haematologica
Journal of the Ferrata Storti Foundation

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

by Rami Komrokji, Zaker Schwabkey, Zena Komrokji, Najla Al Ali, Luis Aguirre, Maximilan Stahl, Somedeb Ball, Emily Mason, Michael Savona, Valeria Santini, Angela Consagra, Uwe Platzbecker, Anne Sophie Kubasch, Yazan Madanat, Pierre Fenaux, Lin-Pierre Zhao, Mikkael A. Sekeres, Namrata Chandhok, Matteo Della Porta, Luca Lanino, Amy DeZern, David Sallman, Eric Padron, Zhuoer Xie, Koji Sasaki, Kensuke Takaoka, Akhil Jain, Monica Del Rey Gonzalez, Maria Diez Campelo and Guillermo Garcia-Manero

Received: December 18, 2025.
Accepted: April 30, 2026.

Citation: Rami Komrokji, Zaker Schwabkey, Zena Komrokji, Najla Al Ali, Luis Aguirre, Maximilan Stahl, Somedeb Ball, Emily Mason, Michael Savona, Valeria Santini, Angela Consagra, Uwe Platzbecker, Anne Sophie Kubasch, Yazan Madanat, Pierre Fenaux, Lin-Pierre Zhao, Mikkael A Sekeres, Namrata Chandhok, Matteo Della Porta, Luca Lanino, Amy DeZern, David Sallman, Eric Padron, Zhuoer Xie, Koji Sasaki, Kensuke Takaoka, Akhil Jain, Monica Del Rey Gonzalez, Maria Diez Campelo and Guillermo Garcia-Manero. Myelodysplastic syndrome with concomitant SF3B1 mutation and deletion of chromosome 5 long arm: outcomes and response to treatment.
Haematologica. 2026 May 7. doi: 10.3324/haematol.2025.300396 [Epub ahead of print]

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

Rami Komrokji*[1] , Zaker Schwabkey*[1], Zena Komrokji[1], Najla Al Ali[1], Luis Aguirre[2], Maximilian Stahl[2], Somedeb Ball[3], Emily Mason[3], Michael Savona[3], Valeria Santini[4], Angela Consagra[4], Uwe Platzbecker[5], Anne Sophie Kubasch[5], Yazan Madanat[6], Pierre Fenaux[7], Lin-Pierre Zhao[7], Mikkael A. Sekeres[8], Namrata Chandhok[8], Matteo Della Porta[9], Luca Lanino[9], Amy DeZern[10], David Sallman[1], Eric Padron[1], Zhuoer Xie[1], Koji Sasaki[11], Kensuke Takaoka[11], Akhil Jain[11], Monica Del Rey Gonzalez[12], Maria Diez Campelo**[12], Guillermo Garcia-Manero**[11]

* Equally contributed first author
** Equally contributed senior author

1 Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL
2 Department of Internal Medicine, Section of Medical Oncology and Hematology, Yale University School of Medicine and Yale Cancer Center
3 Vanderbilt University Medical Center, Nashville, TN
4 MDS Unit, Hematology, AOUC, University of Florence, Florence, Italy;
5 Department for Hematology, Cell Therapy, Hemostaseology and Infectious Diseases, University Medical Center Leipzig, Leipzig, Germany
6 Division of Hematology and Oncology, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX
7 Department of Hematology, Université de Paris, Saint-Louis Hospital, Paris, France; 8 8 Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL
9 IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
10 The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
11Department of Leukemia, The University of Texas, MD Anderson Cancer Center, Houston, TX
12 Department of Hematology, Salamanca-IBSAL University Hospital, Salamanca, Spain

Corresponding author

Rami Komrokji
Moffitt Cancer Center, Magnolia Campus
12902 USF Magnolia Drive, Tampa, FL 33612
Tel: 786-473-8108
e-mail: rami.komrokji@moffitt.org

Key words: Myelodysplastic syndromes, SF3B1, deletion 5q

Short Title: SF3B1/del5q MDS

Data presented at American Society of Hematology 2024 annual meeting, *Blood* 2024; 144 (Supplement 1): 1845.

