Anemia Response With Imetelstat in Patients With Myelofibrosis From IMbark per Updated Clinical Criteria

Aaron T. Gerds,[1] Rami S. Komrokji,[2] Yiqun Yang,[3] Libo Sun,[3] Michelle Mudge-Riley,[3] Jeff Braziunas,[3] John O. Mascarenhas[4]

[1]Cleveland Clinic Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland, OH, USA; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Geron Corporation, Foster City, CA, USA; [4]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Background

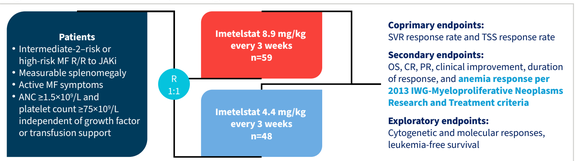
- Myelofibrosis (MF) is characterized by bone marrow fibrosis, splenomegaly, and constitutional symptoms, as well as ineffective hematopoiesis, which often manifests as symptomatic anemia[1]
- Imetelstat is a first-in-class, direct, and competitive inhibitor of telomerase enzymatic activity approved for the treatment of certain patients with lower-risk myelodysplastic syndromes with red blood cell (RBC) transfusion-dependent (TD) anemia who are relapsed/refractory (R/R) to, or ineligible for, erythropoiesis-stimulating agents[2,3]
- In the IMbark Phase 2 trial (NCT02426086), single-agent imetelstat showed clinically meaningful improvement in symptom response and improved overall survival (OS) in patients with intermediate–2–risk or high-risk MF relapsed or refractory to a Janus kinase inhibitor (JAKi)[4]
  - Spleen response at week 24 with an active dose of 8.9 mg/kg imetelstat (equivalent to 9.4 mg/kg imetelstat sodium) was modest, but clinically meaningful for patients with high disease burden who were R/R to JAKi. Specifically, 37% of these patients experienced a spleen volume reduction of at least 10%[4]
  - With 46.2 months' follow-up, median OS was 30.7 months in IMbark patients treated with 8.9 mg/kg imetelstat compared with 15.4 months in a closely matched real-world cohort treated with best available therapy[5]
  - Clinical improvement per modified 2013 International Working Group (IWG)-Myeloproliferative Neoplasms Research and Treatment criteria was achieved with imetelstat 8.9 mg/kg and 4.4 mg/kg in 25.4% and 16.7% of patients who were RBC-TD, respectively[4]
- In line with the evolving treatment landscape and lack of uniformity among clinical trial readouts, the IWG updated the definitions of transfusion status and anemia response in myelofibrosis in 2024[6]

This post hoc analysis evaluated anemia response with single-agent imetelstat in the IMbark trial using the revised IWG 2024 criteria

Methods

- IMbark was a global, multicenter, single-blind, randomized Phase 2 study (**Figure 1**)
- Baseline RBC-TD status and overall, major, and minor anemia responses were analyzed according to the IWG 2024 criteria (**Table 1**)

Figure 1. IMbark Study Design



ANC, absolute neutrophil count; CR, complete remission; IWG, International Working Group; JAKi, Janus kinase inhibitor; MF, myelofibrosis; OS, overall survival; PR, partial remission; R, randomized; R/R, relapsed or refractory; SVR, spleen volume reduction; TSS, total symptom score.

Table 1. Definition of Baseline Disease Characteristics and Response per IWG 2024[6]

Outcomes	Definition by IWG 2024
Anemia response (all patients)	**Major or minor response**
RBC-TD patients	
Baseline Hb	Average of pretransfusion Hb in the 12 weeks before first dose
Baseline transfusion burden	Number of transfusion units in the 12 weeks before the first dose
Major anemia response	12 weeks no transfusion and Hb ≥1.5 g/dL increase
Minor anemia response	≥50% reduction in transfusion in 12 weeks (and not meeting criteria for major response)
12-week RBC-TI	No transfusions in any consecutive 12 weeks
Non-RBC-TD patients	Not meeting criteria for TD
Baseline Hb	Average of lowest 3 pretransfusion Hb levels in 12 weeks, including 1 in 28 days, before first dose
Baseline transfusion burden	Number of transfusion units in the 12 weeks before the first dose
Major anemia response	12 weeks no transfusion and Hb ≥1.5 g/dL increase
Minor anemia response	12 weeks no transfusion and Hb ≥1.0 g/dL increase (and not meeting criteria for major response)

Hb, hemoglobin; IWG, International Working Group; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independence.

