Myelodysplastic syndrome with concomitant *SF3B1* mutation and deletion of chromosome 5 long arm: outcomes and response to treatment

Myelodysplastic syndromes/neoplasms (MDS) are a group of heterogeneous clonal bone marrow (BM) failures. In their revised classification schema, the World Health Organization (WHO) and International Classification Consensus (ICC) recognize unique molecular entities. A molecular classification precedes morphologic classification.[1-3]

Both MDS-*SF3B1* and isolated del(5q) MDS are recognized by the WHO and the ICC 2022 as unique, molecularly defined MDS entities.[1-3] Del5q and *SF3B1* can occur concomitantly with what appears to be a different underlying biology, clinical features, and outcomes. Studies including the Molecular Revised International Prognostic Scoring System (IPSS-M) indicate that concomitant *SF3B1* mutation with del(5q) is associated with less favorable outcomes.[4] *SF3B1*^{del5q} accounted for 7% of all *SF3B1* cases in the IPSS-M cohort.

Lenalidomide is the treatment of choice for isolated del(5q) MDS and luspatercept is for MDS-*SF3B1*.[5-7] We studied a large cohort of *SF3B1*^{del5q} patients to describe molecular, clinical features, and outcomes. We assessed the hematologic response to various therapies. We also compared this group to patients with isolated del5q and the MDS-*SF3B1* group.

This was a multicenter international retrospective analysis (12 centers) for patients with concomitant del5q/*SF3B1* (*SF3B1*^{del5q}). The study was approved by the Institutional Review Board and Ethics Committee of each center. To be included in this study, patients had to have MDS with less than 5% myeloblasts, and no complex karyotype. Hematologic improvement (HI) was defined as an increase in hemoglobin (Hb) of 1.5 g/dL or more in non-transfusion dependent patients, or red blood cell (RBC) transfusion independence among transfusion dependent patients for eight weeks or more.[8] We identified 2 control cohorts from the Moffitt MDS database: one with MDS-*SF3B1* and one with isolated del5q-MDS. Descriptive statistics were used to describe the baseline characteristics and response rates. The χ^2 test was used to compare categorical variables and the ANOVA test for continuous variables. Kaplan-Meier estimates were used for overall survival (OS) and log rank test for comparison. Cox regression was used for hazard ratios.

The 77 LR-MDS patients with *SF3B1*^{del5q} were diagnosed with MDS between 2013-2022, the median age at diagnosis was 70 years (range: 30-87 years), 74% were female, 97% white, and 13% classified as therapy-related MDS (t-MDS). The mean Hb was 9.3 g/dL (range: 5-13), mean platelets were 272x10^9/L (range: 32-1330), and mean ANC was 2.01x10^9/L (range: 1-11). The majority of patients (70%) were lower risk by IPSS-M and 35.5% were RBC-transfusion dependent (RBC-TD) (Table 1). Data on BM ring sideroblasts were available for 53 patients; 34 out of 53 patients (64%) had ring sideroblasts ≥5%. Most patients had isolated del5q (66/77 patients) and trisomy 8 was the most common co-occurring cytogenetic abnormality. The most common *SF3B1* hotspot was K700E and the median variant allele frequency (VAF) was 24.5%. The most common other concomitant somatic mutations (MT) were *TP53* (26%), *DNMT3A* (23%), and *TET2* (21%) (Figure 1). The median *TP53* VAF was 16% (8/20 patients with *TP53* MT had VAF ≥20% and none had VAF >50%). R248W *TP53* was the most common hotspot (20%). Baseline characteristics were similar across study centers.

First-line therapy was lenalidomide for 46 patients (61%), erythropoiesis stimulating agents (ESA) for 18 (23%), luspatercept for 4 (5%), and hypomethylating agents (HMA) for 6 (8%); information was missing for 3 patients. Among 72 patients who were evaluable for response, the HI rate to any first-line therapy was 51.4% (37 patients). The HI rate to lenalidomide, ESA, HMA, and luspatercept was 64%, 42%, 20%, and no response, respectively.

Forty-seven patients received second-line therapy: 12 (26%) lenalidomide, 4 (9%) luspatercept, 22 (47%) HMA, one ESA, and 8 (17%) other treatments. Among 39 evaluable patients, the HI rate was 43% (17 patients). The second-line HI rate was similar for the three drugs, at 46% (5/11 patients), 50% (2/4 patients), and 47% (8/17 patients) for lenalidomide, luspatercept, and HMA, respectively.

