Impact of Mutational Status on Clinical Response to Imetelstat in Patients With Lower-Risk Myelodysplastic Syndromes in the IMerge Phase 3 Study

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Introduction

- In patients with MDS, *SF3B1* (involved in RNA splicing), *TET2, DNMT3A*, and *ASXL1* (involved in epigenetic regulation) are commonly mutated genes, and quantification of these and other gene mutations indicates disease burden and guides disease management[1-9]
  - In particular, a mechanistic link between the high prevalence of the *SF3B1* mutation in MDS with ring sideroblasts has been established[1-3,10]
- Imetelstat is a first-in-class, direct and competitive inhibitor of telomerase activity that specifically targets dysplastic clones, enabling recovery of effective hematopoiesis[11-14]
- In the IMerge phase 3 clinical trial (NCT02598661) of patients with RBC transfusion-dependent non-del(5q) LR-MDS relapsed/refractory to/ineligible for ESAs, imetelstat showed higher RBC-TI for ≥8 weeks, ≥24 weeks, and ≥1 year (40%, 28%, and 18%) than placebo (15%, 3%, and 2%)[15]
  - Additionally, compared with placebo, treatment with imetelstat improved cytogenetic response rate, had a higher rate of patients achieving ≥50% reduction in bone marrow RS cells (41% vs 10%) and greater VAF reduction of the *SF3B1, TET2, DNMT3A,* and *ASXL1* genes that correlated with clinical end points of RBC-TI response, longer duration of TI, and increase in hemoglobin levels[16]

Aim

- To evaluate the impact of MDS-associated mutations on the clinical efficacy (RBC-TI response rates) of imetelstat in patients with LR-MDS enrolled in IMerge

Methods

- Mutations of 36 genes associated with MDS were tested by NGS on DNA samples from peripheral blood collected at study entry
  - After DNA extraction from leukocytes, a targeted, amplicon-based NGS was performed at Quest Diagnostics using DNA bait-capture methodology on the NextSeq® (Illumina®) platform and a LeukoVantage® MDS Gene Panel covering 36 MDS-relevant genes
  - Spectrum of *SF3B1* hot-spot mutations included E622D, R625C/L/G, H662Q/N/D/Y, T663P, K666R/T/Q/N, K700E, A744P, and E783K
- Additional analysis of RBC-TI responses was performed across 4 mutation subgroups, defined based on genes involved in different biological functions,[17] including:
  - RNA spliceosome (*SF3B1, U2AF1, SRSF2, and ZRSR2*)
  - Epigenetic modifiers (*TET2, DNMT3A, IDH1, IDH2, ASXL1,* and *EZH2*)
  - Transcription regulation (*RUNX1, BCOR, ETV6, SETBP1, GATA2, CEBPA, PHF6, NPM1,* and *STAT3*)
  - Receptors/kinases (*CSF3R, FLT3, JAK2, KRAS, KIT, MPL, NRAS,* and *PTPN11*)
- Poor-prognosis mutation was defined as presence of *TP53, EZH2, ETV6, RUNX1,* or *ASXL1*[18]
- For between-group comparisons within each mutation status group, the *P* value was based on Fisher exact test

Results

Baseline mutational profile

- As of October 13, 2022, baseline mutation data were available in 165 of 178 patients enrolled in IMerge phase 3; mutated genes with frequency >10% in this study are listed in **Table 1**
- Of patients with mutation data, 161 (97.6%) had ≥1 mutation detected: 107 patients (97.3%) in the imetelstat-treated group and 54 patients (98.2%) in the placebo-treated group
- Proportions of frequently occurring mutations were well balanced between the treatment groups (**Table 1**)
- *SF3B1* mutations were detected at baseline in nearly 75% of the patients in the imetelstat-treated group and 78% of those in the placebo-treated group
- Poor-prognosis mutations were identified in 20% of samples in either treatment group: each group had 2 patients with *TP53* and 2 patients with *RUNX1* mutations, and there were 18 vs 6 patients with *ASXL1* mutations, 2 vs 1 patient with *ETV6* mutations, and 0 vs 2 patients with *EZH2* in the imetelstat- vs placebo-treated groups, respectively