Results

- Baseline characteristics are presented in **Table 2**
- Median baseline hemoglobin was relatively high in patients from both cohorts (9.7 g/dL and 9.9 g/dL in patients randomized to imetelstat 8.9 mg/kg and 4.4 mg/kg, respectively)
  - Hemoglobin levels at baseline were not routinely assessed in IMbark, resulting in limited data in some of the patient subgroups
- Among patients who were RBC-TD at baseline, median transfusion burden at baseline was 7 (3-19) and 8 (3-21) in patients randomized to imetelstat 8.9 mg/kg and 4.4 mg/kg, respectively

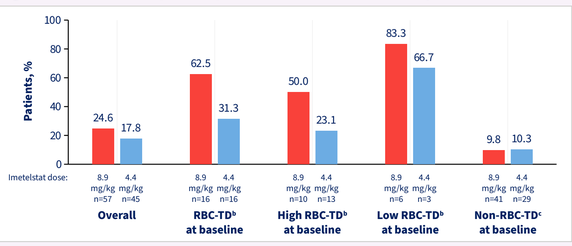
Table 2. Baseline Disease Characteristics per IWG 2024

Characteristic	8.9 mg/kg imetelstat	4.4 mg/kg imetelstat
Overall, N	59	48
Hb, median (range), g/dL[a]	n=43 9.7 (6.4-13.7)	n=32 9.9 (7.6-15.0)
Transfusion burden, median (range), units/12 weeks	1 (0-19)	1 (0-21)
RBC-TD patients, N	16	16
Hb, median (range), g/dL[a]	n=2 9.3 (9.1-9.4)	n=3 7.9 (7.6-9.7)
Transfusion burden, median (range), units/12 weeks	7 (3-19)	8 (3-21)
High RBC-TD patients, N	10	13
Hb, median (range), g/dL[a]	n=1 9.4 (9.4-9.4)	n=2 7.7 (7.6-7.9)
Transfusion burden, median (range), units/12 weeks	10 (6-19)	8 (6-21)
Low RBC-TD patients, N	6	3
Hb, median (range), g/dL[a]	n=1 9.1 (9.1-9.1)	n=1 9.7 (9.7-9.7)
Transfusion burden, median (range), units/12 weeks	4 (3-5)	4 (3-4)
Non-RBC-TD patients, N	43	32
Hb, median (range), g/dL[a]	n=41 9.7 (6.4-13.7)	n=29 10.2 (7.8-15.0)
Transfusion burden, median (range), units/12 weeks	0 (0-10)[b]	0 (0-18)[b]

Hb, hemoglobin; IWG, International Working Group; RBC, red blood cell; TD, transfusion dependent.
[a]Patients with missing baseline Hb were excluded. [b]Patients who had no transfusion within 28 days prior to the first dose are considered non-RBC-TD patients regardless of the total number of transfusion units in 12 weeks.

- In the total IMbark population, anemia response per IWG 2024 (either major or minor) with imetelstat 8.9 mg/kg and 4.4 mg/kg was achieved in 24.6% and 17.8% of patients, respectively (**Figure 2**)
  - In RBC-TD patients, responses were seen in 62.5% and 31.3% of patients, respectively
  - Responses were observed regardless of whether RBC-TD patients had high or low transfusion dependence at baseline

Figure 2. Anemia Response[a] per IWG 2024 (Treated Analysis Set)



IWG, International Working Group; RBC, red blood cell; TD, transfusion dependent; U, units.
[a]Defined as patients with either 50% reduction in transfusion during the 12-week assessment period (TD patients), or a rolling 12-week average hemoglobin increase of ≥1.0 g/dL from baseline, with no transfusion of packed RBC (or whole blood) during the assessment period. [b]RBC-TD at baseline defined as transfusions of ≥3 U of packed RBC (or whole blood) during the 12 weeks before the first dose, and the most recent transfusion episode must have occurred in the 28 days before the first dose; patients requiring ≥6 U were classified as high RBC-TD and those requiring 3-5 U were classified as low RBC-TD. [c]Non-RBC-TD at baseline was defined as not meeting criteria for RBC-TD.

