IMerge: A Phase 3 Study to Evaluate Imetelstat in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment

Uwe Platzbecker1, Pierre Fenaux2, David P. Steensma3, Koen Van Eygen4, Azra Raza5, Ulrich Germing6, Patricia Font7, Maria Diez-Campelo8, Sylvain Thepot9, Edo Vellenga10, Mrinal M. Patnaik11, Jun Ho Jang12, Laurie Sherman13, Souria Dougherty13, Libo Sun13, Fei Huang13, Ying Wan13, Aleksandra Rizo13, Tymara Berry13, Faye Feller13, Valeria Santini14

1Department of Hematology and Cell Therapy, University Clinic Leipzig, Leipzig, Germany, 2Hospital Saint-Louis, Université Paris Diderot, Paris, France, 3Dana-Farber Cancer Institute, Boston, United States, 4Algemeen Ziekenhuis Groeninge, Kortrijk, Belgium, 5Columbia University Medical Center, New York, United States, 6Klinik für Hämatologie, Onkologie and Klinische Immunologie, Universitätsklinik Düsseldorf, Heinrich-Heine-Universität, Düsseldorf, Germany, 7Department of Hematology, Hospital General Universitario Gregorio Marañón, Madrid, 8Hematology Department, The University Hospital of Salamanca, Salamanca, Spain, 9CHU Angers, Angers, France, 10Department of Hematology, University Medical Center Groningen, Groningen, Netherlands, 11Division of Hematology, Mayo Clinic, Department of Internal Medicine, Rochester, MN, United States, 12Department of Hematology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic Of Korea, 13Geron Corporation, Parsippany, NJ, United States, 14MOS Unit, AOU Careggi-University of Florence, Florence, Italy
Disclosure

- **Presenter:** Uwe Platzbecker, MD
- **Affiliations:** Department of Hematology and Cell Therapy, University Clinic Leipzig, Leipzig, Germany
- **Disclosure:**
  - Honoraria and research grant from BMS, Amgen, Novartis, Jazz
  - Honoraria from Geron
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

Iметelstat: First-in-Class Telomerase Inhibitor with Disease-Modifying Potential

Mechanism of Action

- Potent competitive inhibitor of telomerase activity
- **Structure:** Proprietary 13-mer thio-phosphoramidate (NPS) oligonucleotide, with covalently-bound lipid tail to increase cell permeability
- **Disease-modifying potential:** selective killing of malignant stem and progenitor cells enabling normal blood cell production
IMerge Part 1/Phase 2 of Study

- IMerge is an ongoing global two-part, Phase 2/3 study of imetelstat in RBC TD patients with LR-MDS with a primary endpoint of 8-week RBC Transfusion Independence (TI). Patients in Phase 2 received open-label treatment with imetelstat at 7.5 mg/kg IV q 4 weeks.

- Phase 2 enrolled 57 patients: an initial cohort of 32 patients and an expansion cohort of 25 lenalidomide (len) and hypomethylating agent (HMA) naïve patients without del(5q) based on the results from the initial cohort.

**MDS patients:**
- IPSS Low or Int-1
- Relapsed/Refractory to ESA or EPO >500 mU/ml
- TD: ≥ 4 units RBC/8 weeks over 16 week pre-study period