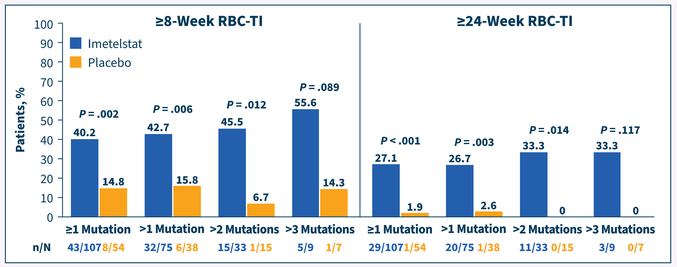
Table 1. Baseline Mutational Profile

Patients, n (%)	Imetelstat (n = 110)	Placebo (n = 55)
≥1 mutation >1 mutation >2 mutations >3 mutations	107 (97.3) 75 (68.2) 33 (30.0) 9 (8.2)	54 (98.2) 38 (69.1) 15 (27.3) 7 (12.7)
***SF3B1* mutations**	82 (74.5)	43 (78.2)
***TET2* mutations**	40 (36.4)	14 (25.5)
***DNMT3A* mutations**	19 (17.3)	9 (16.4)
***ASXL1* mutations**	18 (16.4)	6 (10.9)
***CUX1* mutations**	14 (12.7)	7 (12.7)
RNA spliceosome	96 (87.3)	47 (85.5)
Epigenetic modifiers	69 (62.7)	29 (52.7)
Transcription regulation	10 (9.1)	9 (16.4)
Receptors/kinases	5 (4.5)	2 (3.6)
Poor-prognosis genes	22 (20.0)	11 (20.0)

RBC-TI by number of baseline mutations

- In patients who had ≥1 mutation detected, imetelstat significantly improved the 8-week (*P* = .002) and 24-week (*P* < .001) RBC-TI response rates compared with placebo (**Fig. 1**)
  - Significant rate differences were also noted in patients who had >2 mutations at baseline: 45.5% vs 6.7% for ≥8-week RBC-TI (*P* = .012) and 33.3% vs 0% for ≥24-week RBC-TI (*P* = .014) with imetelstat vs placebo, respectively

Figure 1. Summary of RBC-TI Response Rates by Number of Baseline Mutations



RBC-TI rates by baseline mutation status of the most commonly mutated genes

- Among patients assessed for genes commonly mutated in MDS, those harboring *SF3B1* mutations at baseline had significantly higher rates of RBC-TI responses with imetelstat vs placebo at both 8 weeks (48.8% vs 16.3%; *P* = .001) and 24 weeks (35.4% vs 2.3%; *P* < .001; **Fig. 2**)
- Similar trends were seen with the other commonly mutated genes (**Fig. 2**) and in patients with *SF3B1* hot-spot mutations (≥2 patients in either group), albeit the sample size was small (**Table 2**)

Figure 2. Summary of RBC-TI Response Rates by Baseline Mutation Status of the Most Commonly Mutated Genes (>10% of Patients in Either Group)

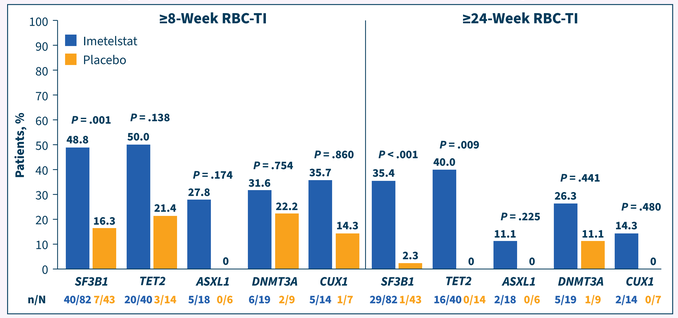


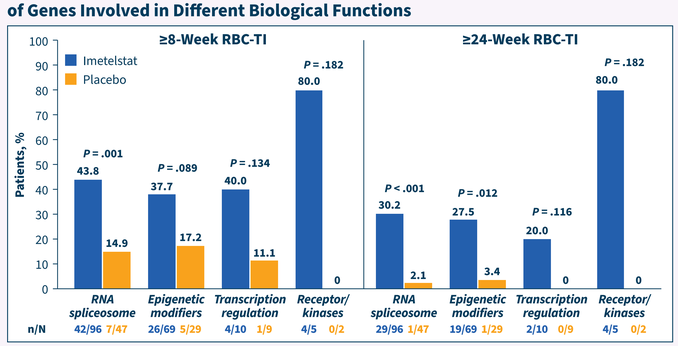
Table 2. Summary of RBC-TI Response Rates by Baseline Mutation Status of *SF3B1* Hot-Spot Mutations