- Overall, major anemia response with imetelstat 8.9 mg/kg and 4.4 mg/kg was achieved in 7.0% and 9.4% of patients, respectively, driven by non-RBC-TD patients (**Table 3**)
  - Because most patients who were RBC-TD at baseline lacked a baseline hemoglobin value and therefore were considered not evaluable in this analysis, major responses were not demonstrated at either dose within this group
  - However, when considering only the 12-week RBC transfusion independence component of major response, 43.8% and 18.8% of RBC-TD patients in the 8.9-mg/kg and 4.4-mg/kg groups, respectively, achieved response
- Minor anemia response with imetelstat 8.9 mg/kg and 4.4 mg/kg was achieved in 19.3% and 11.1% of patients, respectively, driven by RBC-TD patients (**Table 3**)

Table 3. Major and Minor Anemia Response per IWG 2024

Outcomes	8.9 mg/kg imetelstat	4.4 mg/kg imetelstat
Overall	59	48
Major anemia response, n (%)[a]	3/43 (7.0)	3/32 (9.4)
Minor anemia response, n (%)	11/57 (19.3)	5/45 (11.1)
12-week RBC-TI, n (%)	22/59 (37.3)	16/48 (33.3)
RBC-TD patients, N	16	16
Major anemia response, n (%)[a]	0/2 (0)	0/3 (0)
Minor anemia response, n (%)	10/16 (62.5)	5/16 (31.3)
12-week RBC-TI, n (%)	7/16 (43.8)	3/16 (18.8)
Non-RBC-TD patients, N	43	32
Major anemia response, n (%)[a]	3/41 (7.3)	3/29 (10.3)
Minor anemia response, n (%)[a]	1/41 (2.4)	0/29 (0)

Hb, hemoglobin; IWG, International Working Group; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independence.
[a]Patients with missing baseline Hb were excluded.

- A greater proportion of patients who achieved anemia response per IWG 2024 with imetelstat experienced a reduction in total symptom score at week 24 compared with patients who did not achieve an anemia response; however, this difference was not statistically significant (**Table 4**)
  - A similar pattern was observed among patients who were RBC-TD at baseline. In this subgroup, symptom response rates at week 24 were higher among patients who achieved an anemia response with imetelstat 8.9 mg/kg compared with those without an anemia response (50% vs 0%)
- There was a trend toward improvement in bone marrow fibrosis among patients who achieved anemia response per IWG 2024 with imetelstat. However, the number of patients was small, and the findings did not reach statistical significance (**Table 4**)

Table 4. Relationship Between Disease Factors and Anemia Response per IWG 2024

	8.9 mg/kg imetelstat N=59		4.4 mg/kg imetelstat N=48	
	Anemia response[a]		Anemia response[a]	
Outcome	Yes	No	Yes	No
Total symptom score response at 24 weeks, n/N (%)				
Yes	6/14 (42.9)	12/43 (27.9)	1/8 (12.5)	2/37 (5.4)
No	8/14 (57.1)	31/43 (72.1)	7/8 (87.5)	35/37 (94.6)
P value[b]	.333		.452	
Bone marrow fibrosis reduction, n/N (%)				
Yes	6/10 (60.0)	9/25 (36.0)	2/4 (50.0)	2/15 (13.3)
No	4/10 (40.0)	16/25 (64.0)	2/4 (50.0)	13/15 (86.7)
P value[b]	.266		.178	

IWG, International Working Group.
[a]Includes patients who achieved a major or minor anemia response per IWG 2024 criteria. [b]Fisher's exact test.