Conflict of interest

No conflict of interest relevant to this work

Authors declared following conflict of interest outside scope of this manuscript

Komrokji: *Sobi:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *DSI:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Taiho:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Jazz Pharmaceuticals:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AbbVie:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Geron:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Consultancy; *Servier:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *PharmaEssentia:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Sumitomo Pharma:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servio:* Membership on an entity's Board of Directors or advisory committees; *Keros:* Membership on an entity's Board of Directors or advisory committees; *Rigel:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Genentech:* Consultancy; *DSI:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servio:* Honoraria; *CTI biopharma:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Research Funding; *Novartis:* Membership on an entity's Board of Directors or advisory committees. Stahl:*Sobi:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Rigel:* Membership on an entity's Board of Directors or advisory committees; *Kymera:* Membership on an entity's Board of Directors or advisory committees; *Sierra Oncolgy:* Membership on an entity's Board of Directors or advisory committees; *GSK:* Membership on an entity's Board of Directors or advisory committees; *Syndax:* Membership on an entity's Board of Directors or advisory committees. Savona:*AbbVie; Bristol Myers Squibb; CTI BioPharma Corp.; Geron; Karyopharm; Novartis Pharmaceuticals Corporation; Ryvu Therapeutics; and Sierra Oncology, Inc.:* Consultancy; *ALX Oncology Inc.; Astex Pharmaceuticals; Incyte Corporation; and Takeda Pharmaceutical Company Limited.:* Research Funding; *Empath Biosciences; Karyopharm and Ryvu Therapeutics:* Current holder of *stock options* in a privately-held company; *Astex Pharmaceuticals for travel grant.:* Other: Financial or Material Support. Santini:*Ascentage, AbbVie, Bristol Myers Squibb, CTI BioPharma, Geron, Gilead, Novartis, Servier, Syros Pharmaceuticals:* Other: Advisory Board. Platzbecker:*Amgen:* Consultancy, Research Funding; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Research Funding; *MDS Foundation:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Consultancy, Research Funding; *Curis:* Consultancy, Honoraria, Research Funding; *Geron:* Consultancy; *Janssen:* Consultancy, Honoraria, Research Funding; *Merck:* Research Funding; *Novartis:* Consultancy, Research Funding. Kubasch:*Curis:* Research Funding; *BMS:* Honoraria; *Novartis:* Honoraria, Research Funding; *Janssen:* Honoraria, Research Funding. Madanat:*OncLive, MD Education, Sierra Oncology, Stemline, MorphoSys:* Consultancy; *Sierra Oncology, Stemline Therapeutics, Blueprint Medicines, Morphosys, Taiho Oncology, SOBI, Rigel Pharmaceuticals, Geron, Cogent Biosciences and Novartis:* Other: Advisory Board; *Taiho Oncology, Rigel*