Among 38 patients who received ESA at any time, 33 were evaluable for response, with an HI rate of 27%. Among 60 patients who received lenalidomide at any time, 57 were evaluable for response, and the HI rate was 58%, with no difference in response for *TP53* wild-type (WT) (61%) *versus* *TP53* MT (50%, *P*=0.4). The median duration of response was 17.3 months (range: 1.17-86 months). Among 16 patients who received luspatercept at any time, the HI rate was 18%. The median duration of response was 7.5 months (range: 0.7-18.4 months). Finally, 37 patients received HMA at any time of whom 32 were evaluable for response, with an HI of 37% (Figure 2).

There were no differences in baseline characteristics between *TP53* MT and WT, either in response to treatment or in duration of response. The median OS (mOS) for the whole cohort was 66 months (95%CI: 53-79). The mOS was 109 months for *TP53* WT compared to 64 months for *TP53* MT (*P*=0.22). The mOS was 64.2 months for *TP53* patients with VAF <20% (N=12) compared to 52.97 months for those with VAF ≥20% (N=8) (*P*=0.7).

We then compared the 77 MDS *SF3B1*^{del5q} cohort to 361 MDS-*SF3B1* patients and 95 MDS isolated del5q MDS patients (Table 1). MDS-SF3B1 had male predominance (*P*<0.001) and were less RBC transfusion dependent at time of diagnosis (*P*=0.04), while *SF3B1*^{del5q} had more bi/pancytopenia (*P*<0.001) and higher-risk disease according to the IPSS-M (*P*<0.001). Concomitant mutations also differed: *TP53* MT was observed in 26.3%, 14.7%, and 3.9% of SF3B1del5q, del5q MDS, and MDS-SF3B1 patients, respectively (*P*<0.005) (Figure 1). No *JAK2* mutations were seen in the *SF3B1*^{del5q} group. *ASXL1* and *TET2* mutations were also less frequently observed in the *SF3B1*^{del5q} group.

Higher ESA response rates were observed for the MDS-*SF3B1* group. HI to ESA was 27% (9/33) for *SF3B1*^{del5q}, 45% (110/246) for MDS-*SF3B1*, and 36.7% (11/30) for del5q MDS patients (*P*=0.018). Similar response to lenalidomide was seen among del5q and *SF3B1*^{del5q} groups (63.2% and 47%, respectively) (*P*=0.7).

Outcomes for *SF3B1*^{del5q} MDS patients were inferior compared to del5q MDS and MDS-*SF3B1*. HR for *SF3B1*^{del5q} OS was 1.55 (95%CI: 0.95-2.5) (*P*=0.079) compared to del5q MDS and 1.49 (95%CI: 1.02-2.17) (*P*=0.038) compared to MDS-*SF3B1*. Median OS was 66, 99.5, and 103 months, respectively, for *SF3B1*^{del5q}, del5q, and MDS-*SF3B1* (*P*=0.086) (Figure 2). The rate of acute myeloid leukemia transformation was 20%, 12%, and 5%, respectively (*P*<0.005).

The WHO and the ICC 2022 have adopted molecular-defined MDS entities.[2] Del5q-MDS is defined by the presence of isolated del5q with up to one additional chromosome abnormality other than -7/del(7) and less than 5% myeloblasts.[2] MDS-*SF3B1* is defined by the WHO 2022 in the presence of *SF3B1* somatic mutations with low blasts with no concomitant del5q, monosomy 7, complex karyotype, and no biallelic *TP53*.[1] The ICC 2022 requires the presence of *SF3B1* MT with a VAF ≥10%, and absence of del5q, -7, inv3/t(3;3), complex karyotype, and no multi-hit *TP53* or *RUNX1* mutation.[3] MDS-*SF3B1* accounts for 13% of MDS, while del5q MDS accounts for 5%. Both entities are associated with favorable outcomes, with a median OS of 8-9 years and 6-7 years, respectively.[2]

Chan *et al*. reported outcomes of 63 patients with del 5q MDS. *TP53* was the most common mutation observed

