Imetelstat (RYTELO)
National Drug Mini-Monograph
July 2025
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: 1L, first-line; 2L, second-line; AC, active-controlled; ARR, absolute risk reduction; CO, crossover; CCyR, complete cytogenetic response; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HI-E, hematologic improvement-erythroid; IST, immunosuppressive therapy; MC, multicenter; MN, multinational; PC, placebo-controlled; PCyR, partial cytogenetic response; Q, GRADE quality of evidence; RBCT, red blood cell transfusion; RCT, randomized clinical trial; RR, relative risk; VAF, variant allele frequency

FDA APPROVAL INFORMATION	
Description / MOA	Imetelstat is a first-in-class, small-molecule, 13-mer oligonucleotide telomerase inhibitor. The imetelstat molecule has a sequence complementary to the ribonucleic acid (RNA) component of human telomerase and binds to the RNA region, thereby acting as a competitive inhibitor of human telomerase. Telomerase synthesizes short deoxyribonucleic acid (DNA) repeats at the 3'-end of DNA in chromosomes. While rarely found in somatic cells, it is overexpressed in virtually all cancer cell types and confers cancer cell immortality.
Indication Under Review[1]	Treatment of adults with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring four or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESAs).
Dosage Regimen	7.1 mg/kg IV over 2 hours every 4 weeks.
Dosage Forms Under Review	For injection: 47 mg and 188 mg powder in single-dose vials for reconstitution

EFFICACY CONSIDERATIONS	
Trial	**Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomized, double-blind, placebo-controlled, phase 3 trial**[2]
Design	MN DB PC phase 3 RCT (2:1); stratification by prior RBC transfusion (RBCT) burden (4–6 units or ≥6 units over an 8-week period during the 16 weeks preceding randomization) and International Prognostic Scoring System (IPSS) risk group (i.e., low or intermediate-1) *Primary Endpoint*: Percentage of patients with RBCT independence (RBC-TI) for ≥8 consecutive weeks.
Population	Adults ≥18 years; biopsy-confirmed MDS within previous 12 weeks; low or intermediate-1 risk disease (IPSS), RBCT dependence (RBC-TD) requiring ≥4 units over an 8-week period during 16 weeks before randomization; relapsed, refractory, or ineligible for ESAs (because of endogenous erythropoietin concentration >500 mU/mL); no prior lenalidomide or hypomethylating agent (HMA); did not have del(5q) MDS. *Baseline Characteristics (N = 178)*: Median age 72 yrs; 62% male; median Hg 7.9 g/dL; mean sEPO 399 mU/mL; median previous RBCT burden 6 units over 8 weeks (corresponds to high transfusion burden[3]); ring sideroblasts 62%. Previous treatment: ESA 90%, luspatercept 6%.
Intervention	Randomized 2:1 imetelsat (n=118): placebo (n=60) Imetelstat 7.1 mg/kg IV every 4 weeks until progressive disease or unacceptable toxicity Stratification by RBC transfusion burden, IPSS risk score
Comparator	Placebo
Other Therapies	Supportive care, including RBCTs

Results

Primary Endpoint: Percentage of patients with RBCT independence (RBC-TI) for ≥8 consecutive weeks.

RBC-TI Response at median follow-up of 19 vs. 17 months

Outcome	Imetelstat	Placebo	RR (95% CI)	ARR (95% CI)	Q
RBC-TI x ≥ 8 wks, n/N (%)	47/118 (40)	9/60 (15)	2.6 (1.40, 5.05)	25 (9.9, 36.9)	L[αβ]
RBC-TI x ≥ 24 wks, n/N (%)	33/118 (28)	2/60 (3%)	8.4 (2.08, 33.79)	25 (12.6, 34.2)	L[αβ]

[α] Downgraded for indirectness (RBC-TI is a predictor / surrogate for overall survival)
[β] Downgraded for imprecision (wide CI; optimal information size not met)