Pharmaceuticals, Novartis: Consultancy; *Blueprint Medicines, MD Education, and Morphosys:* Other: travel; *BMS, Kura Oncology, BluePrint Medicines, Geron:* Consultancy. Fenaux:*Jazz Pharmaceuticals:* Honoraria, Research Funding; *Astex:* Research Funding; *Janssen:* Research Funding; *Agios:* Research Funding; *Novartis:* Research Funding; *Servier:* Research Funding; *AbbVie:* Honoraria, Research Funding; *BMS:* Honoraria, Research Funding. Sekeres:*Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Kurome:* Membership on an entity's Board of Directors or advisory committees; *Schroedinger:* Membership on an entity's Board of Directors or advisory committees. Della Porta:*Bristol Myers Squibb:* Consultancy. DeZern:*servier:* Membership on an entity's Board of Directors or advisory committees; *Shattuck Labs:* Membership on an entity's Board of Directors or advisory committees; *Keros:* Membership on an entity's Board of Directors or advisory committees; *geron:* Other: dsmb; *Astellas:* Honoraria; *Appellis:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibbs:* Membership on an entity's Board of Directors or advisory committees. Sallman:*Abbvie:* Consultancy; *Agios:* Consultancy; *Axiom:* Consultancy; *Gilead:* Consultancy ; *Celyad:* Consultancy; *Froghorn:* Consultancy; *Incyte:* Consultancy; *Intellisphere, LLC:* Consultancy; *Johnson & Johnson:* Consultancy; *Kite:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Magenta Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *NextTech:* Consultancy; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AvenCell:* Membership on an entity's Board of Directors or advisory committees; *Astellas:* Membership on an entity's Board of Directors or advisory committees; *BlueBird Bio:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *Dark Blue Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Intellia:* Membership on an entity's Board of Directors or advisory committees; *Jasper Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *NKARTA:* Membership on an entity's Board of Directors or advisory committees; *Orbital Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Rigel Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Shattuck Labs:* Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees; *Syndax:* Membership on an entity's Board of Directors or advisory committees; *Syros:* Membership on an entity's Board of Directors or advisory committees; *Apera:* Research Funding; *Jazz:* Research Funding. Sasaki: *Enliven:* Research Funding; *Pfizer:* Consultancy; *Novartis:* Consultancy, Research Funding; *Daiichi-Sankyo:* Consultancy; *Otsuka:* Other: Lecture fees; *Chugai:* Other: Lecture fees. Diez-Campelo: *SYROS:* Membership on an entity's Board of Directors or advisory committees; *Gilead:* Other: Travel reimbursement; *ASTEX/OTSUKA:* Membership on an entity's Board of Directors or advisory committees, Other: TRAVEL TO MEETINGS; *HEMAVAN:* Membership on an entity's Board of Directors or advisory committees; *BMS/Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Advisory board fees; *AGIOS:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *BLUEPRINT MEDICINES:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *KEROS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *CURIS:* Membership on an entity's Board of Directors or advisory committees. Garcia-Manero: *Onconova:* Research Funding; *Merck:* Research Funding; *H3 Biomedicine:* Research Funding; *Genentech:* Research Funding; *Genentech:* Other: Personal fees; *Astex:* Other: Personal fees; *Forty Seven:* Research Funding; *Helsinn:* Other: Personal fees; *Amphivena:* Research Funding; *Astex:* Research Funding; *Janssen:* Research Funding; *AbbVie:* Research Funding; *Novartis:* Research Funding; *Helsinn:* Research Funding; *Bristol Myers Squibb:* Other: Personal fees, Research Funding; *Curis:* Research Funding; *Aprea:* Research Funding.

Author contributions

All authors provided patient related data, RSK designed study, analyzed data and wrote manuscript, ZK and NA analyzed data, all authors reviewed manuscript and provided final approval

Data sharing statement:

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

Key points

- *SF3B1*^{del5q} is a unique MDS subtype with co-occurrence of del5q molecular abnormality and *SF3B1* mutation.

- *SF3B1*^{del5q} clinically and molecularly resembles more del5q MDS rather than MDS-*SF3B1* and it is associated with inferior outcome compared to both del5q MDS and MDS-*SF3B1*.

- Lenalidomide activity among *SF3B1*^{del5q} patients was similar to del5q MDS reported responses.

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

Both MDS-*SF3B1* and isolated del(5q) MDS are recognized by WHO and 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 hematological 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 IRB and Ethics committee. To be included in this study, patients had to have MDS with less than 5% myeloblasts, no complex karyotype. Hematological improvement (HI) was defined as a hemoglobin (Hgb) increase of 1.5 g/dl or more in non-transfusion dependent patients, or red blood cell transfusion independence among transfusion dependent patients for 8 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 Chi-square test was used for comparing categorical variables and the

ANOVA test for continuous variables. Kaplan-Meier estimates were used for overall survival and log rank test for comparison. Cox regression was used for hazard ratios.