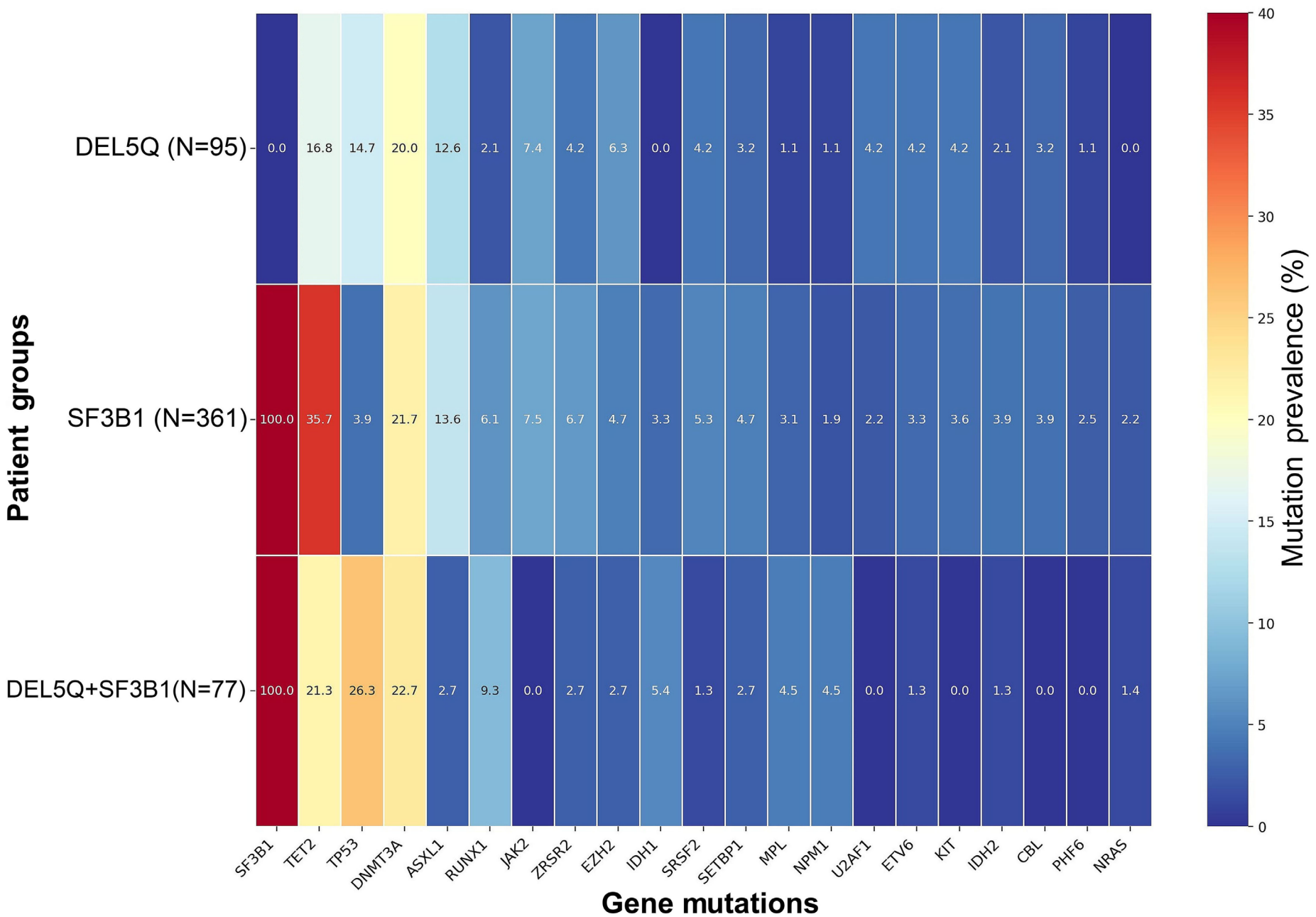


Figure 1. Heatmap of somatic gene mutations among *SF3B1*^{del5q}, myelodysplastic syndromes/neoplasms (MDS)-*SF3B1* patients and isolated del5q MDS patients.

in 24% of patients, followed by *SF3B1* in 10%. *TP53* did not impact OS; however, the presence of *SF3B1* did, with median OS of 23.9 months for *SF3B1* mutant compared to 83.5 months for the WT.[9]

