EFFICACY OF IMETELSTAT IS INDEPENDENT OF MOLECULAR SUBTYPES IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER RISK MDS (LR-MDS) RELAPSED/REFRACTORY (R/R) TO ERYTHROPOIESIS STIMULATING AGENTS (ESA)

EUROPEAN HEMATOLOGY ASSOCIATION

EP910

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U.Platzbecker[1], P. Fenaux[2], K. V. Eygen[3], A. Raza[4], U. Germing[5], P. Font[6], M. Diez-Campelo[7], S. Thepot[8], E. Vellenga[9], M. M. Patnaik [10], J. H. Jang[11], L. Sherman[12], S. Dougherty[12], T. Berry[12], F. Feller[12], L. Sun[12], Y. Wan[12], A. Rizo[12], F. Huang[12], V. Santini[13]

[1]University Clinic Leipzig, Leipzig, Germany, [2]Hospital Saint-Louis, Universitey Paris Diderot, Paris, France, [3]Algemeen Ziekenhuis Groeninge, Kortrijk, Belgium, [4]Columbia University Medical Center, New York, United States, [5]Heinrich-Heine-Universität, Düsseldorf, Germany, [6]Hospital General Universitario Gregorio Marañon, Madrid, [7]The University Hospital of Salamanca, Salamanca, Spain, [8]CHU Angers, Angers, France, [9]University Medical Center Groningen, Groningen, Netherlands, [10]Mayo Clinic, Rochester, MN, United States, [11]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic Of, [12]Geron Corporation, Parsippany, NJ, United States, [13]AOU Careggi-University of Florence, Florence, Italy

INTRODUCTION

- Myelodysplastic syndromes (MDS) are characterized by clonal myeloproliferation arising from malignant progenitor cell clones that have multiple genetic abnormalities.[1]
- Patients with red blood cell (RBC) transfusion-dependent (TD), lower risk MDS (LR-MDS) that has relapsed or is refractory to erythropoiesis-stimulating agents (ESAs) have limited treatment options. New approaches are needed.
- Higher telomerase activity, overexpression of human telomerase reverse transcriptase (hTERT) and shorter telomeres predict for shorter overall survival in LR-MDS.[2, 3]
- Imetelstat is a 13-mer lipid-conjugated oligonucleotide that specifically targets the RNA template of human telomerase and is a potent, first-in-class competitive inhibitor of telomerase enzymatic activity[4, 5] (**Figure 1**). It has disease-modifying potential to selectively kill malignant stem and progenitor cells enabling normal blood cell production (**Figure 2**). [6,7]
- IMerge (MDS3001, NCT02598661) is a Phase 2/3 global study of imetelstat for red blood cell (RBC) transfusion dependent (TD), non-del(5q) patients with ESA-R/R LR-MDS. Phase 2 results indicated that imetelstat achieved durable transfusion independence (TI) with a manageable safety profile.[8] With a median follow-up of 24 months for Phase 2, 42%, 32% and 29% of 38 patients achieved ≥8-week (w), ≥24-w and 1-year (y) TI, respectively.[9]

Figure 1. Imetelstat binds to the RNA template as a competitive inhibitor to prevent maintenance of telomeres

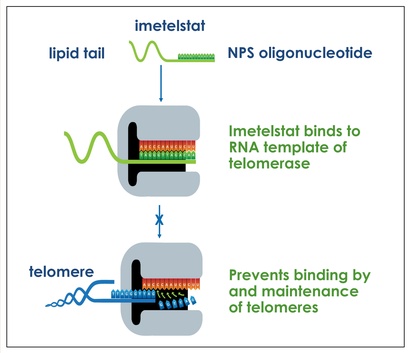
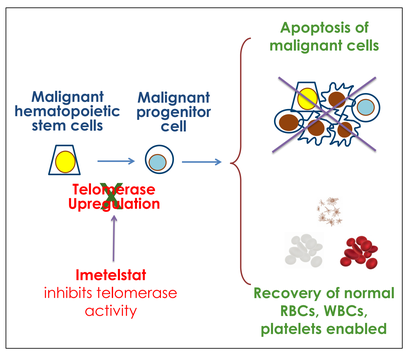


Figure 2. Imetelstat selective killing of malignant stem and progenitor cells enabling normal blood cell production



OBJECTIVES

- To evaluate clinical efficacy of imetelstat in molecularly defined subtypes based on cytogenetic and mutation profiles.