Among 77 LR-MDS patients with *SF3B1*^{del5q}, patients were diagnosed with MDS between 2013-2022, the median age at diagnosis was 70 years (30-87), 74% were female, 97% white, and 13% classified as t-MDS. The mean Hgb was 9.3 g/dl (5-13), mean platelets 272 $\times 10^9$/L (32-1330), and mean ANC 2.01 $\times 10^9$/L (1-11). The majority of patients (70%) were lower risk by IPSS-M and 35.5% were red blood cell transfusion dependent (RBC-TD) (Table-1). Data on bone marrow ring sideroblasts were available for 53 patients: 34 out of 53 patients (64%) had ring sideroblasts ≥ 5%. Most patients had isolated del5q (66/77 pts) 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 pts with *TP53* MT had VAF ≥20% and none with VAF > 50%). R248W *TP53* was the most common hot spot (20%). Baseline characteristics were similar across contributing centers.

First-line therapy was lenalidomide for 46 patients (61%), erythropoiesis stimulating agents (ESA) for 18 patients (23%), luspatercept for 4 patients (5%), and hypomethylating agents (HMAs) for 6 patients (8%) and missing information in 3 patients. Among 72 evaluable patients 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 2nd line therapy: 12 (26%) lenalidomide, 4 (9%) luspatercept, 22 (47%) HMA, 1 ESA, and 8 (17%) other treatments. Among 39 evaluable patients, the HI rate

was 43% (17 patients). The 2nd 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* WT (61%) vs *TP53* MT (50%, p=.4). The median duration of response was 17.3 months (1.17-86). Among 16 patients who received luspatercept at any time, the HI rate was 18%. The median duration of response was 7.5 months (0.7-18.4). Finally, 37 patients received HMA at any time, 32 evaluable for response, with an HI=37% (Figure-2).

There were no differences in baseline characteristics between *TP53* MT and WT, neither in response to treatment nor in duration of response. The median overall survival (mOS) for the whole cohort was 66 months (mo) (95%CI 53-79). The mOS was 109 mo for *TP53* WT compared to 64 mo for *TP53* MT (p=0.22). The mOS was 64.2 mo for *TP53* patients with VAF < 20% (n=12) compared to 52.97 mo 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 more male predominance (p <.001) and were less RBC-TD at time of diagnosis (p=0.04), while *SF3B1*^{del5q} had more bi/pancytopenia (p <0.001) and higher-risk disease by IPSS-M (p <0.001). Concomitant mutations also differed (Figure-1). *TP53 MT* was observed in 26.3%, 14.7%, and 3.9% *SF3B1*^{del5q}, del5q MDS, and MDS-*SF3B1* patients, respectively (p<0.005). 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 pts, p=0.018). Similar response to lenalidomide was seen among del5q and *SF3B1*^{del5q} group (63.2 % and 47% respectively, p=07).

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=.038) compared to MDS-*SF3B1.* Median OS was 66, 99.5, and 103 mo, respectively, for *SF3B1*^{del5q}, del5q, and MDS-*SF3B1* (p=0.086) (Figure-2). The rate of AML transformation was 20%, 12%, and 5%, respectively (p<.005).

The WHO and ICC 2022 adopted molecular-defined MDS entities [2]. Del5q-MDS is defined by the presence of isolated del5q with up to one additional chromosome abnormality except -7/del(7) and less than 5% myeloblasts [2]. MDS-*SF3B1* is defined by 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 variant allelic frequency (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 in 24% of patients, followed by *SF3B1* in 10%. *TP53* did not impact OS; however, the presence of *SF3B1* did, median OS was 23.9 months for *SF3B1* mutant compared to 83.5 months for the WT. [9].

The IPSS-M 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*$^{\alpha}$ (25% of the pts 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 multihit, 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*-wild-type. The median duration of cytogenetic responses was shorter in patients with *SF3B1* mutations compared with those with *SF3B1*-wild type (12·0 [95% CI 5·57–21·97] *vs* 24·6 [3·53–82·80] months) [11].

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

To our knowledge, this is the largest cohort of concomitant *SF3B1*^{del5q} MDS patients to date. We report a mOS of 66 mo, which is better than what was 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, 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 label 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, possible underlying molecular biology and potential mechanism of resistance to luspatercept is warranted.

