Imetelstat for Anemia in Myelodysplastic Syndrome: Effectiveness and Value

Evidence Report

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Prepared for

CTAF
CALIFORNIA TECHNOLOGY ASSESSMENT FORUM

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Jeffrey Tice served as the lead author for the report. Shahariar Mohammed Fahim and Belén Herce-Hagiwara led the systematic review and authorship of the comparative clinical effectiveness section of this report. Josh J. Carlson and Linda Luu developed the cost-effectiveness model and authored the corresponding sections of the report. Marina Richardson conducted analyses for the budget impact model. Daniel Ollendorf provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Anna Geiger, Becca Piltch, Grace Ham, and Yasmine Kayali for their contributions to this report.

About ICER

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For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer.org/who-we-are/people/independent-appraisal-committees/ctaf.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:

Expert Reviewers

Hedwig Blommestein, PhD
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Dr. Hedwig Blommestein served as a consultant for Pfizer BV, as paid to institute, and participated in an advisory board discussing global, multi-disciplinary insights and perspectives on designing and communicating robust and relevant evidence based on real-world data in patients with multiple myeloma.

Peter Greenberg, MD
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Dr. Peter Greenberg has received manufacturer support in the area of MDS, through research trial funding from the following health care companies: Novartis, Gilead, Bristol Myers Squibb, and Aprea.

Daneen Sekoni, MHSA
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Cancer Support Community
The Cancer Support Community receives greater than 25% of funding from health care companies, and received direct service, policy, and psychosocial research support from Bristol Myers Squibb and Geron Corporation.

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of the draft report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from who we requested input from, or who have submitted public comments so far, please visit: https://icer.org/wp-content/uploads/2024/02/MDS_Stakeholder-List_02012024.pdf

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List of Acronyms and Abbreviations Used in this Report

95% CI	95 percent confidence interval
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
AML	acute myeloid leukemia
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
ESA	erythropoiesis-stimulating agent
FACIT	Functional Assessment of Chronic Illness Therapy
G-CSF	granulocyte-colony stimulating factor
HCRU	Health care resource utilization
HIB	high transfusion burden
HI-E	hematologic improvement-erythroid
HMA	hypomethylating agent
HR MDS	high-risk MDS
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System-Revised
IWG	International Working Group
LIB	low transfusion burden
LR MDS	lower-risk MDS
MDS	myelodysplastic syndrome
N	number
NA	not applicable
NR	not reported
RA	refractory anemia
RAEB-1	refractory anemia with excess blasts type 1
RARS	refractory anemia with ring sideroblasts
RBC	red blood cell
RBC-TI	red blood cell transfusion independence
RCMD	refractory cytopenias with multilineage dysplasia
RS-	ring sideroblast negative
RS+	ring sideroblast positive
SCT	stem cell transplant
SD	standard deviation
SE	standard error
sEPO	serum erythropoietin
SQ	subcutaneous
TI	transfusion independent
WHO	World Health Organization

Executive Summary

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.[1] 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.[2] Between 60,000 and 170,000 people are currently living with MDS in the United States (US).[3] The economic burden of MDS is substantial: annual medical costs alone may reach $220,000 for lower-risk MDS patients.[4]

Approximately 40% of lower-risk MDS patients become dependent on blood transfusions to treat their anemia[5,6] 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).[5,7] Lenalidomide is an option for patients with the del(5q) subtype, which accounts for approximately 10% of the MDS population.[5,8]

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 non-significant trend towards greater improvement in fatigue (50% vs. 40%).[9]

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 (Table ES1). 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.

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.

Table ES1. Evidence Ratings

Population	Treatment	Comparator	Evidence Rating
Lower Risk MDS Without del(5q) Subtype	Imetelstat	Placebo/Best Supportive care	P/I
RS+ Subgroup	Imetelstat	Luspatercept	I

MDS: myelodysplastic syndrome, RS+: ring sideroblast positive

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.

Table ES2. Incremental Cost-Effectiveness Ratios

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Imetelstat + BSC (Overall)	**Best Supportive Care (Overall)**	$1,197,000	$1,029,000	$1,162,000
Imetelstat + BSC(RS+)	**Luspatercept + BSC (RS+)**	More costly, less effective	More costly, less effective	More costly, less effective
	Best Supportive Care (RS+)	$ 1,297,000	$1,115,000	$1,269,000

evLYs: equal value of life years gained; QALY: quality-adjusted life year; BSC: best supportive care; RS: ringed sideroblast

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.

