PTPN11 mutations define a rare but highly adverse subset of myelodysplastic syndromes

PTPN11 encodes the protein SHP2 and acts as a stimulator of the RAS/MAPK pathway. Gain-of-function mutations in *PTPN11* are associated with Noonan Syndrome, juvenile myelomonocytic leukemia (JMML), and hematological neoplasms.[1] In a study of 78 patients spanning the spectrum of myeloid neoplasms, *PTPN11* mutations were associated with poor overall survival (OS), but this study included only 14 patients with myelodysplastic syndrome (MDS).[2] Therefore, the clinical and genetic characteristics of *PTPN11*-mutated (*PTPN11*mut) MDS require further evaluation.

To better characterize *PTPN11*mut MDS, we analyzed a cohort of 1,783 patients with newly diagnosed MDS (World Health Organization 2016) and available *PTPN11* testing presenting to our center between 2011 and 2023. This study was approved by the institutional review board. *PTPN11* mutations were rare and identified in only 30 (2%) patients. *PTPN11* mutations were mostly located within the autoinhibitory N-SH2 domain (14/30, 47%) or PTPase (14/30, 47%) domain as previously described (Figure 1A).[1,3] Germline testing was not routinely performed, but this cohort did not include any known cases of Noonan Syndrome or RASopathy. The median age of the patients with *PTPN11*mut MDS was 67 years (range, 39-82) and eight (27%) had therapy-related disease. When compared to *PTPN11*-wild-type (*PTPN11*wt) patients, those with *PTPN11* mutations were more likely to be female (70% *vs*. 35%; *P*<0.001), had lower baseline hemoglobin (median 9.0 *vs*. 9.4 g/dL; *P*=0.047), higher bone marrow blasts (median 9.5% *vs*. 4.0%; *P*<0.001), higher revised International Prognostic Scoring System (IPSS-R) scores (median 6.0 *vs*. 4.0; *P*=0.004), and were more likely to have IPSS-R very