References

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
2. Komrokji RS, Lanino L, Ball S, et al. Data-driven, harmonised classification system for myelodysplastic syndromes: a consensus paper from the International Consortium for Myelodysplastic Syndromes. Lancet Haematol. 2024;11(11):e862-e872.
3. 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.
4. Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evid. 2022;1(7):EVIDoa2200008.
5. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med. 2005;352(6):549-557.
6. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med. 2020;382(2):140-151.
7. Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023;402(10399):373-385.
8. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642-4649.
9. Chan O, Ali NA, Sallman D, Padron E, Lancet J, Komrokji R. Therapeutic outcomes and prognostic impact of gene mutations including TP53 and SF3B1 in patients with del(5q) myelodysplastic syndromes (MDS). Clin Lymphoma Myeloma Leuk. 2022;22(7):e467-e476.
10. Montoro MJ, Palomo L, Haferlach C, et al. Influence of TP53 gene mutations and their allelic status in myelodysplastic syndromes with isolated 5q deletion. Blood. 2024;144(16):1722-1731.
11. Díez-Campelo M, López-Cadenas F, Xicoy B, et al. Low dose lenalidomide versus placebo in non-transfusion dependent patients with low risk, del(5q) myelodysplastic syndromes (SintraREV): a randomised, double-blind, phase 3 trial. Lancet Haematol. 2024; 11(9): e659-e670.

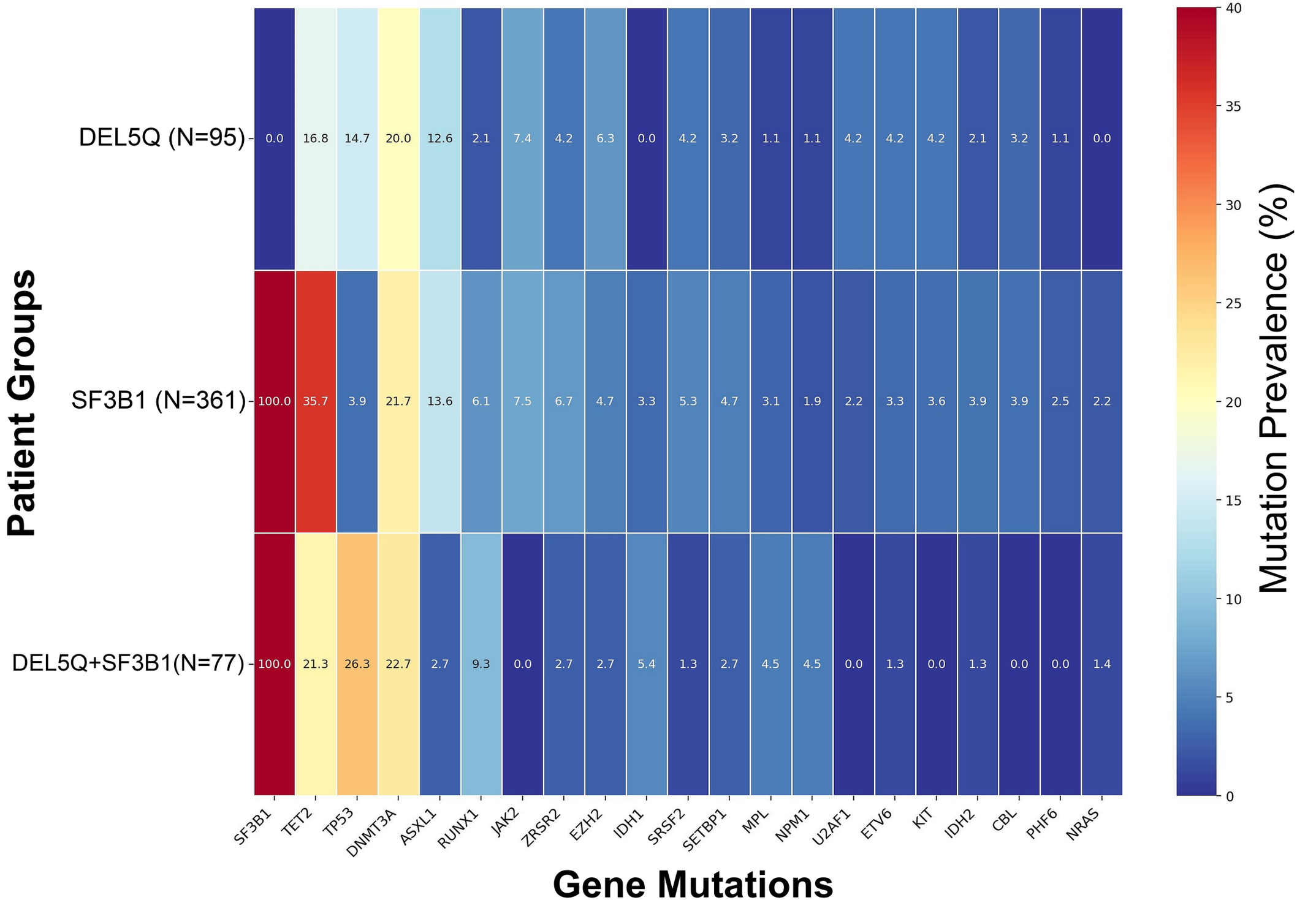
Table 1. Baseline Characteristics.