1. Background

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.[1] MDS can arise *de novo* or be secondary to chemotherapy. Anemia (low red blood cell counts), thrombocytopenia (low platelet counts), and leukopenia (low white blood cell counts) are common among patients with MDS. 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.[2]

Between 60,000 and 170,000 people are currently living with MDS in the United States (US).[3] The estimated age-adjusted incidence rate of MDS among the general population is about four per 100,000 people. Men are diagnosed with MDS at about twice the rate of women. MDS is more common in non-Hispanic Whites and the elderly.[10] The economic burden of MDS is substantial: annual medical costs alone may reach $220,000 for lower-risk MDS patients.[4]

Diagnosis of MDS typically involves a bone marrow biopsy and molecular genetic testing.[11] The conventional MDS classification, developed by the World Health Organization (WHO) in collaboration with the Society for Hematopathology and the European Association of Hematopathology, has undergone multiple revisions; its most recent, the 5th edition, was released in 2022.[12] Important phenotypes that guide treatment considerations include the del(5q) mutation (loss of the long arm of the 5th chromosome) and MDS with ring sideroblasts. The risk of MDS progressing to AML has been classified by the International Prognostic Scoring System (IPSS) using factors including the percent of blast cells in bone marrow, changes in chromosomes, and number of cytopenias.[13,14] Two recent versions of IPSS, revised (IPSS-R) and molecular (IPSS-M), modified the existing parameters to refine the prognostic information as lower (very low, low, or intermediate) or higher risk (high or very high).

Approximately 40% of lower-risk MDS patients become dependent on blood transfusions to treat their anemia[5,6] Because transfusion dependence is burdensome, achieving transfusion independence is a priority. Current guidelines suggest a minimum of 16-weeks of transfusion independence is clinically meaningful and addresses the need for long-term transfusion independence for patients with MDS.[15] First-line therapy is the class of erythropoiesis stimulating agents (ESAs). However, some patients do not respond, and others stop responding 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 (approximately 35% of the MDS population).[5,7] Lenalidomide is an option for patients with the del(5q) subtype, which accounts for approximately 10% of the MDS population.[5,8]

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. Imetelstat will be administered as a 7.1 mg/kg infusion every four weeks (equivalent to 7.5 mg/kg of imetelstat sodium used in trials).[16]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Imetelstat (Rytelo™, Geron Corporation)	Telomerase inhibitor	Intravenous infusion	Starting dose: 7.1 mg/kg every 4 weeks* Dose reduction #1: 6 mg/kg every 4 weeks Dose reduction #2: 4.7 mg/kg every 4 weeks

kg: kilogram, mg: milligram
* Equivalent to 7.5 mg/kg of imetelstat sodium[16]

2. Patient and Caregiver Perspectives

Given the unique physical, mental, and psychological make-up of each individual patient, understanding what is clinically meaningful to patients necessitates collecting patient experience data (as well as caregiver experiences). Patient experience includes quality of life beyond survivability, psychosocial impacts of a condition or therapy, patient-reported outcomes, supportive services, and control in their treatment decisions and care.

In speaking with patients and their caregivers, we heard that the number one priority of patients is to have a better quality of life. Anemia, with its associated symptoms of fatigue and shortness of breath, is a major contributor to poor quality of life. The other major contributor to poor quality of life is emotional distress due to uncertainties about prognosis and challenges in understanding the diagnosis.

Patients and caregivers consistently talked about the impact of fatigue on quality of life. They report feeling so weak in their legs that they are unable to walk. “All you can do is lay around,” said one patient. “All he wants is to have energy… to be able to play with the grandkids again.” “I have no quality of life… I don’t want to live like this anymore.”

The last statement also alludes to the burden of anxiety and depression that often comes with the diagnosis of MDS. Patients expressed frustration that this was not acknowledged and addressed by their treating physicians. One noted that mental health specialty care “needs to be part of the treatment package.” The burden of receiving blood transfusions also contributes to poor quality of life. Receiving a single transfusion can require a full day or longer. Blood must be drawn for a type and screen to ensure compatibility and this often has to be done the day prior to the transfusion. Once patients have received many units of blood over time, it becomes harder and harder to find safe blood to transfuse because patients develop antibodies to the available blood. Sometimes patients leave the infusion center without receiving a transfusion because they become frustrated with the time delays. In addition, it becomes harder to find a good vein for the IV transfusion, which causes multiple painful needle sticks each time a blood test or transfusion is needed. Eventually, this may lead to the implantation of a device that provides long-term access to the vascular system, but that adds the burden of cleaning and maintaining the device to patients and caregivers.

The need for frequent blood draws, blood transfusions, and doctors’ visits can be overwhelming. Patients have to arrange everything around their medical care. They report “There is no social life.” and feeling unable to schedule vacations or even dinners or outings with friends and family.

Iron chelation therapy, which is used to treat an overload of iron that can occur after multiple transfusions, can also cause side effects including severe diarrhea and kidney complications.

Financial stress is a major issue for patients. They often forego working to keep up with their many doctors' visits and because of their severe fatigue. In addition, their caregivers may reduce their working hours or stop working to support their loved ones, which reduces available resources. In addition, out-of-pocket costs for available treatments can be very high. One patient said, "I'm paying a fortune for luspatercept." And another said of his co-pays: "We can't afford that."

