Infusion-Related Reactions and Management in Patients With Red Blood Cell Transfusion-Dependent Relapsed or Refractory Lower-Risk Myelodysplastic Syndromes Treated With Imetelstat From the IMerge Phase 3 Trial

Donglan Xia,[1] Patrick Brooks,[2] Qi Xia,[2] Shyamala Navada,[2] Tymara Berry,[2] Yazan F. Madanat[1]

[1]The University of Texas Southwestern Medical Center, Dallas, TX, USA; [2]Geron Corporation, Foster City, CA, USA

Background/Significance

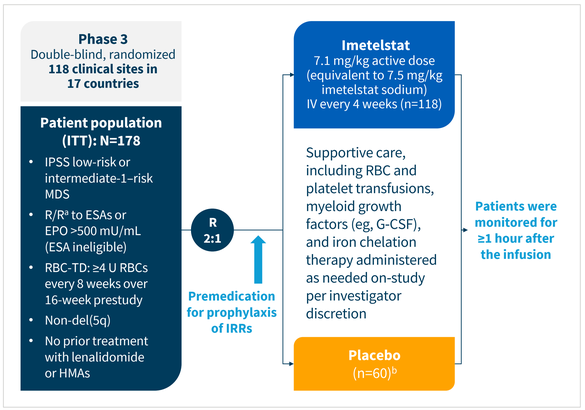
- Myelodysplastic syndromes (MDS) are hematologic malignancies marked by ineffective hematopoiesis, cytopenias, and an elevated risk of progression to acute myeloid leukemia[1]
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity, approved in the United States (US) and Europe for the treatment of certain patients with low- to intermediate-1–risk MDS with red blood cell (RBC) transfusion-dependent (TD) anemia who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA)[2,3]
  - Imetelstat is administered as an intravenous (IV) infusion over 2 hours every 4 weeks
- Approval was based on the pivotal Phase 3 IMerge trial (NCT02598661), a multinational, randomized, double-blind, Phase 2/3 trial of imetelstat versus placebo in patients with RBC-TD, ESA-relapsed, refractory, or ineligible, and non-del(5q) lower-risk MDS[4]
  - Results showed higher rates of ≥8-week, ≥24-week, and ≥1-year RBC transfusion independence with imetelstat versus placebo
  - The most common adverse events (AE) were thrombocytopenia and neutropenia, which were generally reversible and manageable with dose modifications

The current analysis was conducted to describe the incidence and management of infusion-related reactions (IRR) in IMerge to support label recommendations

Interventions

- A schematic overview of this analysis of the IMerge Phase 3 study is presented in **Figure 1**

Figure 1. IMerge Phase 3 Schematic Overview



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IRR, infusion-related reaction; ITT, intention-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; R, randomization; RBC, red blood cell; R/R, relapsed or refractory; TD, transfusion dependent; U, units.
[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, or darbepoetin alfa 150 µg or equivalent per week) without an Hb rise of ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U every 8 weeks or transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥8 weeks of ESA treatment. [b]One patient was randomized but not treated.

- **In the IMerge trial**, patients were premedicated with an antihistamine (25-50 mg diphenhydramine or equivalent) and a corticosteroid (100-200 mg hydrocortisone or equivalent) either IV or orally ≈1 hour before study infusion for prophylaxis of IRRs
  - If an IRR developed, infusion was temporarily interrupted and managed through supportive care
  - If AE intensity returned to grade 3 for a third time, or if an AE was grade 4, treatment was discontinued

Evaluation

- The data cutoff date for this analysis was October 13, 2022
- The safety set for this analysis included 177 patients (1 patient who was randomized to the placebo arm did not receive treatment)

Premedication Use

- The summary of glucocorticoid and antihistamine preinfusion medications for both the imetelstat and placebo arms is presented in **Table 1**
  - The 3 most common corticosteroids were hydrocortisone, dexamethasone, and methylprednisolone
  - The 3 most common antihistamines were dexchlorpheniramine, diphenhydramine, and chlorphenamine