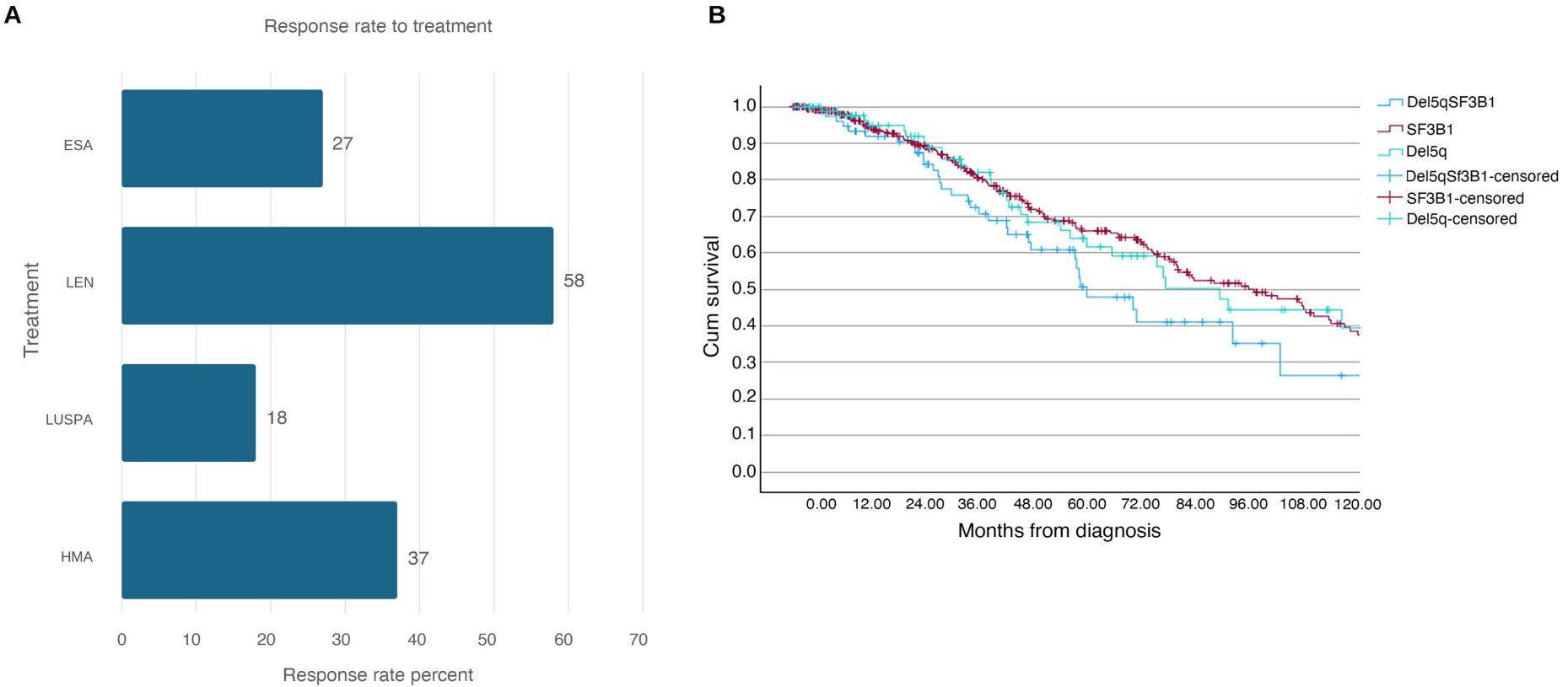
Characteristic	Del5qSF3B1	SF3B1	Del5q	P value
n	77	361	95	
Age at diagnosis (median)	70	71	73.2	0.49
Race (white)	75 (97.4%)	334 (93.8%)	81 (88%)	0.2
Gender (Male)	20 (26%)	245 (64.5%)	47 (40%)	< 0.001
Bone marrow blasts (%) (mean±SD)	2.1 ± 1.3	1.6 ± 0.9	2.0 ± 1.1	<0.001
Hemoglobin(g/dl) (mean±SD)	9.3 ± 1.4	9.5 ± 1.6	9.5 ± 2.0	0.51
White Blood Cell Count (×10³/μL) (mean±SD)	4.5 ± 2.6	5.3 ± 4.5	4.9 ± 3.5	0.3
Absolute Neutrophil Count (×10³/μL) (mean±SD)	2.4 ± 1.7	3.0 ± 3.2	2.6 ± 1.9	0.2
Platelet Count (×10³/μL) (mean±SD)	272.4 ± 186.4	247.0 ± 115	230 ± 162	0.13
Bi/pancytopenia	26 (40%)	81 (22.4%)	32 (33.7%)	<0.001
RBC transfusion dependent	27 (35.5%)	89 (24.7%)	33 (34.7%)	0.04
IPSS-M risk category				< 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%)	