METHODS

- Bone marrow aspirates from screening were used for cytogenetic analysis by karyotyping.
- Peripheral blood samples were collected to analyze mutations by next-generation sequencing using the Illumina TruSight Myeloid Panel of 54 genes.
- Correlation analyses between molecular profiles and clinical efficacy, including TI ≥8-w, ≥24-w, ≥1-y, and hematologic improvement-erythroid (HI-E) response per International Working Group 2006 guidelines, were performed for patients in the Phase 2 part of IMerge study.

RESULTS

Table 1. Durable TI, hematologic improvement with imetelstat treatment

Parameters	n = 38
8-week TI, n (%)	**16 (42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0 (23.1 – 140.9*)**
Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥ 3.0 g/dL during TIc, n (%)	12 (32)
24-week TI, n (%)	**12 (32)**
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	11 (29)
HI-E per IWG 2006, n (%)	**26 (68)**
≥1.5 g/dL increase in Hb lasting ≥ 8 weeks[d], n (%)	13 (34)
Transfusion reduction by ≥ 4 units/8 weeks, n (%)	26 (68)
Duration of HI-E, weeks, median (95% CI)[a]	**92.7 (37.1, 149.4)**)
Major and Minor Response per IWG 2018	
Major response: 16-week TI, n (%)	**14 (37)**
Minor response: ≥ 50% transfusion reduction/16 weeks, n (%)	21 (55)

38 patients with non-del(5q) LR MDS R/R to ESA
Clinical cutoff for analyses: 4 Feb 2020
[a] Kaplan Meier method;
[b] Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment;
[c] Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks).
[d] All patients also achieved 8-week TI.
CI, confidence interval;
Hb, hemoglobin;
HI-E, hematologic improvement-erythroid;
IWG 2006, International Working Group Response Criteria 2006;
TI, Transfusion Independence

***Longest TI > 2.7 years**

Figure 3. Mutation profile and risk groups vs clinical response (N=31 with sequencing data for mutations)

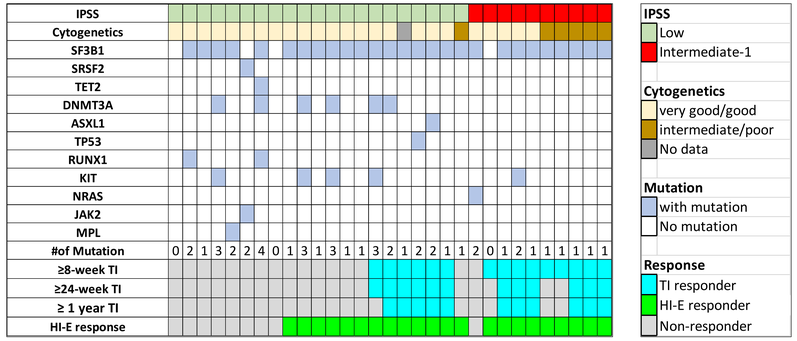


Figure 4. Meaningful & durable TI, HI-E seen in patients across different IPSS risk (A) or cytogenetic risk (B) groups