- Median (range) number of cycles for imetelstat and placebo: 8 (5–17) and 8 (6–15), respectively.
- RBC-TI for at least 1 year was achieved in 21 patients (18%) vs 1 patient (2%).
- The median (95% CI) duration of RBC-TI was 51.6 vs 13.3 weeks, respectively.
- Response RBC-TI ≥ 8 weeks in patients with RS: (imetelstat vs. placebo)
  - 33 (45%) of 73 vs 7 (19%) of 37 (difference 26%; 95% CI 5.9, 42.2).
- Response RBC-TI ≥ 8 weeks in patients without RS (imetelstat vs. placebo)
  - 14 (32%) of 44 vs 2 (9%) of 23 (difference 23%, 95% CI –1.3, 40.6).
- 8-week or 24-week RBC-TI correlated with complete or partial cytogenetic response (C/PCyR) and ≥ 50% reduction from baseline in variant allele frequency (VAF) of the most frequently mutated genes in the study patients (*SF3B1*, *TET2*, *DNMT3A*, and *ASXL1*).

Authors' Conclusions

The results suggested that, in RBC-TD patients with LR-MDS anemia who relapsed after initial response to ESA, were refractory to ESA, or were ineligible for ESA, imetelstat produced durable (up to 1 year) RBC-TI, reduced transfusion burden, and improved Hg. Unlike other treatments, imetelstat efficacy remained robust regardless of ring sideroblasts (RS) and high transfusion burden. Achievement of RBC-TI for at least 24 weeks (and even 1 year) have not been previously shown in this study population. Imetelstat also showed potential disease-modifying effects.

MDS3001 Trial

Imetelstat Achieves Meaningful and Durable Transfusion Independence in High Transfusion-Burden Patients With Lower-Risk Myelodysplastic Syndromes in a Phase II Study[4]

Design

MC OL SA phase 2 observational study

Primary Endpoint: 8-week RBC-TI

Population

Adults ≥18 years; biopsy-confirmed diagnosis of MDS (2008 WHO criteria); LR-MDS ineligible for ESA (sEPO >500 mU/mL) or relapsed / refractory to ESA; RBC-TD (requiring ≥4 RBC units over an 8-week period during the previous 16 weeks); ECOG Performance Status score 0–2.

ESA relapsed / refractory refers to patients who received ≥8 weeks of treatment with a minimum dose of epoetin alfa 40,000 U/week, epoetin beta 30,000 U/week, or darbepoetin alfa 150 mcg (or equivalent agent / dose) either (1) without having achieved Hg increase of ≥1.5 g/dL or RBCT requirement decrease of ≥4 units over 8 weeks; or (2) with increasing transfusion dependence or reduction in Hg by ≥1.5 g/dL in the absence of another explanation.

Subset population: No prior HMA or lenalidomide, and non-del(5q).

Intervention

Imetelstat 7.5 mg/kg IV every 4 weeks

Comparator

None

Results

For overall population (N = 57) and subset population (n = 38), respectively:

- 8-week RBC-TI: 37% and 42%
- 24-week RBC-TI: 23% and 29%
- Duration of response, median (range): 65 (17 to 141) weeks and 86 (8 to 141) weeks

Authors' Conclusions

In patients who had ESA relapsed / refractory LR-MDS and were heavily RBC-TD, imetelstat produced meaningful and durable RBC-TI and high hematologic improvement-erythroid (HI-E) rates regardless of RS presence.

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Other Warnings (imetelstat vs. pbo)	Thrombocytopenia (gr 3-4: 65 vs. 8%), neutropenia (gr 3-4: 53 vs. 1.7%), infusion-related reactions, embryofetal toxicity
Top 5 AEs	Decreased platelets (PLTs), decreased white blood cells (WBCs), decreased neutrophils, increased aspartate transferase (AST), increased alkaline phosphatase (ALP)
Drug Interactions	Imetelstat is an inhibitor of OATP1B1 and OATP1B3. It does not inhibit or induce CYP450 enzymes.
Immunogenicity	Antidrug antibodies to imetelstat occurred in 28 (17%) of 166 LR-MDS patients. There were no clinically significant effects of the antibodies on the pharmacokinetics, safety, or efficacy of imetelstat.
IMerge Safety Comparisons	Rates of grade 3–4 bleeding, grade 3–4 infections, and febrile neutropenia were similar for imetelstat and placebo.