Patients, n/N (%)	≥8-Week RBC-TI		≥24-Week RBC-TI	
	Imetelstat (n = 82)	Placebo (n = 43)	Imetelstat (n = 82)	Placebo (n = 43)
E622D	2/8 (25.0)	1/2 (50.0)	2/8 (25.0)	1/2 (50.0)
R625C/L/G	4/7 (57.1)	0/5 (0)	2/7 (28.6)	0/5 (0)
H662Q/N/D/Y	7/12 (58.3)	0/5 (0)	6/12 (50.0)	0/5 (0)
T663P	2/2 (100)	0	2/2 (100)	0
K666R/T/Q/N	2/6 (33.3)	0/7 (0)	0/6 (0)	0/7 (0)
K700E	18/41 (43.9)	5/22 (22.7)	12/41 (29.3)	0/22 (0)
A744P	2/2 (100)	0	2/2 (100)	0
E783K	1/2 (50.0)	0	1/2 (50.0)	0

RBC-TI rates by baseline mutation status of 4 sets of genes involved in different biological functions

- Consistent with the presence of baseline *SF3B1* mutations, patients with mutations in genes regulating RNA spliceosome had significantly higher rates of ≥8-week and ≥24-week RBC-TI responses with imetelstat than with placebo: 43.8% vs 14.9% (*P* = .001) and 30.2% vs 2.1% (*P* < .001), respectively (**Fig. 3**); similar trends were noted with the other gene sets, albeit there was no significant difference between groups

Figure 3. Summary of RBC-TI Response Rates by Baseline Mutation Status of 4 Sets of Genes Involved in Different Biological Functions



RBC-TI rates by baseline mutation status of poor-prognosis genes

- Imetelstat treatment indicated higher ≥8-week (**Table 3**) and ≥24-week RBC-TI response rates versus placebo in patients with poor-prognosis genes mutated at baseline: 31.8% vs 0% and 9.1% vs 0%, respectively

Table 3. Summary of 8-Week RBC-TI Response Rates by Baseline Mutation Status of Poor-Prognosis Genes

Patients, n/N (%)	Imetelstat (n = 22)	Placebo (n = 11)
Poor prognosis	7/22 (31.8)	0/11 (0)
***ASXL1* mutations**	5/18 (27.8)	0/6 (0)
***TP53* mutations**	2/2 (100)	0/2 (0)
***ETV6* mutations**	1/2 (50.0)	0/1 (0)
***RUNX1* mutations**	0/2 (0)	0/2 (0)
***EZH2* mutations**	0	0/2 (0)

Conclusions

- **Overall, in patients with various baseline mutational profiles, imetelstat treatment led to higher RBC-TI rates than placebo**
- **A significantly higher percentage of imetelstat-treated than placebo-treated patients with baseline mutations in *SF3B1*, a gene commonly mutated in MDS and involved in regulation of RNA spliceosome, achieved 8- and 24-week RBC-TI**
- **RBC-TI responses in patients receiving imetelstat occurred regardless of the presence of mutations associated with poor prognosis or the number of mutations**
- **RBC-TI responses with imetelstat were observed across different molecularly defined subgroups, suggesting that clinical benefit of imetelstat in patients with LR-MDS is independent of the underlying molecular pattern**

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ABBREVIATIONS

ASXL1, additional sex combs like-1; BCL, B-cell lymphoma; *BCOR*, BCL-6 corepressor; *CEBPA*, CCAAT enhancer-binding protein alpha; *CSF3R*, colony-stimulating factor 3 receptor; *CUX1*, cut-like homeobox 1; *DNMT3A*, DNA (cytosine-5)-methyltransferase 3A; ESA, erythropoiesis-stimulating agent; *ETV6*, ETS variant transcription factor 6; *EZH2*, enhancer of zeste 2 polycomb-repressive complex 2 subunit; *FLT3*, Fms-like tyrosine kinase 3; *GATA*, glutamyl-tRNA amidotransferase, subunit A; *GATA2*, GATA-binding protein 2; *IDH*, isocitrate dehydrogenase (NADP+); *JAK2*, Janus kinase 2; *KRAS*, Kirsten rat sarcoma virus; LR-MDS, lower-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; NADP, nicotinamide adenine dinucleotide phosphate; NGS, next-generation sequencing; NPM, nucleophosmin; *NRAS*, neuroblastoma RAS; *PHF6*, PHD finger protein 6; *PTPN11*, protein tyrosine phosphatase nonreceptor type 11; RBC, red blood cell; RS, ring sideroblasts; *RUNX1*, RUNX family transcription factor 1; *SETBP1*, SET-binding protein 1; *SF3B1*, splicing factor 3b subunit 1; *SRSF2*, serine and arginine-rich splicing factor 2; *STAT3*, signal transducer and activator of transcription 3; *TET2*, tet methylcytosine dioxygenase 2; TI, transfusion independence; *U2AF1*, U2 small nuclear RNA auxiliary factor 1; VAF, variant allele frequency; *ZRSR2*, zinc finger (CCCH type), RNA-binding motif and serine/arginine rich 2.

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