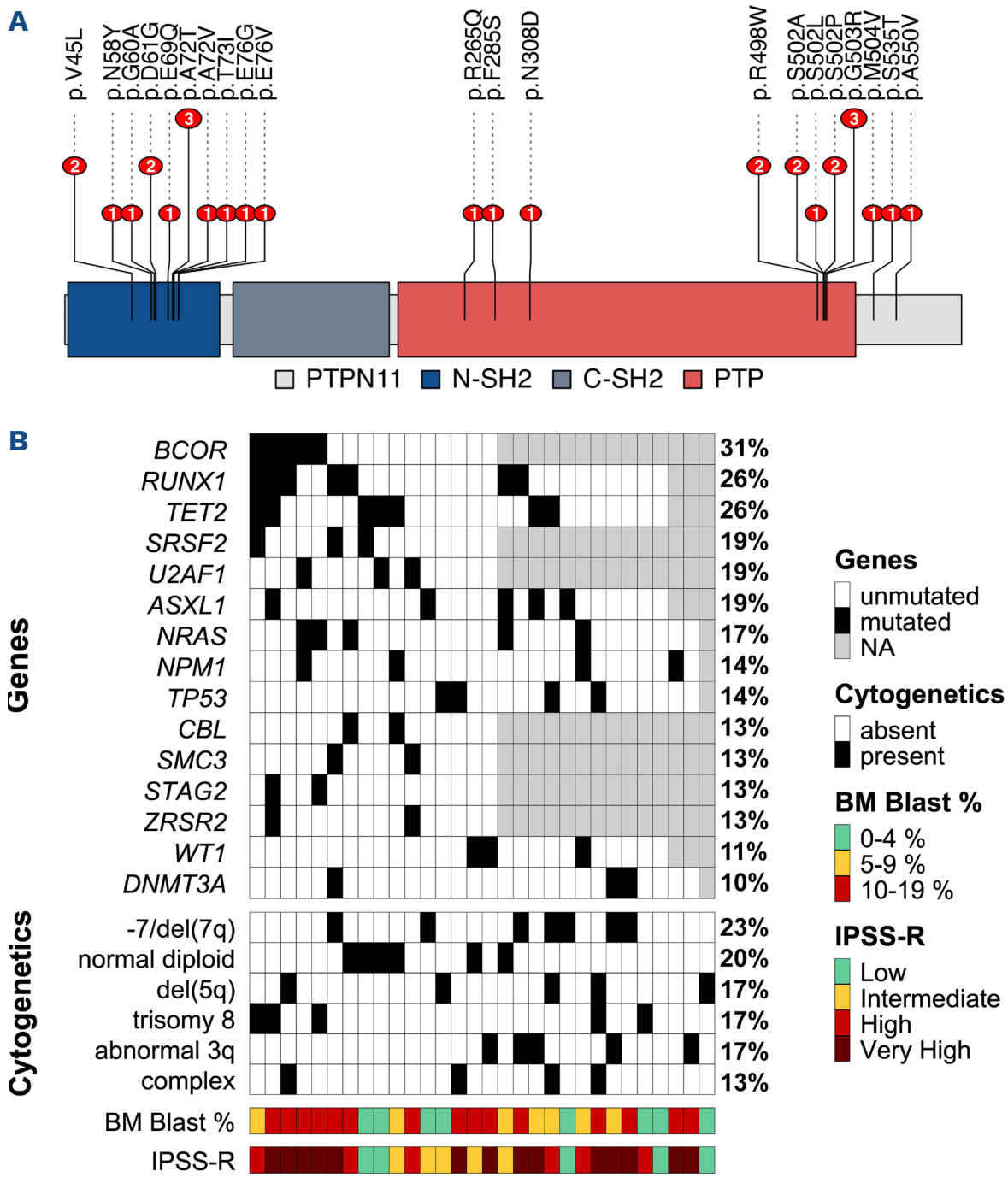

Figure 1. Genetic characteristics of *PTPN11*-mutated myelodysplastic syndrome. (A) Lollipop plot depicting *PTPN11* mutations identified in this cohort. (B) Oncoprint depicting co-mutations present in ≥10% of patients, cytogenetic findings present in ≥10% of patients, bone marrow (BM) blast percentage, and revised International Prognostic Scoring System (IPSS-R) scores in patients with *PTPN11*-mutated myelodysplasticsyndrome. NA: not available.

high-risk disease (47% *vs*. 25%; *P*=0.037) (Table 1). Although PT*PNN11*mut MDS had a higher frequency of IPSS-M very high risk compared to *PTPN11*wt, this was not statistically significant. There were no significant differences in sex distribution between the two *PTPN11* mutation types. The most common cytogenetic findings in *PTPN11*mut MDS were -7/del(7q) (23%), normal cytogenetics (20%), del(5q) (17%), trisomy 8 (17%), and abnormal 3q (17%). The most common co-mutations were *BCOR* (5/16, 31%), *RUNX1* (7/27, 26%), *TET2* (7/27, 26%), *SRSF2* (3/16, 19%), *U2AF1* (3/16, 19%), and *ASXL1* (5/27, 19%) (Figure 1B).

The most common treatment consisted of hypomethylating agent (HMA)-based therapy in 15 (50%) patients, including six (20%) treated with HMA monotherapy and nine (30%) with HMA plus a second agent on clinical trial (either rigosertib, midostaurin, telaglenastat, ipilimumab, sabatolimab, durvalumab, magrolimab, or lenalidomide). The remaining patients received acute myeloid leukemia (AML)-type therapy, including intensive chemotherapy (high-dose cytarabine-based) in two (7%) patients, low-intensity chemotherapy (cladribine plus low-dose cytarabine) in two (7%) patients, and HMA plus venetoclax in one (3%) patient. Ten (33%) patients received best supportive care or unknown therapy. Seven (23%) patients underwent allogeneic stem cell transplantation (SCT) after a median of 5.0 months.

Eighteen (60%) patients were evaluable for response per the International Working Group (IWG) 2023 criteria. The overall response rate was 39% (7/18, consisting of 7 complete

Table 1. Baseline characteristics in *PTPN11*-mutated *versus PTPN11*-wild-type myelodysplastic syndrome.

Variable	*PTPN11*-mutated MDS N=30 (1.68%)	*PTPN11*-wild-type MDS N=1,753 (98.3%)	*P*[1]
Age, years, median (range)	67 (39-82)	69 (18-94)	0.338
Sex, N (%) Male Female	 9 (30) 21 (70)	 1,132 (65) 621 (35)	<0.001
Therapy-related MDS, N (%)	8 (27)	557 (32)	0.693
Hemoglobin, g/dL, median (range)	9.0 (6.1-13.7)	9.4 (3.2-16.5)	0.047
Platelets, x10^9/L, median (range)	74 (7-456)	88 (5-807)	0.482
White blood cells, x10^9/L, median (range)	3.30 (0.70-9.00)	3.10 (0.50-185.10)	0.738
Absolute neutrophil count, x10^9/L, median (range)	1.20 (0.10-6.21)	1.45 (0.02-112.91)	0.633
Bone marrow blasts, %, median (range)	9.5 (1.0-19.0)	4.0 (0.0-19.0)	<0.001
Cytogenetic risk by IPSS-R Very Good Good Intermediate Poor Very Poor	 0 (0) 10 (33) 10 (33) 7 (23) 3 (10)	 44/1,716 (3) 842/1,716 (49) 264/1,716 (15) 167/1,716 (10) 399/1,716 (23)	0.006
IPSS-R score, median (range)	6.0 (2.0-9.0)	4.0 (0.0-10.0)	0.004
IPSS-R higher *versus* lower risk, N (%) >3.5 points ≤3.5 points	 22 (73) 8 (27)	 957/1,714 (56) 757/1,714 (44)	0.064
IPSS-R category, N (%) Very Low Low Intermediate High Very High	 0 (0) 5 (17) 5 (17) 6 (20) 14 (47)	 189/1,714 (11) 446/1,714 (26) 354/1,714 (21) 300/1,714 (18) 425/1,714 (25)	0.037
IPSS-M category, N (%) Very Low Low Moderate Low Moderate High High Very High	 0 (0) 1/15 (7) 1/15 (7) 2/15 (13) 2/15 (13) 9/15 (60)	 66/1,039 (6) 218/1,039 (21) 141/1,039 (14) 94/1,039 (9) 190/1,039 (18) 330/1,039 (32)	0.283