Patients and caregivers found patient support communities and organizations to be of tremendous value. However, they had to find the organizations themselves. They feel that a list of local and national organizations should be given to patients at the time of diagnosis. When we asked patients what they would like in a better medicine to treat their anemia they highlighted several factors. First, they wanted a pill, rather than an IV drug or subcutaneous injection. Second, they wanted it to be portable, so that they could make plans to travel again. Finally, it has to be affordable.

The time-consuming nature, symptom burden, and side effects of repeated blood transfusions make caregivers a necessity, as even low risk MDS patients with mild anemia report fatigue and decreased physical functioning. The introduction of new treatment options that reduce transfusion burden without creating additional challenges from side effects or other complications has the potential to be life-changing for many MDS patients.

According to the Cancer Support Community's *Cancer Experience Registry*– an online survey-based research study that incorporates the PROMIS (Patient Reported Outcome Information Measurement System) and contains a national sample of 150 MDS patients, blood transfusion was the most common treatment reported. These respondents reported elevated symptoms of fatigue, anxiety, and pain as well as deficits in physical and social functioning, and worse quality of life across multiple domains compared to the general population and even (in some domains) compared to cancer patients with other types of hematologic and solid tumor cancers. Forty-three percent of MDS respondents reported moderate to severe impairment in physical function, and 41% reported moderate to severe symptoms of fatigue. Many MDS patients expressed future-oriented concerns such as the progression of cancer (47%), anxiety about the future (46%), and preparations for the end of life (32%). In light of how transfusion dependence interrupts daily life, 37% of MDS respondents report being moderately to very seriously concerned about changes or disruptions to work, school, or home life. Furthermore, 41% of MDS respondents reported having to cope with their symptoms and concerns without the assistance of a caregiver. With respect to financial toxicity, almost a third (31%) of MDS respondents reported concerns about health insurance or money. MDS respondents endorsed a variety of strategies to mitigate the financial burden of treatment, including tapping into personal assets: 28% used retirement funds; 15% depleted savings; and 1% filed for bankruptcy. Of those taking prescription medication for MDS in the past 12 months, 10% reported engaging in medication scrimping to save money in the prior year, such as skipping doses, taking less medication, or delaying a refill.

The *Cancer Experience Registry* also contains a national sample of 24 MDS caregivers. The top 10 self-focused concerns reported by respondents were worrying about the future (83%), feeling sad or depressed (67%), exercising (67%), feeling lonely or isolated (58%), changes in work, school, home (50%), feeling nervous or afraid (46%), keeping up with health care needs (46%), eating and nutrition (46%), providing physical care to the patient (29%), and managing insurance and bills (25%). Whereas patient focused concerns reported by MDS caregivers included worrying about the future (83%), patient's pain (67%), changes in patient's mood (58%), feeling lonely or isolated (58%), changes in patient's memory or thinking (54%), and patient's eating and nutrition (50%).

Findings from a recent analysis of concerns provided by cancer caregivers underscore the importance of providing support to caregivers given their role in a patient's well-being.[17] Caregivers were screened by Cancer Support Community's Cancer Support Source-Caregiver™ (CSS-CG), designed to help facilitate the early identification of family caregivers in need of support services. Of note, concern about the patient's physical pain or discomfort and their cancer progressing/recurring were top concerns for which caregivers most frequently requested information and referrals. Many cancer caregivers also endorsed receiving information and referrals for self-focused concerns and desired support for these needs.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Detailed methods for the systematic literature review assessing the evidence on imetelstat for the treatment of anemia in MDS are available in Supplement Section D1.

Scope of Review

We evaluated the clinical effectiveness of imetelstat compared to placebo for the treatment of anemia in adults with lower risk MDS who are transfusion dependent, without del(5q) subtype, and relapsed or refractory to previous treatment with ESAs. We also compared imetelstat to luspatercept in the subgroup of patients with ring sideroblasts (RS+). All patients received best supportive care. We sought evidence on patient-important outcomes including transfusion independence, transfusion burden, fatigue, quality of life, and adverse events. The full scope of the review is described in Supplement Section D1.

Evidence Base

We identified two trials that met our search criteria: IMerge comparing imetelstat to placebo and MEDALIST comparing luspatercept to placebo.[18,19] Both trials were at low risk of bias for the primary outcome.

Imetelstat

The IMerge trial included a Phase II, single-arm, open-label study, and a Phase III, double-blind, randomized, placebo-controlled trial. The IMerge Phase III trial was the focus of our comparative effectiveness assessment. See Supplement Sections D1-D2 for more details on the study design, efficacy, and safety data of the Phase II study.