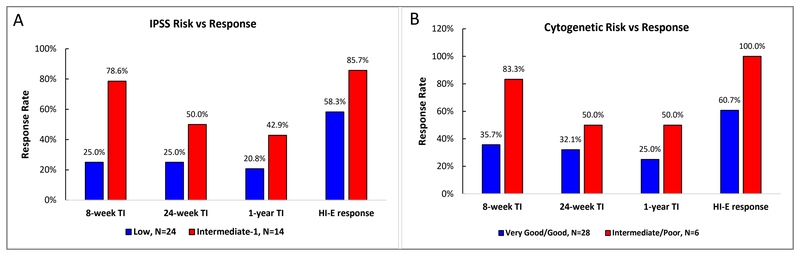


Figure 5. Clinical response was independent of mutation status (A), or mutations in genes involved in different biological functions (B)

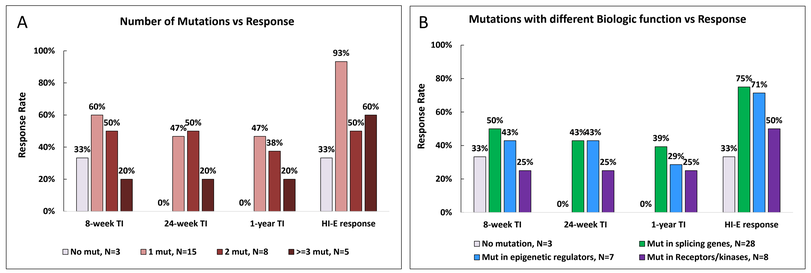
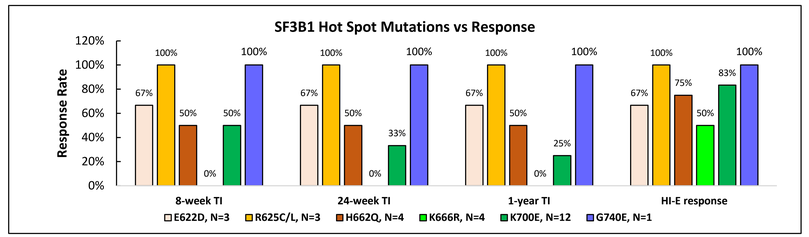


Figure 6. HI-E response was seen in patients with different SF3B1 hot spot mutations, durable TI was observed in patients with all SF3B1 hot spot mutations except K666R



SUMMARY

- Imetelstat treatment showed meaningful and durable TI in 38 heavily TD, non-del(5q), HMA/Len naïve, LR-MDS patients with substantial increase in hemoglobin (**Table 1**).
- No statistically significant difference in response rate was observed in patients between IPSS low and Int-1 risk group or between very good/good and int poor cytogenetic risk groups, though a high rate of TI and HI-E was observed in the poor risk group (**Fig. 4**).
- Of 31/38 patients with baseline mutation data, 28 (90.3%) patients had at least one mutation, among which 15 (53.6%), 8 (28.6%) and 5 (17.9%) patients had 1, 2 and ≥3 mutations, respectively. 3 patients had no mutation detected (**Fig. 3**). Clinical response was independent of mutation status, or number of mutations (**Fig. 5**).
- The most frequently mutated gene was SF3B1 (87.1%, n=27), consistent with the predominance of ring sideroblast phenotypes (n=23). SF3B1 hot spot mutations were detected: 3 (11.1%) E622D, 3 (11.1%) R625C/L, 4 (14.8%) H662Q, 4 (14.8%) K666R, 12 (44.4%) K700E and 1 (3.7%%) G740E, respectively. Durable TI was observed in patients with these hot spot mutations except K666R, and HI-E response was seen in patients with all hot spot mutations (**Fig. 6**).

CONCLUSIONS

Imetelstat demonstrated clinical efficacy across different molecularly defined subgroups of heavily transfused LR-MDS ESA-R/R patients, including those with poor prognosis, who have limited treatment options.

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CONTACT INFORMATION

- IMerge (MDS3001): https://www.geron.com/patients/imerge-study
- ClinicalTrials.gov Identifier:NCT02598661; Email mds3001-info@geron.com

IMerge