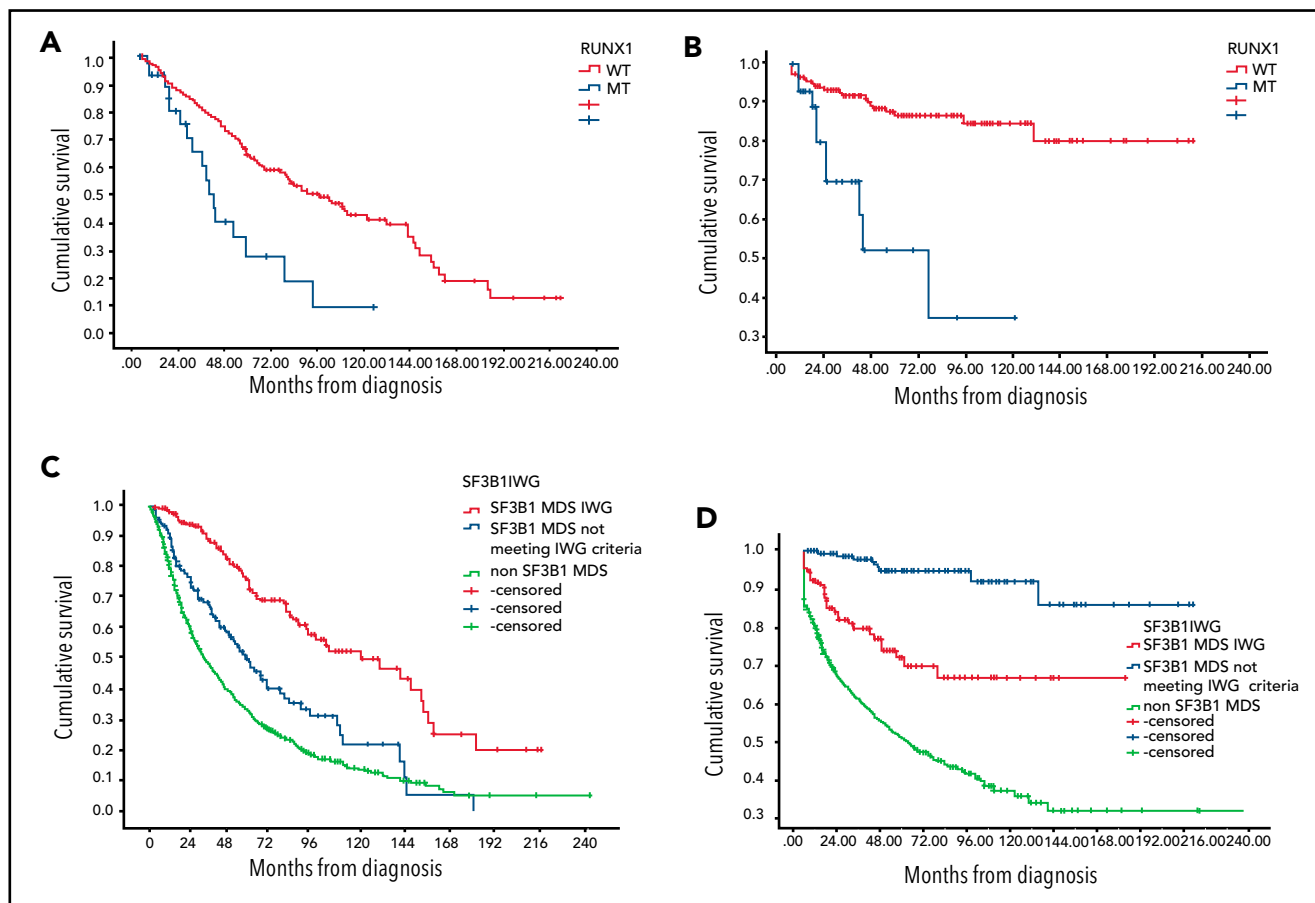

Figure 1. Kaplan-Meier estimates of overall survival and leukemia-free survival. (A) OS based on *RUNX-1* MT status among *SF3B1* MT MDS patients. (B) Leukemia-free survival based on *RUNX-1* MT status among *SF3B1* MT MDS patients. (C) OS based on *SF3B1* mutation status by new proposal IWG criteria. (D) Leukemia-free survival based on *SF3B1* mutation status by new proposal IWG criteria.

SF3B1 MT patients compared with 40% among those with WT.[5] Recent data from a phase 2 clinical study with imetelstat suggest potential preferential and disease modifying activity among small number of *SF3B1* MT patients.[6]

We reclassified our patients based on IWG *SF3B1* new proposal criteria.[1] Notably, 175 patients were classified as MDS-*SF3B1* by the new proposed criteria, 145 patients with *SF3B1* MT not meeting the new proposed criteria, and 1412 *SF3B1* WT MDS patients (Table 1). The median OS was 120 months (95% CI, 77-164 months), 55 months (95% CI, 42-69 months), and 31.5 months (95% CI, 28-35 months), respectively ($P < .005$; Figure 1C). The median leukemia-free survival was not reached among all *SF3B1* MT patients compared with 58 months among *SF3B1* WT patients ($P < .005$) (Figure 1D). The rate of AML transformation was 4.7%, 22%, and 38%, respectively ($P < .005$). t-MDS was observed in 10%, 9%, and 17% of the 3 above-mentioned groups. Excluding t-MDS, the median OS was 142, 57, and 36 months, respectively ($P < .005$). There was no difference in response rates to erythroid stimulating agents, hypomethylating agents, and lenalidomide between patients classified as *SF3B1* by IWG new criteria compared with other *SF3B1* MT MDS.

In summary, we confirm and validate the findings reported recently by Malcovati et al that *SF3B1* MT MDS should be classified as a unique disease entity based on the new proposal criteria. Furthermore, we demonstrate that *SF3B1* MT retained favorable prognostic value in the context of t-MDS and worse outcome among patients with isolated del(5q), and we compliment the IWG findings by reporting responses to current available therapies based on *SF3B1* MT status.

Authorship

Contribution : R.K. wrote the manuscript, designed the research study, and analyzed and interpreted data; V.V., O.C., N.A.A., and D.S. collected and analyzed data and approved the final manuscript; E.P. designed the research study and approved the final manuscript; and D.A.S. reviewed data, designed the research study, and approved the final manuscript.

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Footnote

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TO THE EDITOR:

The use of IV immunoglobulin in the treatment of vaccine-induced immune thrombotic thrombocytopenia

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