IMerge enrolled adults with a confirmed diagnosis of MDS (WHO 2016 criteria), who were low to intermediate-1 risk using the IPSS criteria and did not have del(5q). In addition, participants were required to be relapsed or refractory to ESA treatment and transfusion dependent with at least four red blood cell (RBC) transfusions over eight weeks (Table 3.1). Participants who had prior treatment with hypomethylating agents (HMA) or lenalidomide, a history of hematopoietic stem cell transplant, or clinically significant cardiovascular diseases were excluded from the trial. The primary endpoint was the proportion of participants achieving eight weeks of transfusion independence during the 52-week treatment phase.[18]

The trial randomized 178 patients to receive imetelstat (N = 118) or placebo (N = 60) intravenously every four weeks. Baseline characteristics were well balanced between arms (Table 3.2). Trial participants had a median age of 72 years and 62% were male. The majority of enrolled participants (93%) had lower-risk MDS based on IPSS-R, and nearly two-thirds (62%) were RS+. The RBC transfusion burden was low (≥4 to ≤6 units over 8 weeks) for 53% of participants and high (>6 units over 8 weeks) for 47% of participants. See Table 3.2. and Supplement Table D3.2 for more detailed baseline characteristics.[18]

Luspatercept

MEDALIST was a Phase III, double-blind, randomized, placebo-controlled trial. The trial included a screening period of four weeks, a treatment phase for 24 weeks, and an additional double-blind extension phase after week 25.

The MEDALIST trial enrolled adults with a confirmed diagnosis of MDS (WHO 2016 criteria), with disease classified as very low, low, or intermediate risk using IPSS-R (Table 3.1). All participants were RS+ and did not have the del(5q) subtype. In addition, participants were required to be relapsed or refractory to ESA treatment and transfusion dependent with at least two RBC transfusions over eight weeks. Key exclusion criteria included previous treatment with an HMA or lenalidomide, either allogeneic or autologous stem cell transplantation, or having a diagnosis of AML. The primary endpoint was the proportion of participants achieving eight weeks of transfusion independence during the 24-week trial period.[19]

The trial randomized 229 participants to receive luspatercept (N = 153) or placebo (N = 76) subcutaneously every three weeks. Baseline characteristics were similar across the arms (Table 3.2). Participants were mostly older adults, with lower risk MDS based on IPSS-R, ESA treatment-experienced (95%), and with a median of five units of RBC transfusions per 8-week period. All participants were RS+, with a majority of them (95%) classified as MDS with refractory cytopenia with multilineage dysplasia.[19] See Table 3.2 below and Supplement Table D3.2 for more details.

It is worth noting in Table 3.2 that the baseline characteristics of the patients in the MEDALIST trial are similar to those of the IMerge trial despite some differences in their inclusion criteria.

Table 3.1 Overview of Key Studies

Treatment Clinical Trial	Design Sample Size	Included Population	Primary Outcome
Imetelstat IMerge[18]	Phase III, double-blind, placebo-controlled RCT N = 178	• Adults diagnosed with MDS according to WHO criteria* • IPSS: low or intermediate-1 • Non-del(5q) subtype • Transfusion burden of ≥4 units/8 weeks • Refractory/relapsed to ESAs • No prior use of HMAs or lenalidomide • ECOG 0, 1, or 2	RBC-TI for eight consecutive weeks (52-week trial period)
Luspatercept MEDALIST[19]	Phase III, double-blind, placebo-controlled RCT N = 229	• Adults diagnosed with MDS with ring sideroblasts (RS+) according to WHO criteria* • IPSS-R: very low, low, intermediate • Non-del(5q) subtype • Transfusion burden of ≥2 units/8 weeks • Refractory/intolerant/ineligible to ESAs • No prior use of HMAs or luspatercept • ECOG 0, 1, or 2	RBC-TI for eight consecutive weeks (24-week trial period)

ECOG: Easter Cooperative Oncology Group, ESA: erythropoiesis-stimulating agent, HMA: hypomethylating agents, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-Revised, RBC-TI: red blood cell transfusion independence, WHO: World Health Organization

* WHO criteria are based on peripheral blood and bone marrow findings and cytogenetics

Table 3.2 Baseline Characteristics of the Phase III Trials

Trial		**IMerge[18]**		**MEDALIST[19]**	
Arms		**Imetelstat**	**Placebo**	**Luspatercept**	**Placebo**
N		118	60	153	76
Median age, years		72	73	71	72
Male sex – n (%)		71 (60%)	40 (67%)	94 (61%)	50 (66%)
WHO Classification n (%)	**RS+**	72 (62%)	37 (62%)	153 (100%)	76 (100%)
	RS-	44 (37%)	23 (38%)	0 (0%)	0 (0%)
IPSS-R Risk Category* n (%)	**Very low**	3 (3%)	2 (3%)	18 (12%)	6 (8%)
	Low	87 (74%)	46 (77%)	109 (71%)	57 (75%)
	Intermediate	20 (17%)	8 (13%)	25 (16%)	13 (17%)
Prior Transfusion Burden (U/8 weeks) n (%)	**<4**	0 (0%)	0 (0%)	46 (30%)	20 (26%)
	≥4 to ≤6	62 (53%)	33 (55%)	41 (27%)	23 (30%)
	>6	56 (48%)	27 (45%)	66 (43%)	33 (43%)
Hemoglobin (g/dL) – Median (range)		7.9 (5.3-10.1)	7.8 (6.1-9.2)	7.6 (6-10)	7.6 (5-9)
Prior Treatment with ESAs – n (%)		108 (92%)	52 (87%)	148 (97%)	70 (92%)