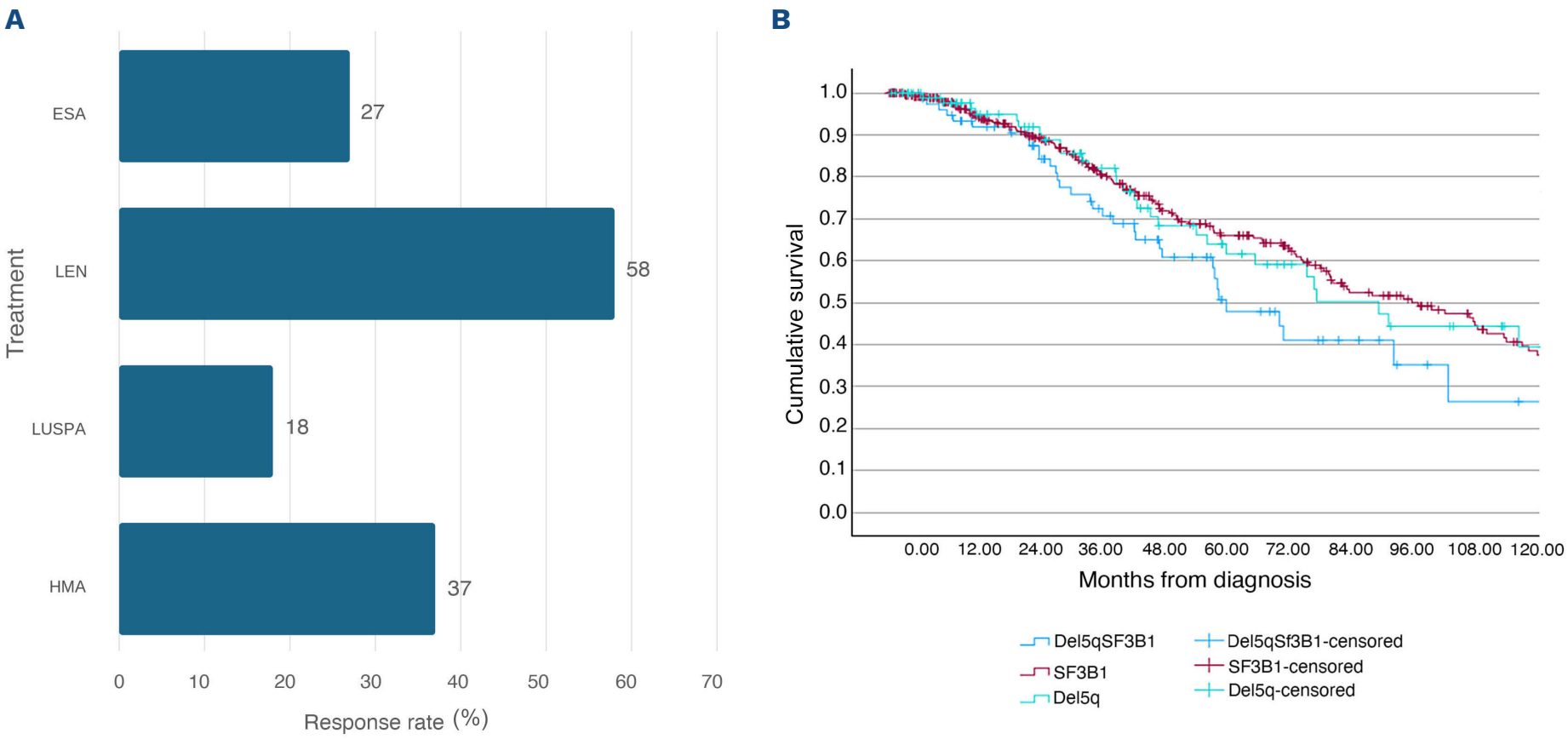


Figure 2. Outcomes of *SF3B1*^{del5q} myelodysplastic syndromes/neoplasms. (A) Response to treatment and (B) Kaplan-Meier estimates for overall survival. ESA: erythropoiesis stimulating agent; HMA: hypomethylating agents; LEN: lenalidomide; LUSPA: luspatercept.

Table 1. Baseline characteristics.

