IMETELSTAT DEMONSTRATES AN ACCEPTABLE SAFETY PROFILE IN MYELOID MALIGNANCIES

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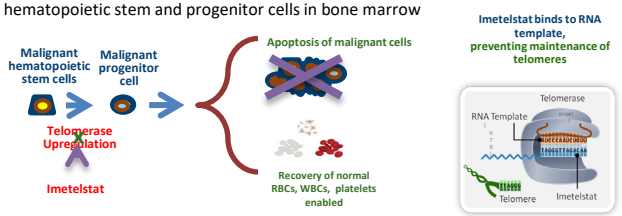
INTRODUCTION

- Imetelstat is a first-in-class telomerase inhibitor being developed for treatment of hematologic malignancies. Imetelstat induces selective apoptosis of malignant hematopoietic stem and progenitor cells in bone marrow



- Phase 2 data from MYF2001/ IMbark study in imetelstat treated patients with Janus kinase (JAK) inhibitor relapsed and refractory (R/R) intermediate 2 (Int-2) and high risk (HR) myelofibrosis (MF) demonstrated clinical benefit in symptom response rate and a potential overall survival (OS) benefit.
- Phase 2 data from Part 1 of MDS3001/ IMerge in imetelstat treated patients with high transfusion burden low risk (LR) and intermediate 1 (Int-1) risk myelodysplastic syndrome (MDS) R/R to erythropoiesis stimulating agents (ESAs) demonstrated meaningful and durable transfusion independence.
- Clinical and biomarker data in both studies indicate potential disease-modifying activity.
- The most frequently reported adverse events (AEs) were manageable and reversible cytopenias, with limited clinical consequences[1,2] .

OBJECTIVE

To further characterize hematologic and non-hematologic AEs, including the AEs of Interest (AEI), hepatic AEs and grade ≥3 liver function tests (LFTs) in these Phase 2 studies

METHODS

These safety analyses focus on patients in two Phase 2 hematologic malignancy studies:

- IMbark/MYF2001 patients with JAK inhibitor R/R Int-2/HR MF, treated with imetelstat 9.4 mg/kg IV q 3 weeks as of 7 Feb 2020; N=59
- IMerge/MDS3001 Part 1 (Phase 2 portion) patients with LR/Int-1 non-del(5q) transfusion dependent ESA R/R MDS patients, all lenalidomide and hypomethylating agent-naïve, treated with imetelstat 7.5 mg/kg IV every 4 weeks as of 21 Oct 2020; N=38

AEs were monitored and reported from the time of screening until 30 days after treatment discontinuation. Dose modification, including dose hold and reduction was performed based on protocol-defined criteria for grade ≥ 3 cytopenias and non hematologic AE related to imetelstat treatment.

An independent hepatic expert committee (HEC) reviewed all LFT and AEI data quarterly.

RESULTS

On MYF2001 with a median treatment duration of 32.7 weeks (0.1- 144.1), 41% and 32% of patients had grade 3/4 thrombocytopenia and neutropenia respectively. On Part 1 MDS3001 with a median treatment duration of 37.1 weeks (0.1- 168.1), 61% and 55% of patients had grade 3/4 thrombocytopenia and neutropenia respectively.

The cytopenias experienced on study were generally of short median duration with resolution prior to the next cycle of treatment and leading to treatment discontinuation in less than 16% of the treated patients.

Table 1: Characteristics of Cytopenias

	MYF2001 9.4 mg/kg q 3 weeks (n=59)		MDS3001 Part 1 7.5 mg/kg q 4 weeks (n=38)	
	G3/4 Thrombo-cytopenia	G3/4 Neutropenia	G3/4 Thrombo-cytopenia	G3/4 Neutropenia
Median duration	2.0 weeks	1.3 weeks	1.1 weeks	1.7 weeks
Median time to onset	9.0 weeks (~ 3 cycles)	9.0 weeks (~3 cycles)	4.0 weeks (~1 cycle)	4.7 weeks (~1 cycle)
Reversible within 4 weeks	47/65 events 72.3%	47/56 events 83.9%	86/95 events 90.5%	68/79 events 87.3%
Cytopenias leading to treatment discontinuation	6/59 (10%)	3/59 (5%)	6/38 (15.8%)	1/38 (2.6%)
Median time to first dose reduction	21.4 weeks (Cycle 6.5)		10.8 weeks (Cycle 3)	

Importantly, clinical consequences of cytopenias including grade ≥3 hemorrhagic events or febrile neutropenia occurred in <11% of pts (Table 2).