ESA: erythropoiesis-stimulating agent, g/dL: grams per deciliter, IPSS-R: International Prognostic Scoring System-Revised, N: total number, RBC: red blood cell, U: units, WHO: World Health Organization

* Only one patient in the imetelstat arm of the IMerge trial was high-risk when IPSS-R criteria were applied

Evaluation of Clinical Trial Diversity

We rated the demographic diversity (race/ethnicity, sex, age) of the participants in the trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[20] The assessment of race and ethnicity representation in the IMerge trial yielded a rating of "fair" for its good representation of White and Asian populations but inadequate enrollment of Black or African American and Hispanic adults. The MEDALIST trial was rated "poor" for failing to adequately represent Black or African American and Hispanic adults and lacking data on the Asian population. Both trials were rated "good" for sex, aligning with the higher prevalence of MDS in males. Regarding age, the rating for IMerge was inconclusive because data related to the subgroup of participants ≥65 years old was not available, while the MEDALIST trial was rated as "good", reflecting the higher prevalence of MDS in this demographic. See Supplement D1 for full details of CDR methods and results.

3.2. Results

Clinical Benefits

Overall Population in Scope

We first describe the comparison between imetelstat and placebo in adults with lower-risk MDS without the del(5q) subtype who are transfusion dependent and ineligible for or refractory to ESAs.

Subsequently, we focus on the subset of patients in the IMerge trial with RS+ MDS, and compare the effectiveness of imetelstat in this subgroup to the effectiveness of luspatercept in the MEDALIST trial. These comparisons are indirect through their respective placebo groups.

Imetelstat

Transfusion Independence

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). More participants in the imetelstat arm met the clinically meaningful threshold of transfusion independence for at least 16 weeks compared to placebo (31% vs. 7%, p<0.001).[15,18] The median duration of transfusion independence was 52 weeks for imetelstat compared to 13 weeks for placebo (p<0.001).[5]

Patient-Reported Outcomes: FACIT-Fatigue

Patient-reported fatigue was measured using the FACIT-Fatigue score. See Supplement Section A1 for details on this measure. Treatment with imetelstat resulted in an improvement of at least three points sustained for at least two cycles in more participants compared to placebo (50% vs. 40%), although this difference was not statistically significant.[9]

Overall Survival, Progression Free Survival, and Progression to AML

Data on overall survival and progression-free survival is currently immature (Table 3.3). Median progression-free survival was not reached in either group as of January 15, 2024. Overall survival and progression to higher-risk MDS or AML were similar in the two arms.[5] To date, 13 (11%) participants in the imetelstat arm and eight (13%) in the placebo arm progressed to higher-risk MDS with two participants in each group further progressing to AML.[5,18] See Supplement Table D3.3 for more details.

Table 3.3. IMerge Phase III Results[5,18]

Arms	Imetelstat	Placebo
N	118	60
8-week RBC-TI – n (%)	47 (40%)	9 (15%)
16-week RBC-TI – n (%)	37 (31%)	4 (7%)
Sustained Meaningful Improvement in FACIT-Fatigue* – n (%)	59 (50%)	23† (40%)
Progression to Higher Risk MDS‡ – n (%)	13 (11%)	8 (13%)
Progression to AML‡ – n (%)	2 (2%)	2 (2%)
Mortality‡ **–** n (%)	35 (30%)	15 (25%)

AML: acute myeloid leukemia, n: number, N: total number, FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy, RBC-TI: red blood cell transfusion independence
* Increase of ≥3 points on the FACIT-Fatigue score for ≥2 consecutive cycles
† Out of 57 evaluable patients
‡ Data from the latest follow-up as of January 15, 2024

Ring-Sideroblast Positive (RS+) Subpopulation

To compare the efficacy of imetelstat to luspatercept, we focused on the subset of IMerge participants who were RS+ (110 out of 178). While the participants in the two trials are similar in terms of age, sex, baseline hemoglobin, prior use of ESAs, and IPSS-R classification (see Table 3.1), the baseline characteristics of the RS+ subset of the IMerge trial are not publicly available.

Imetelstat

Similar to participants in the overall trial, a higher proportion of RS+ patients receiving imetelstat were transfusion independent for at least eight consecutive weeks compared to those receiving placebo (45% vs. 19%, p=0.016). A third of the patients (33%) in the RS+ subgroup experienced 24-week transfusion independence compared to 5% in the placebo group (p=0.003). Additionally, the median duration of 8-week transfusion independence was greater in the imetelstat arm compared to placebo (47 vs. 17 weeks; p=0.035).[18] See Table 3.4.

