#4248

IMerge: A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment

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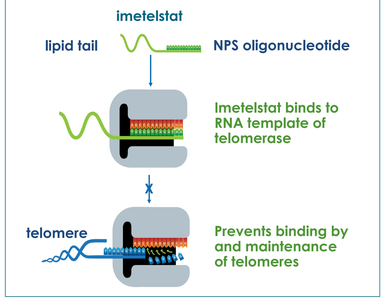
BACKGROUND

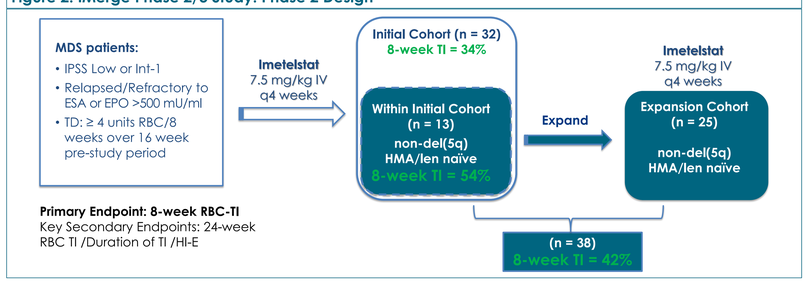
- Myelodysplastic syndromes (MDS) are characterized by clonal myeloproliferation arising from malignant progenitor cell clones that have multiple genetic abnormalities.[1]
- Patients with red blood cell (RBC) transfusion-dependent (TD), lower risk MDS (LR-MDS) that has relapsed or is refractory to erythropoiesis-stimulating 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**), and has demonstrated clinical activity in myeloid malignancies, including TD LR-MDS patients.[6-8]

Figure 1. Imetelstat binds to the RNA template preventing maintenance of telomeres



- **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 **(Figure 2)**.
- The results from Phase 2 of IMerge demonstrated clinical benefit of imetelstat treatment in TD LR-MDS [9,10], supporting initiation of the Phase 3 (**Figure 3**).

Figure 2. IMerge Phase 2/3 Study: Phase 2 Design



RESULTS FROM PHASE 2 OF IMerge[10]

- Imetelstat treatment showed meaningful and durable TI in 38 heavily TD, non-del(5q), HMA/Len naïve, LR-MDS patients (**Table 1**).
- Transfusion independence was observed across different clinical subgroups (**Figure 4**).
- No new safety signal was identified. Reversible cytopenias were the most frequent AEs, without significant clinical consequences (**Figure 5**). 11% of infusion related reactions with 5% >=Grade 3 were observed.
- Biomarker data suggested potential impact on malignant clone and disease modification by imetelstat treatment (**Figure 6**).

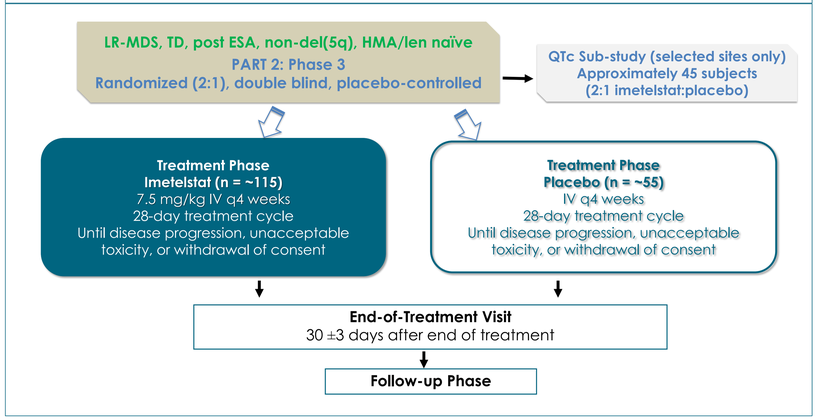
Table 1. Meaningful & Durable Transfusion Independence

