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)


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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 dependence (TbD), lower risk MDS (LR-MDS) that has relapsed or is refractory to erythropoiesis-stimulating agents (ESAs) has 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 first-in-class competitive inhibitor of telomerase enzymatic activity.1 (Figure 1). It has a disease-modifying potential to selectively kill malignant stem and progenitor cells enabling normal blood cell production (Figure 2).4, 5 IMiD (MDSX01, NCT02598664) is a Phase 2/3 global study of imetelstat for red blood cell (RBC) transfusion dependent (TbD), non-del(5q) patients with ESA-R/ESA-LR-MDS. Phase 2 results indicated that imetelstat achieved durable transfusion independence (TI) with a manageable safety profile.6 With a median follow-up of 24 months for Phase 2, 42%, 32% and 29% of 38 patients achieved 28-week (w), 224-w and 1-year (y) TI, respectively.7

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-week (w), ≥24-w and 1-year (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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>24-week TI</th>
<th>1-year TI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HI-E response</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Intermediate/Poor, N=6</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>100%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>H662Q, N=4</td>
<td>32.1%</td>
<td>25.0%</td>
</tr>
<tr>
<td>G740E, N=1</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Intermediate-1, N=14</td>
<td>50%</td>
<td>67%</td>
</tr>
<tr>
<td>Mut in splicing genes, N=28</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1 mut, N=15</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

CONCLUSIONS

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

REFERENCES


CONTACT INFORMATION

- iMerge [MDSX01]: https://www.geron.com/patients/imerge-study
- ClinicalTrials.gov Identifier: NCT02598661; Email iMerge@geron.com