**Primary Endpoint:** 8-week RBC-TI
**Key Secondary Endpoints:** 24-week RBC TI /Duration of TI /HI-E
## Result from IMerge Part 1/Phase 2 of Study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8-week TI, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Time to onset of 8-week TI, weeks, median (range)</td>
<td></td>
</tr>
<tr>
<td>Duration of TI, weeks, median (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cumulative duration of TI ≥ 8 weeks&lt;sup&gt;b&lt;/sup&gt;, median (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hb rise ≥ 3.0 g/dL during TI&lt;sup&gt;c&lt;/sup&gt;, n (%)</td>
<td>16 (42)</td>
</tr>
<tr>
<td></td>
<td>8.3 (0.1-40.7)</td>
</tr>
<tr>
<td></td>
<td>*<em>88.0 (23.1 – 140.9</em>)**</td>
</tr>
<tr>
<td></td>
<td>12 (32)</td>
</tr>
<tr>
<td><strong>24-week TI, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hb rise ≥ 3.0 g/dL during TI&lt;sup&gt;c&lt;/sup&gt;, n (%)</td>
<td>12 (32)</td>
</tr>
<tr>
<td></td>
<td>11 (29)</td>
</tr>
<tr>
<td><strong>1-year TI, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (29)</td>
</tr>
<tr>
<td><strong>HI-E per IWG 2006, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>≥1.5 g/dL increase in Hb lasting ≥ 8 weeks, n (%)</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Transfusion reduction by ≥ 4 units/8 weeks, n (%)</td>
<td>13 (34)</td>
</tr>
<tr>
<td>Duration of HI-E, weeks, median (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>92.7 (37.1, 149.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Kaplan Meier method;  
<sup>b</sup> Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment;  
<sup>c</sup> Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb/8 weeks).  
CI, confidence interval; Hb, hemoglobin  

*Longest TI > 2.7 years

Platzbecker et al, EHA 2020, S183  
Platzbecker et al, ASH 2020, Abstract #658
Part 2/Phase 3 Study Design

TD non-del(5q) LR-MDS, R/R to ESA, HMA/len naïve
Randomized, double blind, placebo-controlled

Treatment Phase
Imetelstat (n = ~115)
7.5 mg/kg IV q4 weeks, 28-day treatment cycle
Until disease progression, unacceptable toxicity, or withdrawal of consent

Treatment Phase
Placebo (n = ~55)
IV q4 weeks, 28-day treatment cycle
Until disease progression, unacceptable toxicity, or withdrawal of consent

End-of-Treatment Visit
30 ±3 days after end of treatment

Follow-up Phase

Primary endpoint: 8-week RBC TI
Phase 3 Inclusion And Exclusion Criteria

**Inclusion Criteria**

- Man or woman >=18 years of age.
- International Prognostic Scoring System (IPSS) low risk or intermediate-1 risk MDS; non-del(5q).
- RBC transfusion dependent, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to Study Entry; pre-transfusion hemoglobin (Hb) should be less than or equal to 9.0 gram per deciliter (g/dL) to count towards the 4 units total.
- Relapsed/Refractory to ESA or EPO.
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.

**Exclusion Criteria**

- Participant has known allergies, hypersensitivity, or intolerance to imetelstat or its excipients.
- Participant has received an investigational drug or used an invasive investigational medical device within 30 days prior to Study Entry or is currently enrolled in an investigational study.
- Prior treatment with imetelstat.
- Have received corticosteroids greater than 30 milligram per day (mg/day) prednisone or equivalent, or growth factor treatment within 4 weeks prior to study entry.
- Prior treatment with a hypomethylating agent [e.g. azacitidine, decitabine].
- Prior treatment with lenalidomide.
- Has received an erythropoiesis-stimulating agent (ESA) or any chemotherapy, immunomodulatory, or immunosuppressive therapy within 4 weeks prior to study entry (8 weeks for long-acting ESAs).
Study End Points

Primary endpoint:
- 8-week RBC TI.

Secondary endpoints:
- 24-week RBC TI; Duration of TI; Time to 8-week RBC TI.
- HI-E per IWG 2006; MDS response per IWG.
- Overall survival, progression free survival.
- Time to progression to acute myeloid leukemia.
- Safety.
- Pharmacokinetics and immunogenicity.
- QT interval in a subset of subjects.
- Patient-Reported Outcomes.

Exploratory endpoints
- Biomarkers: Telomerase activity, Telomere length, hTERT.
- Cytogenetic responses.
- Baseline mutation status and change of mutation burden.
Study Status

Trial Enrollment

- Approximately 130 sites are planned across North America, Europe, Middle East and Asia.
- Enrollment of the Phase 3 study was opened in August 2019; the study is currently enrolling.

Trial registration

- This study is registered at ClinicalTrials.gov (NCT02598661).

Contact information

- MDS3001-info@Geron.com