Characteristic	del5q*SF3B1*	*SF3B1*	del5q	*P*
Total N	77	361	95	-
Median age at diagnosis, years	70	71	73.2	0.49
Race, White, N (%)	75 (97.4)	334 (93.8)	81 (88)	0.2
Male, N (%)	20 (26)	245 (67.9)	47 (49.5)	<0.001
BM blasts, %, mean±SD	2.1±1.3	1.6±0.9	2.0±1.1	<0.001
Hb, g/dL, mean±SD	9.3±1.4	9.5±1.6	9.5±2.0	0.51
WBC, x10^9/L, mean±SD	4.5±2.6	5.3±4.5	4.9±3.5	0.3
ANC, x10^9/L, mean±SD	2.4±1.7	3.0±3.2	2.6±1.9	0.2
Platelet, x10^9/L, mean±SD	272.4±186.4	247.0±115	230±162	0.13
Bi/pancytopenia, N (%)	26 (40)	81 (22.4)	32 (33.7)	<0.001
RBC transfusion dependent, N (%)	27 (35.5)	89 (24.7)	33 (34.7)	0.04
IPSS-M risk category, N (%)				<0.001
Very low	3 (3.9)	92 (25.5)	10 (10.5)	
Low	25 (32.5)	186 (51.5)	56 (58.9)	
Moderate/low	26 (33.8)	29 (8)	10 (10.5)	
Moderate/high	10 (13)	17 (4.7)	8 (8.4)	
High	4 (5.2)	4 (1.1)	1 (1.1)	
Very high	1 (1.3)	5 (1.4)	1 (1.1)	
Missing	8 (10.4)	28 (7.7)	12 (9.5)	

ANC: absolute neutrophil count; BM: bone marrow; Hb: hemoglobin; IPSS-M: Molecular Revised International Prognostic Scoring System; N: number; RBC: red blood cell; SD: standard deviation; WBC: white blood cell.

The IPSS-M has incorporated somatic mutation data to refine the prognosis.[4] *SF3B1* was associated with favorable outcomes; however, the association was strongly affected by the co-mutational pattern. The IPSS-M defined 3 *SF3B1* groups: *SF3B1*^{5q} (7%) with concomitant *SF3B1* and del5q, *SF3B1*$^{\beta}$ (15%) where there is co-mutation between SF3B1 and any gene from *BCOR, BCORL1, NRAS, RUNX1, SRSF2* or *STAG2*, and *SF3B1*$^{\alpha}$ (78%) as any other mutant SF3B1. The median OS for *SF3B1*^{5q} was around 2.5 years compared to 5-6 years for *SF3B1*$^{\alpha}$. Twenty-five percent of the patients with *SF3B1*^{5q} had 5-20% blasts.

Montoro *et al*. assessed a large cohort of del5q MDS (N=682).[10] *TP53* and *SF3B1* were the most common mutations observed in 20% and 19% of patients, respectively. High-risk *TP53* mutations, defined by a VAF >20% or multi-hit, and *SF3B1* mutations were independently associated with worse outcomes.

The SintraREV study was a randomized clinical trial in del5q MDS patients between lenalidomide *versus* observation. All patients with *SF3B1* mutations who received lenalidomide achieved erythroid and cytogenetic responses compared to (67%) erythroid response and (79%) cytogenetic response in *SF3B1* WT. The median duration of cytogenetic responses was shorter in patients with *SF3B1* mutations compared with those with *SF3B1* WT (12.0 [95%CI: 5.57-21.97] *vs*. 24.6 [3.53-82.80] months).[11]

Our study has several limitations, namely its retrospective nature, small sample size, and missing data on some key elements, such as ring sideroblasts in a subset of patients, IPSS-M risk score (not available for all patients), baseline serum erythropoietin level, and dosing.

To our knowledge, this is the largest cohort of concomitant *SF3B1*^{del5q} MDS patients to date. We report a mOS of 66 months, which is better than that reported in the IPSS-M for this group. Contrary to the IPSS-M, our analysis was limited to patients with less than 5% myeloblasts. The mOS of *SF3B1*^{del5q} was still inferior to either isolated del5q or *SF3B1*. Response to lenalidomide was similar to isolated del5q, whereas response to luspatercept was inferior to MDS-*SF3B1*, all be it, in a small sample size, especially as first-line therapy, and half of the patients who received luspatercept were beyond second-line. Luspatercept was approved for MDS in 2019 and indications were expanded to allow front-line therapy in 2023. *SF3B1*^{del5q} is a unique MDS entity better classified as del5q MDS rather than MDS-*SF3B1*. Patients should be treated as del5q MDS using ESA and lenalidomide initially. Further exploration of the response to luspatercept, its underlying molecular biology, and the potential mechanism of resistance to the drug, is warranted.

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Contributions

RSK designed the study, analyzed the data, and wrote the manuscript. ZK and NA analyzed data. All authors provided patient-related data, reviewed the manuscript, and approved the final version for publication.

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Data-sharing statement

The data collected for this study was multicenter reflecting the patients of each center, for which, data sharing is not available.

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