REPORT AT A GLANCE: ANEMIA IN MYELODYSPLASTIC SYNDROME

AUGUST 2024

KEY FINDINGS

Population	Treatment	Comparator	Evidence Rating	Annual WAC	Health-Benefit Price Benchmark
Lower Risk MDS Without del(5q) Subtype	Imetelstat (Rytelo, Geron Corporation)	Placebo/Best Supportive care	Promising, but Inconclusive (P/I)	$365,197	$94,800 to $113,000 per year
Ring Sideroblast Positive Subgroup		Luspatercept	Insufficient (I)		

"Patients that have anemia related to MDS may have to plan around frequent blood transfusions, which can significantly affect their daily activities. Imetelstat is a new treatment option for adults with low-to-intermediate MDS and transfusion-dependent anemia. While available clinical evidence suggests that imetelstat may reduce or eliminate the need for transfusions, its impact on the severe fatigue that often accompanies MDS anemia is less clear. There is no evidence to suggest that imetelstat reduces the progression or trajectory of MDS itself, and there are some key side effects of concern. As a result, we view the evidence as promising but inconclusive, and the current list price is not at all aligned with the modest benefit we do see."

– ICER's Chief Scientific Officer and Director of Health Technology Assessment Methods and Engagement, Dan Ollendorf, PhD, MPH

THEMES AND RECOMMENDATIONS

- Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.
- Payers should establish site-of-service policies that cover home infusion or care at other low-cost sites when feasible.
- Specialty societies should ensure adequate training of community hematologists about new therapies like imetelstat.
- Patient groups should seek relationships with clinical specialty societies to exercise their joint power to advocate for drug prices that do not exceed a fair value for added clinical benefit.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Myelodysplastic syndromes (MDS) are a group of disorders characterized by abnormal blood-forming cells in the bone marrow, resulting in the reduction of peripheral blood cells, an elevated risk of acute myeloid leukemia (AML), and reduced survival. The most bothersome symptom for patients is severe fatigue, although they may also experience bleeding, night sweats, bone pain, fever, weight loss, and recurrent infections. Between 60,000 and 170,000 people are currently living with MDS in the United States (US). The economic burden of MDS is substantial: annual medical costs alone may reach $220,000 for lower-risk MDS patients.

Approximately 40% of lower-risk MDS patients become dependent on blood transfusions to treat their anemia. Because transfusion dependence is burdensome, achieving transfusion independence is a priority. First-line therapy is the class of erythropoiesis stimulating agents (ESAs). However, some patients stop responding or do not respond at all to ESAs. Luspatercept was recently approved as a first-line treatment for lower-risk MDS patients with anemia and for lower-risk MDS patients with anemia after ESA failure. It is particularly effective in patients with ring sideroblasts (RS+, approximately 35% of the MDS population). Lenalidomide is an option for patients with the del(5q) subtype, which accounts for approximately 10% of the MDS population.

Imetelstat (Rytelo™, Geron Corporation) is an oligonucleotide telomerase inhibitor that blocks the interaction between telomerase and telomeres, leading to the increased destruction of malignant cells with high telomerase activity. This can improve hematopoiesis in the bone marrow. Imetelstat was approved by the Food and Drug Administration (FDA) on June 6, 2024, as a treatment for transfusion-dependent anemia in lower-risk MDS patients who have not responded to, lost response to, or are ineligible for ESAs.

The IMerge trial randomized adults with lower risk MDS without the del(5q) subtype who are transfusion dependent and ineligible for or refractory to ESAs to imetelstat or placebo. Of the 118 participants treated with imetelstat, 40% achieved at least eight weeks of transfusion independence compared to 15% in the placebo arm (treatment difference: 25%, 95% CI 10% to 37%; $p<0.001$). Treatment with imetelstat was associated with a statistically non-significant trend towards greater improvement in fatigue (50% vs. 40%).