OTHER CONSIDERATIONS	
FDA Comments[5]	• There is a high unmet need with few treatment alternatives for LR-MDS anemia. • *Efficacy*. The only observed benefit was in RBC-TI. There were no statistically significant treatment differences on secondary endpoints related to disease-modifying effects, such as HI-E (International Working Group 2006 criteria), complete remission, partial remission, and overall survival. Exploratory patient-reported outcomes in the phase 3 study also did not show benefits (i.e., there were no improvements in fatigue and other anemia-related symptoms). • *Safety*: High rates of grade 3–4 neutropenia (71% vs 7% with imetelstat vs placebo, respectively) and thrombocytopenia (65% vs 8%, respectively) resulted in a higher need for cytopenia treatments (e.g., myeloid growth factors and platelet transfusions) and higher rates of infections and hemorrhagic events with imetelstat vs placebo, although treatments were similar in rates of grade 3–4 hemorrhages and infections. • *Uncertainties:* Impact of imetelstat on resource utilization and applicability of results to the US population.
ICER Indirect Comparisons[6]	• In an ICER subset analysis aiming to indirectly compare imetelstat with luspatercept in RS-positive patients (aligning with the approved indication for luspatercept), there were no significant treatment differences in achieving 8-week transfusion independence after 52 weeks of imetelstat therapy and 48 weeks of luspatercept therapy. • Evidence of a net benefit with imetelstat relative to best supportive care is promising but inconclusive. Reduction in RBCT is a clear benefit, but there is only modest sustained improvement in fatigue (50% vs 40%) and greater risk of grade 3 and 4 adverse events such as hematocytopenias (moderate-certainty evidence).
Uncertainties	• Imetelstat effects on progression of MDS to acute myeloid leukemia (AML) or on overall survival • Generalizability of results to luspatercept (or lenalidomide)-treated patients • Applicability of results to VHA

GUIDELINE / GUIDANCE PLACE IN THERAPY AND TREATMENT ALTERNATIVES

- Treatment options for low to intermediate risk MDS with RBC transfusion dependent (RBC-TD) anemia are based on patient subgroups.
- ESAs are typically 1L and effective when serum EPO ≤ 500 mU/mL.
- When the EPO level > 500 mU/mL, then absence/presence of mutations such as del(5q), *SF3B1*, and ring sideroblast (RS) status are considered.
  - Lenalidomide is recommended for those with MDS-del(5q).
  - Luspatercept is considered for non-del(5q) patients with *SF3B1* mutation and/or RS (MDS-RS).
- Imetelstat is not included in the VHA MDS Oncology Clinical Pathway or the European Society for Medical Oncology (ESMO) MDS Guidelines at this time; NCCN guidelines have included imetelstat

NCCN MDS Guidelines,[7] Abbreviated, Focused Summary of Treatment for LR-MDS with Symptomatic Anemia[1]

MDS-*SF3B1* (low blasts): No del(5q) ± other cytogenetic abnormalities (CGAs) with ring sideroblasts (RS) ≥15% (or RS ≥5% with an *SF3B1* mutation)

sEPO	Place in Therapy	Drug
NA	1L, Preferred	• Luspatercept-aamt (category 1)
	1L, Other Recommended	• Imetelstat (if sEPO >500 mU/mL [ineligible for ESAs])
>500 mU/mL (ESA ineligible)	2L, Preferred†	• Imetelstat (if not previously used) • Luspatercept-aamt (category 1; if not previously used)
	2L, Other Recommended†	• Lenalidomide (consider)
≤500 mU/mL	2L, Preferred†	• Imetelstat (category 1)
	Other Recommended†	• ESA ± G-CSF

† If no response or relapse with luspatercept-aamt

No del(5q) ± other CGAs with RS <15% (or RS <5% with an *SF3B1* mutation)

sEPO	Place in Therapy	Drug
>500 mU/mL (ESA ineligible) and poor probability to respond to IST	1L, Preferred	• Azacitidine (Or clinical trial)
	1L, Other Recommended	• Decitabine • Imetelstat (if not previously used) • Oral decitabine and cedazuridine
	1L, Useful In Certain Circumstances	• Lenalidomide (consider)
≤500 mU/mL	1L, Preferred	• ESA* or luspatercept-aamt
	2L, Preferred‡	• Imetelstat (category 1) • Luspatercept-aamt (if not previously used)
	2L, Other Recommended	• Epoetin alfa ± G-CSF or lenalidomide • Darbepoetin alfa ± G-CSF or lenalidomide
	3L, Preferred§	• Imetelstat (if not previously used; category 1)
	3L, Useful in Certain Circumstances	• Ivosidenib (if m*IDH1*) (category 2B) • Olutasidenib (if m*IDH1*) (category 2B)