Results for patient-reported fatigue, survival, and disease progression have not been reported for the RS+ subgroup.

Luspatercept

In the MEDALIST Phase III trial, data relevant to the primary endpoint of 8-week transfusion independence were available for both 24 and 48 weeks of follow-up. We highlighted data over 48 weeks as it more closely matches the 52-week follow-up in the IMerge trial. A higher proportion of patients treated with luspatercept achieved 8-week transfusion independence during 48 weeks compared to the placebo group (45% vs. 16%; p<.00001), similar to the results for imetelstat.[21] See Table 3.4.

Table 3.4. Key Results in Participants with Ring Sideroblasts (RS+)

Trial (Subpopulation)	IMerge (RS+)[18]		MEDALIST[19]			
Follow-up	52 weeks		48 weeks		24 weeks	
Arm	Imetelstat	Placebo	Luspatercept	Placebo	Luspatercept	Placebo
N	73	37	153	76	153	76
8-week RBC TI – n (%)	33 (45%)	7 (19%)	69 (45%)	12 (16%)	58 (38%)	10 (13%)

n: number, N: total number, RBC: red blood cell, RS+: ring sideroblast positive, TI: transfusion independence

The MEDALIST trial did not measure FACIT-Fatigue. Additional patient-reported outcomes from this trial including the EORTC QLQ-C30 and QOL-E are described in Supplement Section D2.[19,22]

Indirect Comparison: Imetelstat versus Luspatercept in RS+ Patients

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 shows similar efficacy, with both interventions being significantly better than placebo and no significant differences between the two active treatments. See Supplement Table D3.3 for detailed methods and additional trial results.

Table 3.5. NMA Results: Primary Endpoint of 8-Week Transfusion Independence

Imetelstat		
0.85 (0.35, 2.25)	**Luspatercept**	
2.48 (1.3, 5.73)	2.92 (1.77, 5.41)	**Placebo**

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. We used 8-week transfusion independence data during 52 weeks from the IMerge trial and 8-week transfusion independence data during 48 weeks from the MEDALIST trial.

Harms

The harms of imetelstat and luspatercept compared to their respective placebo groups are from the Phase III trials (Table 3.6). Additional safety data from the Phase II portion of IMerge is described in Supplement Section D2.

Imetelstat

The overall discontinuation rate was high in both arms (77%) during the 18-month follow-up period, with 16% of participants in the imetelstat group discontinuing due to adverse events compared to none in the placebo group. There were 19 deaths (16%) in the imetelstat arm and eight deaths (13%) in the placebo arm in the primary analysis. With 15 additional months of follow-up, mortality increased to 30% in the imetelstat arm and 25% in the placebo arm.[5,18]

Almost all IMerge trial participants experienced at least one adverse event during the trial. Grade 3/4 adverse events were more common in the imetelstat arm compared to the placebo arm (91%

vs. 48%). The most frequently reported grade 3/4 events were neutropenia and thrombocytopenia, occurring more often in the imetelstat arm (68% and 62%, respectively) compared to placebo (3% and 8%, respectively). Although such events were frequent, more than 80% of the cases of neutropenia and thrombocytopenia resolved to grade 2 or lower within four weeks, managed by dose delays, dose reductions, or use of growth factors. Three patients in the imetelstat arm with grade 3/4 neutropenia had concurrent grade 3/4 infections. No patients with grade 3/4 thrombocytopenia had a concurrent grade 3/4 bleeding event.[23] Other common adverse events experienced in the imetelstat group compared to placebo were infections (42% vs. 34%), bleeding events (21% vs. 12%), grade 3/4 anemia (19% vs. 7%), and grade 3/4 leukopenia (8% vs. 2%).[5,18] See Supplement Table D3.4 for more details.

Luspatercept

During the 24-week follow-up period, fewer patients treated with luspatercept discontinued the trial compared to the placebo (54% vs. 92%). However, discontinuation rates due to adverse events were similar across the two arms. Similarly, fewer patients died in the luspatercept arm compared to placebo (8% vs. 12%), with no deaths deemed to be treatment-related. Progression to higher risk MDS occurred in one patient in both arms, while three patients (2%) in the luspatercept arm and one patient (1%) in the placebo arm progressed to AML.[19] With an extended median follow-up period of around 40 months, the number of patients progressing to higher risk MDS and AML increased in both arms. Nine patients in the luspatercept arm progressed to higher risk MDS and four to AML, while in the placebo arm, three patients progressed to each of these conditions. [24]

Overall, nearly all patients (96%) participating in the MEDALIST trial had at least one adverse event, with a comparable proportion of patients experiencing grade 3/4 adverse events in both treatment arms. Fewer patients in the luspatercept arm experienced grade 3/4 neutropenia compared to those receiving placebo. There was no grade 3/4 thrombocytopenia in either treatment group. Grade 3/4 anemia and infection rates were similar across both arms.[19,25] See Supplement Table D3.4 for more details.