[1]Wilcoxon rank sum test; Fisher's exact test. IPSS-R: revised International Prognostic Scoring System; MDS: myelodysplastic syndrome; IPSS-M: molecular International Prognostic Scoring System.

remissions [CR]). Interestingly, four of five (80%) patients treated with AML-type therapy achieved CR (1 FLAG-IDA, 2 cladribine/low-dose cytarabine, and 1 HMA plus venetoclax) compared to only three of 13 (23%) patients treated with HMA-based therapy. HMA responses were all with HMA-based doublets (combined with rigosertib in 1 patient, ipilimumab in 1 patient, and magrolimab in 1 patient). We observed no formal responses with single-agent HMA. There were no significant differences in the rate of CR between the two types of *PTPN11* mutations (CR rate 20% with N-SH2 domain *vs*. 50% with PTPase domain mutations; *P*=0.3). The rate of AML transformation was four of 15 (27%) with HMA-based therapy and one of five (20%) with AML-type therapy (*P*>0.999). With a median follow-up time of 40.2 months, the median OS was 12.7 months in *PTPN11*mut MDS *versus* 25.6 months in *PTPN11*wt (MDS (*P*=0.015; Figure 2A). OS in *PTPN11*mut MDS (12.7 months) was similar to that of *TP53*mut MDS (11.5 months; *P*=0.173) and markedly worse than other high-risk MDS with *PTPN11*wt/*TP53*wt (26.2 months; *P*<0.01; Figure 2B). When matched 3:1 with controls matched for age, IPSS-R category, and *TP53* status, the median OS was 12.7 months in *PTPN11*mut MDS *versus* 17.0 months in *PTPN11*wt MDS (*P*=0.22). When matched 3:1 using age, IPSS-M category (only available in 15 *PTPN11*mut patients), and *TP53* status, the median OS was 13.8 in *PTPN11*mut MDS *versus* 19.9 months in *PTPN11*wt MDS (*P*=0.53).

We next performed subset analyses for OS within the *PTPTPN11*mut cohort. When stratified by receipt of HMA-based (N=15) *versus* AML-type (N=5) therapy, the median OS was not significantly different between therapy types (median OS 12.7 months with HMA-based therapy *vs*. 16.5 months with AML-type therapy; *P*=0.38). There were no significant differences in OS when patients were stratified by *PTPN11* mutation type (N-SH2 *vs*. PTPase domain), baseline blast %, or IPSS-R risk. The two patients with isolated *PTPN11* mutations (no known co-mutations) were alive at a follow-up of 1.6 and 7.9 months, respectively. Therefore, although patient numbers were small, these subset analyses did not clearly identify a group of patients with favorable outcomes within the *PTPN11*mut cohort. Four of the six patients with *PTPN11* mutations who survived beyond 2 years received allogeneic SCT, indicating an important role for this treatment modality.

We and others previously identified an adverse prognostic impact of *PTPN11* mutations in AML.[4-6] A previous study suggested *PTPN11* mutations may be similarly adverse in MDS (N=14).[2] Our present observations confirm and expand the findings of Swoboda and colleagues. *PTPN11* mutations appear to be very rare in MDS (<2% of cases) but are associated with a highly adverse prognosis, both in terms of response rates and OS. We confirmed the association between *PTPN11* mutations and female sex, increased bone marrow blasts, and higher IPSS-R risk as well as common co-mutations in *BCOR, RUNX1, TET2, SRSF2, U2AF1*, and *ASXL1*, similar to other reports.[2] Co-mutations in *NPM1* and *FLT3*-internal tandem duplications appeared less common in our MDS cohort compared to *PTPN11*mut AML.[4,6] Notably, abnormalities in chromosome 3q, generally rare events in MDS, appeared over-represented in our cohort, being identified in 17% of patients.