* ESA: Epoetin alfa or darbepoietin alfa
† If no response or relapse with luspatercept or imetelstat
‡ If no response or relapse with ESAs or luspatercept-aamt
§ If no response to imetelstat or ESAs ± lenalidomide or G-CSF or luspatercept-aamt or relapse

1 Refer to full NCCN Guidelines for further details.

POTENTIAL PLACE IN THERAPY IN VHA

MDS

- ESAs should be considered as 1L therapy for anemia management in low to intermediate risk MDS with low serum EPO levels; patient factors such as del(5q) status, presence of ring sideroblasts and/or SF3B1 mutation may direct to subsequent lenalidomide or luspatercept therapy.
- Imetelstat is not a first-line (1L) treatment, but it may serve a role as second-line (2L) or third-line (3L) therapy.

Myelofibrosis	• An ongoing phase III trial (IMpactMF) is an open-label investigation of imetelstat vs. best available therapy in patients with intermediate or high-risk myelofibrosis refractory to JAK inhibitor therapy. • A dose-finding, phase II study (NCT02426086) among patients with relapsed/refractory myelofibrosis determined that imetelstat 9.4 mg/kg IV every 3 weeks resulted in a reduction in spleen volume and improved symptom response at 24 weeks. • Current use in myelofibrosis is considered off-label and cannot be recommended at this time; await results of IMpactMF.

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References

1 RYTELO (imetelstat) for intravenous injection [prescribing information online]. Foster City, CA: Geron Corporation. 6/2024. Available at: rytelo_pi.pdf. Accessed 12/9/2024.

2 Platzbecker U, Santini V, Fenaux P, Sekeres MA, Savona MR, Madanat YF, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024 Jan 20;403(10423):249-260. doi: 10.1016/S0140-6736(23)01724-5. Epub 2023 Dec 1. Erratum in: Lancet. 2024 Jan 20;403(10423):248. doi: 10.1016/S0140-6736(24)00057-6.

3 Platzbecker U, Fenaux P, Adès L, Giagounidis A, Santini V, van de Loosdrecht AA, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood. 2019 Mar 7;133(10):1020-1030. doi: 10.1182/blood-2018-06-857102.

4 Steensma DP, Fenaux P, Van Eygen K, Raza A, Santini V, Germing U, et al. Imetelstat Achieves Meaningful and Durable Transfusion Independence in High Transfusion-Burden Patients With Lower-Risk Myelodysplastic Syndromes in a Phase II Study. J Clin Oncol. 2021 Jan 1;39(1):48-56. doi: 10.1200/JCO.20.01895.

5 Center for Drug Evaluation and Research (CDER). Multi-discipline review of imetelstat (RYTELO). Food and Drug Administration (FDA). May 24, 2024. Available at: Review. Accessed on December 19, 2024.

6 Tice JA, Luu L, Fahim SM, Carlson JJ, Herce-Hagiwara B, Richardson M, Dickerson R, Ollendorf D. Imetelstat for Anemia in Myelodysplastic Syndrome: Effectiveness and Value, Final Evidence Report. Institute for Clinical and Economic Review, August 22, 2024. https://icer.org/assessment/myelodysplastic-syndrome-2024/.

7 National Comprehensive Cancer Network (NCCN) in Oncology. Myelodysplastic Syndromes, version 1.2025 — November 15, 2024. Available at: mds.pdf. Accessed 12/10/2024.

8 Mascarenhas J, Komrokji RS, Palandri F, et al. Randomized, Single-Blind, Multicenter Phase II Study of Two Doses of Imetelstat in Relapsed or Refractory Myelofibrosis. J Clin Oncol 2021; 39: 2881-2892.

9 Mascarenhas J, Harrison CN, Kiladjian JJ, et al. Imetelstat in intermediate-2 or high-risk myelofibrosis refractory to JAK inhibitor: IMpactMF phase III study design. Future Oncol 2022; 18: 2393-2402.