Table 3.6. Key Harms

Trial		IMerge[5,18,26]		MEDALIST[19,25]	
Arms		**Imetelstat**	**Placebo**	**Luspatercept**	**Placebo**
N		118	60	153	76
Discontinuations due to Adverse Events		19 (16%)	0 (0%)	13 (8%)	6 (8%)
Any Adverse Events		117 (99%)	59 (100%)	150 (98%)	70 (92%)
Grade 3/4 Adverse Events		107 (91%)	28 (48%)	65 (42%)	34 (45%)
Treatment-Related Adverse Events		97 (82%)	NR	NR	NR
Cytopenias					
Neutropenia	**Any Grade**	87 (74%)	4 (7%)	7 (5%)	7 (9%)
	Grade 3/4	80 (68%)	2 (3%)*	5 (3%)	6 (8%)
Thrombocytopenia	**Any Grade**	89 (75%)	6 (10%)	NR	NR
	Grade 3/4	73 (62%)	5 (8%)*	0	0
Anemia	**Any Grade**	24 (20%)	6 (10%)	11 (7%)	6 (8%)
	Grade 3/4	23 (19%)	4 (7%)*	10 (7%)	5 (7%)
Leukopenia	**Any Grade**	12 (10%)	1 (2%)	NR	NR
	Grade 3/4	9 (8%)	0 (0%)*	NR	NR
Clinical Consequences of Cytopenias					
Infections	**Any Grade**	50 (42%)	20 (34%)	82 (54%)	31 (41%)
	Grade 3/4	13 (11%)	8 (14%)	4/9 (44%)	3/7 (43%)
Bleeding Events	**Any Grade**	25 (21%)	7 (12%)	NR	NR
	Grade 3/4	3 (3%)	1 (2%)	NR	NR
Febrile Neutropenia	**Any Grade**	NR	NR	NR	NR
	Grade 3/4	1 (1%)	0 (0%)	NR	NR

N: total number, NR: not reported

* Out of 59 patients

Subgroup Analyses and Heterogeneity

We sought evidence on other subgroups of interest, including the ring sideroblasts negative (RS-) subgroup based on the WHO classification, IPSS category (low risk vs. intermediate), and baseline transfusion burden (low vs. high transfusion burden). Similar to the broader patient population outlined in the previous section, imetelstat demonstrated consistent efficacy benefits in achieving 8-week transfusion independence, 24-week transfusion independence, and median duration of transfusion independence compared to placebo across all subgroups.[18] Since subgroup effects are not statistically significant, we did not evaluate the credibility of subgroup effect medication using the Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN for RCT).[27]

WHO Classification: RS Negative (RS-)

Data for the RS- subgroup were only available from the IMerge trial. Although a lower response to imetelstat was observed compared to the RS+ subgroup in achieving the primary outcome of 8-week consecutive transfusion independence, treatment differences between imetelstat and placebo remained consistent in both subgroups. In the RS- subgroup, 32% of patients treated with imetelstat achieved the primary endpoint compared to 9% in the placebo arm (p=0.038), and in the RS+ subgroup, the corresponding numbers were 45% versus 19% (p=0.016).[18] See Supplement Table D3.5.

IPSS Risk Category

In the IMerge Phase III trial, treatment differences in achieving 8-week transfusion independence were greater in the intermediate-1 risk subgroup (difference: 35%, 95% CI 9% to 52%; p=0.034) compared to low risk subgroup (difference: 20%, 95% CI -0.1% to 35.2%; p=0.004), with imetelstat demonstrating superiority over placebo in both subgroups.[18] Data related to IPSS risk subgroups were not available from the MEDALIST trial. See Supplement Table D3.5.

Baseline Transfusion Burden

Both IMerge and MEDALIST had patients who had a baseline transfusion requirement of 4 to 6 units per 8-week duration and patients with ≥6 transfusion units per 8-week duration. In the IMerge Phase III trial, the treatment difference in achieving 8-week transfusion independence was comparable across both of these subgroups; 24% (95% CI 2% to 41%) for patients with 4 to 6 units per 8-week and 27% (95% CI 5% to 42%) for patients with ≥6 units per 8-week, respectively.[18] However, in the MEDALIST trial which only included MDS patients with RS+ status, the treatment difference was numerically greater for the 8-week transfusion independence outcome in the low-burden subgroup (difference: 32%, 95% CI 7% to 55%), favoring luspatercept over placebo, compared to the latter (difference: 6%, 95% CI -16% to 27%).[28] See Supplement Table D3.5.

Uncertainty and Controversies

The primary concern about 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. Hematologists are comfortable managing these side effects and in the IMerge clinical trial they did not translate into higher rates of infections, febrile neutropenia, hospitalizations, or bleeding, so this may not turn out to be an important barrier to their use. However, the outcomes may be less favorable in the real world.