Table 1. Glucocorticoid and Antihistamine Premedication Use[a]

	Imetelstat (n=118)	Placebo (n=59)
Glucocorticoids, n (%)		
Hydrocortisone[b]	78 (66)	38 (64)
Dexamethasone[c]	19 (16)	13 (22)
Methylprednisolone[d]	15 (13)	5 (8)
Prednisolone	6 (5)	3 (5)
Dihydrocortisone sodium succinate	2 (2)	2 (3)
Cortisone	1 (1)	0
Deflazacort	1 (1)	0
Prednisone	0	1 (2)
Antihistamines, n (%)		
Dexchlorpheniramine[e]	35 (30)	15 (25)
Diphenhydramine[f]	23 (19)	15 (25)
Chlorphenamine[g]	20 (17)	7 (12)
Clemastine[h]	11 (9)	8 (14)
Bisulepin[i]	10 (8)	4 (7)
Dimetindene maleate	8 (7)	6 (10)
Promethazine	6 (5)	4 (7)
Pheniramine[j]	5 (4)	1 (2)
Levocetirizine	5 (4)	2 (3)
Cetirizine	3 (3)	1 (2)
Promethazine hydrochloride	3 (3)	3 (5)
Loratadine	2 (2)	1 (2)
Dimenhydrinate	1 (1)	0
Desloratadine	0	1 (2)

[a]A patient with multiple premedications was only counted once under each category; [b]Includes hydrocortisone, hydrocortisone sodium succinate, hydrocortisone sodium phosphate, and hydrocortisone hydrogen succinate; [c]Includes dexamethasone and dexamethasone sodium phosphate; [d]Includes methylprednisolone and methylprednisolone sodium succinate; [e]Includes dexchlorpheniramine and dexchlorpheniramine maleate; [f]Includes diphenhydramine and diphenhydramine hydrochloride; [g]Includes chlorphenamine and chlorphenamine maleate; [h]Includes clemastine and clemastine fumarate; [i]Includes bisulepin and bisulepin hydrochloride; [j]Includes pheniramine and pheniramine maleate.

Incidence of IRRs

- IRRs (any grade) occurred in 9 (8%) imetelstat-treated patients and 2 (3%) placebo recipients (**Table 2**)
  - There were no grade 4 IRRs observed on either arm
  - The vast majority of IRRs with imetelstat were grade 1/2 (7 of 9 patients [78%])
  - The only IRR that occurred in >1 imetelstat-treated patient was headache (n=5 [4%])
  - No anaphylaxis or hypersensitivity IRRs occurred
- Of the 2 patients with grade 3 IRRs with imetelstat, 1 patient experienced a hypertensive crisis event (also considered a serious AE) that occurred during cycle 3, and 1 experienced a grade 3 noncardiac chest pain event that occurred during cycle 5; neither patient discontinued treatment due to IRRs

Table 2. Incidence of IRRs

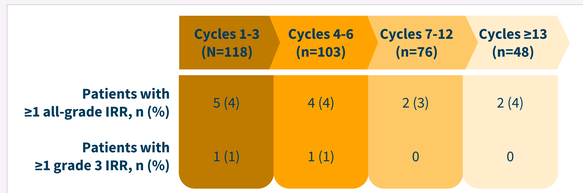
n (%)	Imetelstat (n=118)			Placebo (n=59)		
	Any grade	Grade 3[a]	SAE	Any grade	Grade 3[a]	SAE
Any IRR	9 (8)	2 (2)	1 (1)	2 (3)	0	0
Headache	5 (4)	0	0	0	0	0
Asthenia	1 (1)	0	0	0	0	0
Malaise	1 (1)	0	0	0	0	0
Noncardiac chest pain	1 (1)	1 (1)	0	0	0	0
Arthralgia	1 (1)	0	0	0	0	0
Back pain	1 (1)	0	0	0	0	0
Bone pain	1 (1)	0	0	0	0	0
Abdominal pain	1 (1)	0	0	0	0	0
Diarrhea	1 (1)	0	0	0	0	0
Erythema	1 (1)	0	0	0	0	0
Pruritus	1 (1)	0	0	0	0	0
Urticaria	1 (1)	0	0	0	0	0
Hypertensive crisis	1 (1)	1 (1)	1 (1)	0	0	0
Chest pain	0	0	0	1 (2)	0	0
Cough	0	0	0	1 (2)	0	0
Pyrexia	0	0	0	1 (2)	0	0