Parameters	n = 38
8-week TI, n (%) Time to onset, weeks, median (range) Duration of TI[a], weeks, median (range)	16 (42) 8.3 (0.1 – 40.7) 85.9 (8.0 – 140.9)
24-week TI, n (%)	11 (29)
HI-E per IWG 2006, n (%) ≥1.5 g/dL increase in Hgb lasting ≥ 8 weeks Transfusion reduction by ≥ 4 units/8 weeks	26 (68) 12 (32) 26 (68)
CR + marrow CR + PR (per IWG 2006, central path review), n (%) CR marrow CR PR	9 (24) 5 (13) 4 (10) 0

CR, complete remission; IWG, International Working Group, PR, partial remission. [a]Kaplan Meier method

METHODS FOR PHASE 3 OF IMerge

Figure 3. IMerge Phase 2/3 Study: Phase 3 Design



RESULTS FROM PHASE 2 OF IMerge[10]

Figure 4. 8-week TI Observed Across Different Subgroups

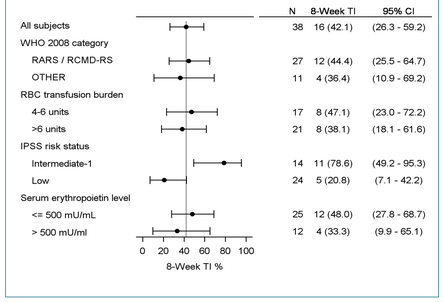
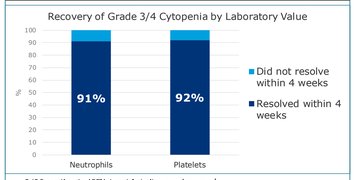


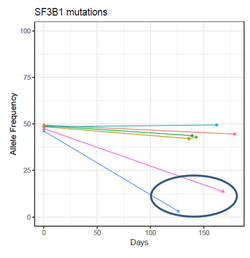
Figure 5. Reversible Grade 3/4 Cytopenias without Significant Clinical Consequences

Hematologic AEs		
TEAE	All Grades N=38 (n, %)	≥Grade 3 N=38 (n, %)
Thrombocytopenia	25 (66)	23 (61)
Neutropenia	22 (58)	21 (55)
Anemia	10 (26)	8 (21)



- 2/38 patients (5%) had febrile neutropenia
- 4/38 patients (10%) had bleeding events, 2/38 (5%) were Grade 3/4

Figure 6. Potential Impact on the Malignant Clone with Imetelstat Treatment



SF3B1 mutated Patient ID	TI duration in SF3B1 patients (weeks)
200078*	48.7
200079	3.6
200081*	52
200083*	32
200088*	56.7
200095*	62.9

Subject	Karyotype	8-wk TI	WHO Classification
200040	46,XY,DEL(7)(Q22)	X	RCMD-RS
200093*	46,XX,Dup/Tri/Qtp(9)(P13P24)	X	RCMD-RS
200061	47,XX,+8	X	RARS
200083*	47,XX,+8	X	RCMD-RS
200088*	47,XY,+8	X	RCMD-RS
200102*	46,XY,T(3;3)(Q21;Q26.2)		RA

*remain on treatment subjects achieved partial cytogenetic response

- 2/6 patients with baseline SF3B1 mutations had reduction in variant allele frequency and maintained TI lasting over a year.
- 5/6 (83%) intermediate or poor cytogenetic risk patients achieved 8-week TI and all had a ringed-sideroblast WHO subtype.
- 3/3 with trisomy 8 achieved 8-week TI and 2/3 achieved 24-week TI.

PHASE 3 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.

PHASE 3 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).

PHASE 3 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.

PHASE 3 STUDY STATUS

- Approximately 90 sites are planned in 12 countries across North America, Europe, Middle East and Asia.
- Enrollment was open for Phase 3 in August 2019.

TRIAL REGISTRATION

- This study is registered at ClinicalTrials.gov (NCT02598661).
- For further information please contact: MDS3001-info@Geron.com

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