To compare the efficacy of imetelstat to luspatercept, we focused on the subset of IMerge participants who were RS+ (110 out of 178). An indirect comparison for the primary endpoint of 8-week transfusion independence after 52 weeks of treatment with imetelstat and 48 weeks of treatment with luspatercept found no significant differences between the two treatments in RS+ patients.

The biggest safety concern regarding imetelstat is the high incidence of grade 3 and 4 cytopenias. They were relatively short lived and managed by dose reduction in subsequent rounds of therapy, but were likely challenging for patients and required additional resources to manage them.

Compared with best supportive care, the net benefit of imetelstat is promising, but inconclusive. There are clear benefits in the reduction of required RBC transfusions, but the sustained improvement in fatigue is modest (50% vs. 40%) and there are substantially more grade 3 and 4 adverse events including thrombocytopenia, neutropenia, and anemia. There is only one relatively small clinical trial, so the level of certainty is at best moderate.

Clinical Analyses

Compared with luspatercept, we rate the evidence for imetelstat as insufficient (I). There is no evidence suggesting greater reductions in red blood cell (RBC) transfusions or improvements in quality of life for imetelstat compared with luspatercept and there are many more grade 3 and 4 hematologic adverse events. There are no head-to-head trials, so the evidence is indirect, which reduces the level of certainty. Finally, there is only one applicable trial for each intervention, resulting in low certainty.

In terms of benefits beyond health and special ethical priorities, there are currently no approved therapies for patients with lower-risk MDS who are transfusion dependent despite ESA therapy and are RS negative. In addition, patients who are RS positive and fail luspatercept may benefit from imetelstat, though we have no data in this population of patients.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

In our lifetime time horizon model, when imetelstat-eligible patients were treated with imetelstat and best supportive care, they experienced small gains in QALYs, evLYs, and life years and a reduction in total red blood cell transfusions compared to patients on best supportive care alone. Our analysis suggests that, at the WAC of $9,884 per 188mg or annual price of $365,197, use of imetelstat exceeds commonly used cost-effectiveness thresholds. In the ring sideroblast subgroup, imetelstat was shown to be more costly and less effective when compared to luspatercept. The conclusions were unchanged in a broad range of scenario analyses and sensitivity analyses.

POTENTIAL BUDGET IMPACT

ICER is not issuing an Access and Affordability Alert for imetelstat, given that all patients expected to be eligible for treatment can be treated without crossing the ICER potential budget impact threshold of $735 million per year.

Public Meeting Deliberations

VOTING RESULTS

ICER's Public Meeting: Voting Results on Clinical Effectiveness and Benefits Beyond Health

ICER assessed, and the independent appraisal committee voted on, the evidence of imetelstat for patients with lower risk myelodysplastic syndrome without the del(5q) mutation who are transfusion dependent and ineligible for, or refractory to ESAs:

- A majority of panelists (11-4) found that current evidence is **not adequate** to demonstrate a net health benefit for imetelstat plus best supportive care when compared to best supportive care alone.

For patients with lower risk myelodysplastic syndrome without the del(5q) mutation who are transfusion dependent and ineligible for, or refractory to ESAs, and are ring sideroblast positive:

- All panelists (15-0) found that current evidence is **not adequate** to demonstrate a net health benefit for imetelstat plus best supportive care when compared to luspatercept plus best supportive care.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.

ICER's Virtual Public Meeting: Voting Results on Long-Term Value for Money

For patients with lower risk myelodysplastic syndrome without the del(5q) mutation who are transfusion dependent and ineligible for, or refractory to ESAs:

- A majority of panelists (14-1) found at the current pricing, imetelstat plus best supportive care (compared to best supportive care alone) represents a **"low"** long-term value for money.

For patients with lower risk myelodysplastic syndrome without the del(5q) mutation who are transfusion dependent and ineligible for, or refractory to ESAs, and are ring sideroblast positive:

- A majority of panelists (13-2) found at the current pricing, imetelstat plus best supportive care (compared to luspatercept plus best supportive care) represents a **"low"** long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.