IRR, infusion-related reaction; SAE, serious adverse event.
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.
[a]There were no grade 4 IRRs observed on either arm.

Timing of IRRs

- IRRs were not time-dependent and may have occurred after 1 year (**Figure 2**)
- Median time to onset of the first all-grade IRR with imetelstat was 85 days (range, 1-603)
  - For the 2 imetelstat-treated patients with grade 3 IRRs, the median time to onset was 107 days (range, 85-128)

Figure 2. Incidence of IRRs by Cycle in Imetelstat-Treated Patients[a]



IRR, infusion-related reaction.
[a]n's = patients with exposure in the corresponding cycles; includes patients with ≥1 IRR event at each respective cycle interval; patients with multiple different IRRs in each cycle interval were only counted once.

Management and Resolution of IRRs

- Paracetamol/acetaminophen was the most frequently administered medication for IRRs, used primarily to manage infusion-related headache and pain
- Other management options were diphenhydramine (erythema/pruritus, urticaria), famotidine (pruritus), hydrocortisone sodium succinate (pruritus), oxycodone hydrocholoride (back/bone pain), and valsartan (hypertensive crisis)
- Twenty-five of 29 (86%) IRRs in the 9 imetelstat-treated patients resolved within 1 day
- Recurrence of IRRs occurred in 4 (3%) imetelstat-treated patients
- Imetelstat treatment interruption due to IRRs occurred in 5 (4%) patients
  - No patients discontinued imetelstat due to an IRR
  - One patient later discontinued imetelstat due to grade 2 pruritus

Discussion

- All patients in IMerge received premedications to mitigate IRRs
- Premedication led to a low overall IRR rate (8%)
  - Most IRR events (89%) were grade 1 or 2
  - There were no grade 4 IRRs
  - Premedication is recommended in the US Prescribing Information for imetelstat[2]
- Incidence of IRRs was similar across all treatment cycles
- Temporary treatment modification, supportive care, and monitoring were adequate to manage most IRRs without the need for therapy discontinuation

Current Recommendations for Managing IRRs Associated With Imetelstat Treatment per the US Prescribing Information[2]

- Premedicate with 25-50 mg or equivalent diphenhydramine and 100-200 mg or equivalent hydrocortisone either IV or orally for at least 30 minutes before dosing to prevent or reduce potential IRRs
- Monitor patients for adverse reactions for ≥1 hour after the infusion has been completed

Management of IRRs[2]

Severity grade[a]	Occurrence	Treatment modification
Grade 2 or 3	First and second	• Interrupt the imetelstat infusion until resolution of the adverse reaction or until the intensity of the reaction decreases to grade 1 • Restart infusion at 50% of the infusion rate administered before the adverse reaction
	Third	• For grade 2, stop infusion; may restart at next cycle • For grade 3, permanently discontinue imetelstat
Grade 4	First	• Stop infusion, administer supportive care as appropriate, and permanently discontinue imetelstat

[a]Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
Grade 1 definition: mild transient reaction; infusion interruption not indicated; intervention not indicated; evaluate and manage symptomatically as needed; patients may complete the infusion if the reaction remained mild, with stable vital signs and without worsening to grade 2.[5]
Grade 2 definition: therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.
Grade 3 definition: prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for clinical sequelae.
Grade 4 definition: life-threatening consequences; urgent intervention indicated.

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ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT02598661

Contact information: Medinfo@geron.com