Although our patient numbers were too small for definitive conclusions, we noted increased response rates with AML-style therapy (80%) compared to HMA-based therapy (23%). Notably, no patients had a formal response to single-agent HMA as was also noted by Swoboda and colleagues.[2] This may be related to the fact that *PTPN11* mutations activate the RAS/MAPK pathway, which is known to confer resistance to HMA, and may be more sensitive to cytarabine-based regimens.[7,8] However, the increased response rates with AML-type therapy did not translate to improved OS within the limitations of our small cohort. Importantly, most long-term survivors underwent allogeneic SCT.

A limitation of our study was the frequent co-occurrence of

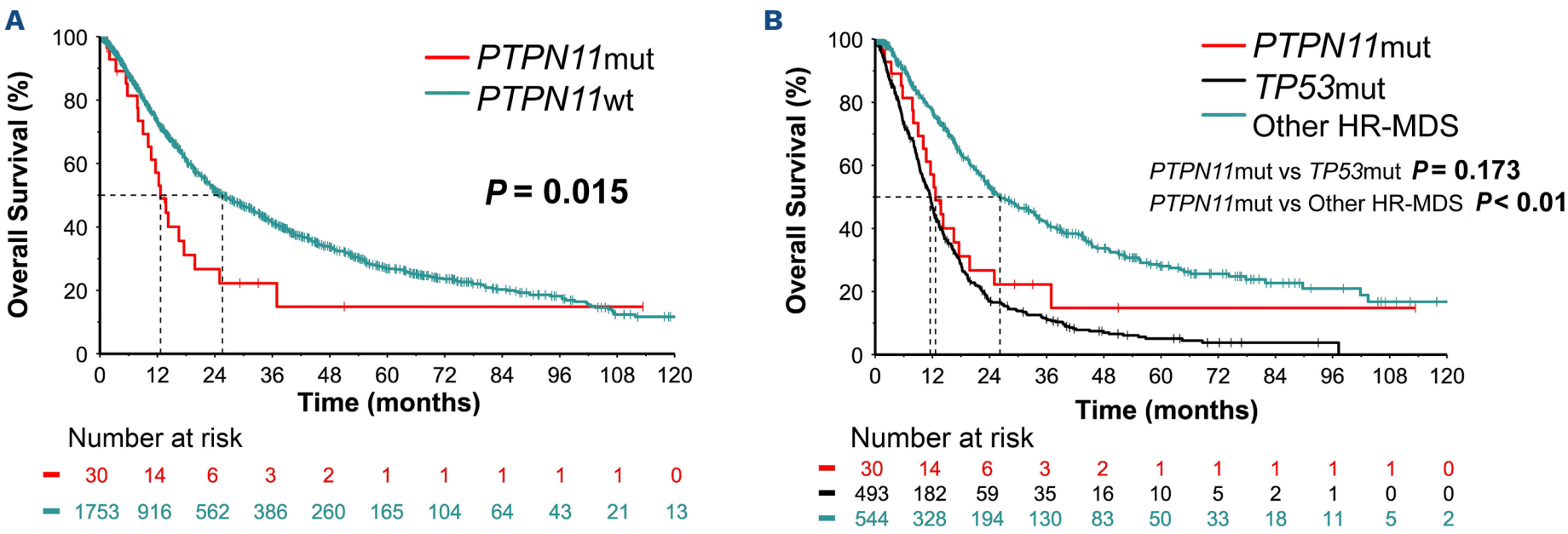

Figure 2. Clinical outcomes of *PTPN11*-mutated myelodysplastic syndrome. (A) Overall survival from diagnosis in patients with *PTPN11*-mutated (*PTPN11*mut) *versus PTPN11*-wild-type (*PTPN11*wt) myelodysplastic syndrome (MDS). (B) Overall survival from diagnosis in *PTPN11*mut *versus TP53*mut MDS *versus* other high-risk (HR)-MDS.

other adverse risk disease features with *PTPN11* mutations, specifically *RUNX1* mutations, monosomy 7/del(7q), and chromosome 3q abnormalities. The small size of our cohort precluded a multivariate analysis to elucidate the specific contribution of *PTPN11 versus* other factors on outcomes. We conclude that a proposed approach to *PTPN11*mut MDS may consist of more aggressive AML-type therapy and/or allogeneic SCT or treatment on a clinical trial, possibly with RAS pathway targeted therapies. Larger patient series are needed to establish the optimal therapy for *PTPN11*mut MDS.

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Contributions

ABaz and HK designed the study. ABaz and ABat performed the data analysis and generated the figures. ABaz performed the statistical analyses. HK and GGM provided ressources. ABaz wrote the manuscript. All authors critically reviewed the manuscript and provided feedback for the final version.

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Data-sharing statement

The data used for this study is not publicly available in order to protect patient confidentiality. Reasonable requests for de-identified data should be directed to the corresponding author.

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