Figures legend

Figure 1 Heat map of somatic gene mutations among *SF3B1*^{del5q}, MDS-*SF3B1* patients and isolated del5q MDS patients.

Figure 2 Outcomes of *SF3B1*^{del5q} MDS (A) response to treatment and (B) Kaplan Meier estimates for overall survival.


Patient Groups
DEL5Q (N=95)
SF3B1 (N=361)
DEL5Q+SF3B1(N=77)
0.0 16.8 14.7 20.0 12.6 2.1 7.4 4.2 6.3 0.0 4.2 3.2 1.1 1.1 4.2 4.2 4.2 2.1 3.2 1.1 0.0
100.0 35.7 3.9 21.7 13.6 6.1 7.5 6.7 4.7 3.3 5.3 4.7 3.1 1.9 2.2 3.3 3.6 3.9 3.9 2.5 2.2
100.0 21.3 26.3 22.7 2.7 9.3 0.0 2.7 2.7 5.4 1.3 2.7 4.5 4.5 0.0 1.3 0.0 1.3 0.0 0.0 1.4
SF3B1 TET2 TP53 DNMT3A ASXL1 RUNX1 JAK2 ZRSR2 EZH2 IDH1 SRSF2 SETBP1 MPL NPM1 U2AF1 ETV6 KIT IDH2 CBL PHF6 NRAS
Gene Mutations
Mutation Prevalence (%)
40
35
30
25
20
15
10
5
0


A
Response rate to treatment
Treatment
ESA
LEN
LUSPA
HMA
27
58
18
37
0
10
20
30
40
50
60
70
Response rate percent
B
Cum survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.00
12.00
24.00
36.00
48.00
60.00
72.00
84.00
96.00
108.00
120.00
Months from diagnosis
Del5qSF3B1
SF3B1
Del5q
Del5qSf3B1-censored
SF3B1-censored
Del5q-censored