Imetelstat in Patients With del(5q) Lower-Risk Myelodysplastic Syndromes: Results From the IMerge Clinical Trial

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Introduction

- The telomerase inhibitor imetelstat is approved for treating select patients with lower-risk myelodysplastic syndromes (LR-MDS) and red blood cell (RBC) transfusion-dependent anemia based on the IMerge trial (NCT02598661)[1,2]
  - In IMerge Phase 3, imetelstat resulted in durable RBC transfusion independence (TI) versus placebo in patients with non-del(5q) LR-MDS, which correlated with reductions in cytogenetic and molecular clonal burden, suggesting disease-modifying potential[3]
- Although patients with del(5q) MDS were excluded from IMerge Phase 3, they could enroll in the IMerge Phase 2/QTc substudy[3-5]
- Telomerase activity supports survival of malignant hematopoietic progenitor cells regardless of cytogenetic subtype, suggesting the mechanistic applicability of telomerase inhibition in this patient population[6]

Study Design and Methods

IMerge Phase 2 + QTc Pooled Patients

- ✓ Del(5q) MDS relapsed/refractory to/ineligible for erythropoietin-stimulating agents
- ✓ RBC transfusion dependent (≥4 units/8 weeks)
- ✓ Prior lenalidomide (LEN) or a hypomethylating agent allowed

Treatment

7.1 mg/kg imetelstat active dose IV every 4 wk

Data cutoff:
October 13, 2023 (Phase 2)
October 13, 2024 (QTc substudy)

Results

- Eight patients with del(5q) LR-MDS were included (Phase 2, n=7; QTc substudy, n=1); baseline characteristics are in **Table 1**
- Median serum erythropoietin level: 601.2 mU/mL (107.0-750.0)
- Treatment cycles: 5-66; imetelstat dose intensity: 4.3-7.1 mg/kg

Efficacy

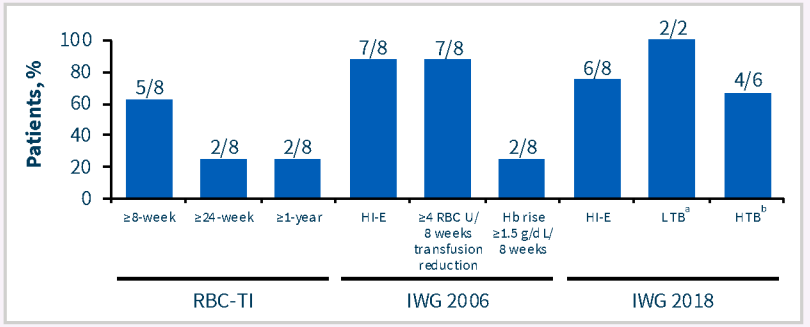
- Imetelstat was efficacious across outcome measures (**Figure 1**)
- Median hemoglobin rise in the ≥8-week RBC-TI period: 2.5 g/dL
- Notably, all patients who had not received prior LEN (n=4) experienced ≥8-week RBC-TI and hematologic improvement-erythroid per International Working Group (IWG) 2006/IWG 2018 criteria with imetelstat (data not shown)

Table 1. Baseline Characteristics of Patients With del(5q) LR-MDS

Patient	IPSS	IPSS-R prognostic risk	RS status	EPO, mU/mL	Transfusion burden / 16 weeks per IWG 2018	Hb, g/dL	Platelets, ×10⁹/L	Neutrophils, ×10⁹/L	Prior therapy[a]
1	Low	Low	Negative	107.0	LTB	7.4	800	2.52	ESA
2	Int-1	Intermediate	Negative	NA	HTB	8.4	210	2.03	ESA, LEN, AZA/DEC
3	Low	Low	Negative	518.8	HTB	7.7	97	3.50	ESA, LEN, AZA/DEC
4	Low	Low	Negative	601.2	HTB	7.5	295	3.64	
5	Int-1	Low	Negative	750.0	HTB	8.1	333	1.77	ESA
6	Low	Very low	Negative	750.0	HTB	7.8	101	1.60	
7	Int-1	Intermediate	Negative	749.9	LTB	8.1	569	1.63	ESA, LEN
8	Low	Low	Negative	311.0	HTB	7.0	139	2.77	ESA, LEN, LUSP

AZA/DEC, azacitidine/decitabine; EPO, erythropoietin; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; HTB, high transfusion burden; Int-1, intermediate-1; IPSS, International Prognostic Scoring System; IPSS-R, Revised IPSS; IWG, International Working Group; LEN, lenalidomide; LR, lower risk; LTB, low transfusion burden; LUSP, luspatercept; MDS, myelodysplastic syndromes; NA, not available; RS, ring sideroblast.
[a]Other prior therapy may have been received by patients.

Figure 1. Efficacy Parameters



Hb, hemoglobin; HI-E, hematologic improvement-erythroid; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; TI, transfusion independence; U, units.
[a]LTB defined as 3-7 RBC U in 16 weeks in ≥2 transfusion episodes; HI-E defined as RBC-TI ≥16 weeks. [b]HTB defined as ≥8 RBC U in 16 weeks in ≥2 transfusion episodes; HI-E defined as RBC-TI ≥16 weeks or ≥50% reduction in RBC U in 16 weeks.

Safety

- Seven serious treatment-emergent adverse events occurred in 4/8 (50.0%) patients (brain contusion, extradural hematoma, febrile neutropenia, thrombosis mesenteric vessel, atypical pneumonia, pneumonia, and neurodegenerative disorder); none were considered related to imetelstat
- Six of 8 (75.0%) patients had grade 3 or 4 neutropenia; 3 of 8 (37.5%) had grade 3 or 4 thrombocytopenia. Most grade 3 and 4 neutropenia (89.7%) and thrombocytopenia (87.5%) events resolved ≤4 weeks

Discussion

- In this post hoc analysis, imetelstat showed activity in patients with del(5q) LR-MDS, including those without prior lenalidomide (current standard of care in first-line del(5q) LR-MDS), although the number of patients was small
- Results are biologically consistent with the mechanism of action of imetelstat and provides preliminary evidence supporting further evaluation of imetelstat in patients with del(5q) LR-MDS with and without prior lenalidomide

References

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Disclosure

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