Table 2: Incidence of Sequalae of Cytopenias

AE Grade ≥3	MYF2001 9.4 mg/kg q 3 weeks (n=59)	MDS3001 Part 1 7.5 mg/kg q 4 weeks (n=38)
Hemorrhagic Events	3 (5.1%)	4 (10.5%)
Febrile Neutropenia	1 (1.7%)	2 (5.3%)

Given the older patient populations in both MYF2001 and Part 1 MDS3001, additional analysis was performed that demonstrated that the cytopenia toxicity profile was generally consistent in patients over 75 years of age compared with the less than 75- year -old population in the respective studies.

Non-hematologic AEs occurring in >20% patients in either study were nausea, diarrhea, abdominal pain, fatigue, asthenia, pyrexia, dyspnea, and back pain and were generally grade 1 -2 events. Infusion related reactions occurred in 27.1% of MF patients and 13.2% of MDS patients and were generally grade 1-2 (Table 3). Patients were premedicated with antihistamine and corticosteroid.

RESULTS

Table 3: Non hematologic AE occurring in >20% of patients with either MF or MDS

	MYF2001 9.4 mg/kg q 3 weeks (n=59)	MDS3001 part 1 7.5 mg/kg q 4 weeks (n=38)
Nausea	20 (33.9%)	5 (13.2%)
Diarrhea	18 (30.5%)	7 (18.4%)
Abdominal pain	14 (23.7%)	3 (7.9%)
Fatigue	16 (27.1%)	6 (15.8%)
Asthenia	14 (23.7%)	6 (15.8%)
Pyrexia	13 (22.0%)	8 (21.1%)
Dyspnea	15 (25.4%)	4 (10.5%)
Back pain	7 (11.9%)	9 (23.7%)
Infusion related reactions	16 (27.1%)	5 (13.2%)

On MYF2001, 2 (3.4%) patients experienced G3 ALP elevations and G3 AST and bilirubin occurred in one (1.7%) patient each. On Part 1 MDS3001, 3 (7.9%) patients experienced G3 AST and G3 ALT and bilirubin occurred in 2 (5.3%) patients each. HEC reviews of this data found no significant imetelstat-related liver injury.

CONCLUSIONS

- Imetelstat related cytopenias are on-target effects based on the selective reduction of malignant cells through telomerase inhibition.
- When managed with the dose modification guidelines in the protocols neutropenia and thrombocytopenia are of short duration, reversible and have limited clinical consequences.
- R/R MF and LR MDSpatients in these Phase 2 studies generally had low rates of G3 liver enzyme and bilirubin elevation, with no evidence of imetelstat-related liver injury
- Differences in disease pathology between MF and MDS (proliferation versus dysplasia) could account for the differences in toxicity profiles in MF versus MDS pts.
- Ongoing randomized Phase 3 studies in MF (MYF3001/IMpactMF; imetelstat versus best available therapy) and MDS (MDS3001 Part 2/IMerge; imetelstat versus placebo) will confirm the safety profile of imetelstat in a controlled setting.

REFERENCES

1 Platzbecker et al, ASH 2020, Oral Presentation, Abstract #658
2 Mascarenhas et al ASH 2020, Oral Presentation, Abstract #57

CONTACT INFORMATION

For additional information on imetelstat Phase 3 studies in MDS and MF visit or contact:

- **IMerge (MDS3001):** https://www.geron.com/patients/imerge-study/ ClinicalTrials.gov Identifier:NCT02598661; Email mds3001-info@geron.com
- **IMpactMF (MYF3001):** https://www.geron.com/patients/impactmf-study/ ClinicalTrials.gov Identifier: NCT04576156; Email myf3001-info@geron.com