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

Valeria Santini,1,2; Amer M. Zeidan,3; Pierre Fenaux,4; Yvazn F. Madanat,5; Tammy Berry,5; Fayle Feller,6; Libo Sun,7; Qi Xi,8; Ying Wan,8; Fen Huang,9; Michael R. Savona,10; and Uwe Platebecker11

1MDS Unit, Hematology, AOUC, University of Florence, Florence, Italy; 2Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; 3Hôpital Saint-Louis, Université de Paris 7, Paris, France; 4Harbans C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; 5Erasmus University Rotterdam, Rotterdam, The Netherlands; 6Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; 7Aston University, Birmingham, United Kingdom; 8University Medical Center, Leipzig, Germany; 9UT Southwestern Medical Center, Dallas, TX, USA; 10NOS, University of Florence, Florence, Italy; 11University Medical Center, Leipzig, Germany

Methods

Mutations of 36 genes associated with MDS were tested by NGS on DNA samples from peripheral blood collected at study entry on 63 patients with MDS – independent of the underlying molecular pattern – enabling recovery of effective hematopoiesis.

In patients with MDS, SF3B1 (involved in splicing regulation) is commonly mutated genes, and quantification of these and other genes indicates disease burden and guides disease management.6,17

In particular, a mechanistic link between the high prevalence of the SF3B1 mutation and the efficacy of imetelstat has been established.18

Imetelstat is a first-in-class, direct and competitive inhibitor of telomerase activity that specifically targets dysplastic clones, enabling recovery of effective hematopoiesis.19,20

In the iMERGE phase 3 clinical trial (NCT02586612), patients with RBC-transcripts dependent non-del5q14 LR-MDS related to ineligible for ESA’s, imetelstat showed higher RBC-TI for all weeks, 42 weeks, and 25 year (40%, 28%, and 18%) than placebo (15%, 3%, and 26%).

Additionally, compared with placebo, treatment with imetelstat improved cytokine response rate, with a higher rate of patients achieving ≤5% reduction in bone marrow RS cells (41% vs 10%) and greater VAF reduction of the SF3B1, TET2, DNMT3A, and ASXL1 genotypes that correlated with clinical end points of RBC-TI response, longer duration of T1, and increase in hemoglobin levels.5

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 splicing, achieved 8- and 24-week RBC-TI rates.

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.

References