- Overall, more all-grade and grade ≥3 cytopenias were observed in patients treated with imetelstat 8.9 mg/kg than in those treated with 4.4 mg/kg (**Table 5**)
- Higher rates of all-grade and grade ≥3 cytopenias were reported among patients who were RBC-TD at baseline compared with non-RBC-TD patients, although the number of RBC-TD patients was small (**Table 5**)

Table 5. Thrombocytopenia and Neutropenia TEAEs by RBC Transfusion Dependence at Baseline

TEAE	8.9 mg/kg imetelstat		4.4 mg/kg imetelstat	
	All-grade	Grade ≥3	All-grade	Grade ≥3
Overall, N	59		48	
≥1 Thrombocytopenia/neutropenia TEAE, n (%)	37 (62.7)	32 (54.2)	13 (27.1)	13 (27.1)
Thrombocytopenia, n (%)	29 (49.2)	24 (40.7)	11 (22.9)	11 (22.9)
Neutropenia, n (%)	21 (35.6)	19 (32.2)	5 (10.4)	5 (10.4)
RBC-TD patients, N	16		16	
≥1 Thrombocytopenia/neutropenia TEAE, n (%)	12 (75.0)	11 (68.8)	7 (43.8)	7 (43.8)
Thrombocytopenia, n (%)	10 (62.5)	8 (50.0)	6 (37.5)	6 (37.5)
Neutropenia, n (%)	8 (50.0)	8 (50.0)	3 (18.8)	3 (18.8)
High RBC-TD patients, N	10		13	
≥1 Thrombocytopenia/neutropenia TEAE, n (%)	7 (70.0)	7 (70.0)	6 (46.2)	6 (46.2)
Thrombocytopenia, n (%)	7 (70.0)	6 (60.0)	5 (38.5)	5 (38.5)
Neutropenia, n (%)	5 (50.0)	5 (50.0)	3 (23.1)	3 (23.1)
Low RBC-TD patients, N	6		3	
≥1 Thrombocytopenia/neutropenia TEAE, n (%)	5 (83.3)	4 (66.7)	1 (33.3)	1 (33.3)
Thrombocytopenia, n (%)	3 (50.0)	2 (33.3)	1 (33.3)	1 (33.3)
Neutropenia, n (%)	3 (50.0)	3 (50.0)	0	0
Non-RBC-TD patients, N	43		32	
≥1 Thrombocytopenia/neutropenia TEAE, n (%)	25 (58.1)	21 (48.8)	6 (18.8)	6 (18.8)
Thrombocytopenia, n (%)	19 (44.2)	16 (37.2)	5 (15.6)	5 (15.6)
Neutropenia, n (%)	13 (30.2)	11 (25.6)	2 (6.3)	2 (6.3)

TEAE, treatment-emergent adverse event; RBC, red blood cell; TD, transfusion dependent.

Conclusions

- In this updated post hoc analysis of IMbark, 24.6% of all patients and a majority (62.5%) of patients with RBC-TD anemia who received **single-agent imetelstat** 8.9 mg/kg achieved an anemia response, despite relatively high baseline Hb levels
- Achievement of an anemia response was associated with a trend toward reduced symptom burden and improved bone marrow fibrosis
- Approximately 44% of patients who were RBC-TD at baseline (median transfusion burden: 7 units/12 weeks) achieved 12-week RBC-TI with **single-agent imetelstat** 8.9 mg/kg
- Higher rates of cytopenias were observed among patients who were RBC-TD at baseline, corresponding with higher rates of anemia response compared with non-RBC-TD patients
  - These results are in line with previous reports in myelodysplastic syndromes suggesting that cytopenias with imetelstat may be predictive of therapeutic benefit[7]
- These findings support the clinically meaningful benefit of imetelstat in myelofibrosis and establish a benchmark for evaluating the effects of imetelstat on anemia in myelofibrosis studies using contemporary response criteria that complement the assessment of overall survival and other efficacy endpoints

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