As noted above, transfusion dependence has an important negative impact on patients' quality of life. However, the available data on fatigue, the most bothersome symptom according to patients living with MDS, suggest that this was only modestly impacted by treatment with imetelstat using the FACIT-Fatigue scale (50% with meaningful improvement with imetelstat compared with 40% with placebo, p-value not reported). Numerically, more fatigue related AEs were reported in the imetelstat group (29% vs. 22%) and the episodes lasted longer in the imetelstat group (median 19.1

weeks vs. 5.7 weeks). It is therefore unclear if imetelstat has a clinically meaningful impact on patients' quality of life.
The evidence base for imetelstat for the treatment of anemia in patients with lower risk MDS comes from one, relatively small, randomized trial. This limits the level of certainty concerning the net clinical benefit of imetelstat, particularly in the small subgroup of patients who are RS- and have the greatest unmet need.

A number of mutations commonly found in patients with MDS (for example SF3B1, TET2, ASXL1, and DNMT3A) have been associated with MDS prognosis. In an exploratory analysis, the trial reported that in evaluable patients, the percent reduction in these gene mutations was numerically greater in the group treated with imetelstat compared to the group treated with placebo. This suggests that imetelstat has the potential to improve outcomes in patients with MDS. However, the currently available data on progression free survival and overall survival do not support this hypothesis.

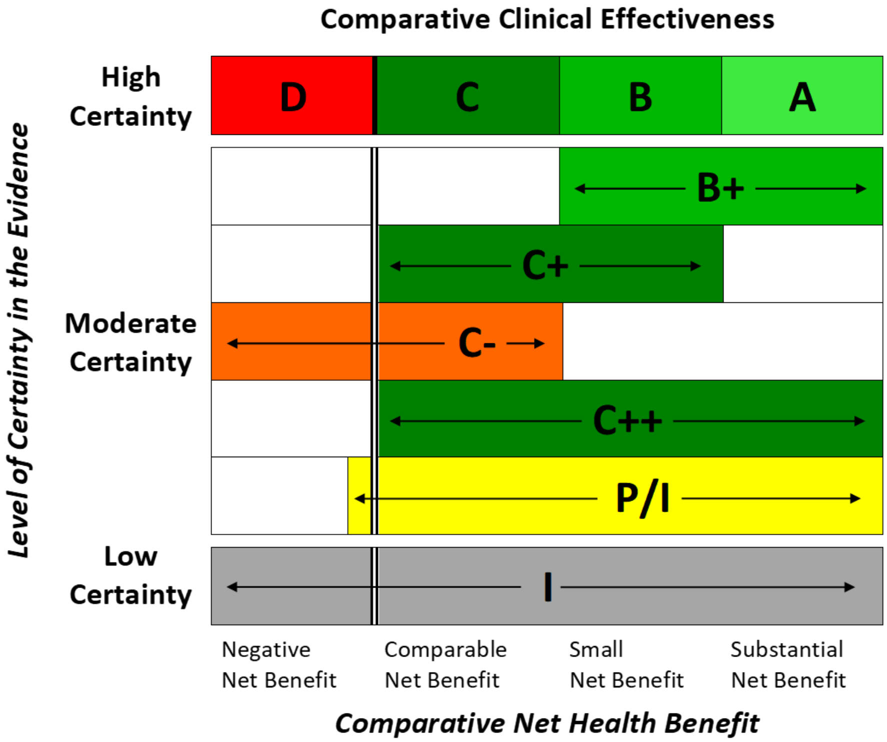
There are some concerns about the generalizability of the IMerge results to the US population. Only 7% (13 patients) of the study population were in the United States and the primary outcome, transfusion independence for at least 8 weeks was much lower in patients randomized to imetelstat in the US (12.5%) compared to those treated elsewhere (41.8%).

Finally, we had insufficient data to feel confident in our comparison of imetelstat to luspatercept in the subgroup of patients who were RS+. However, it is worth noting that while the inclusion criteria of the trials differed, patient characteristics were remarkably similar. In addition, the response rates were nearly identical. Our indirect comparison showed no significant differences in the response rates for the two drugs in patients with RS+ MDS. However, the data from the IMerge trial in the subgroup of RS+ patients were insufficient to have full confidence in the results of the indirect analyses. In addition, data on adverse events and the modified hematologic response-erythroid outcomes were not available for the RS+ subgroup of IMerge.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



*A = "**Superior**" - High certainty of a substantial (moderate-large) net health benefit*
*B = "**Incremental**" - High certainty of a small net health benefit*
*C = "**Comparable**"- High certainty of a comparable net health benefit*
*D= "**Negative**"- High certainty of an inferior net health benefit*
*B+= "**Incremental or Better**" – Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
*C+ = "**Comparable or Incremental**" - Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
*C- = "**Comparable or Inferior**" – Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
*C++ = "**Comparable or Better**" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
*P/I = "**Promising but Inconclusive**" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
*I = "**Insufficient**" – Any situation in which the level of certainty in the evidence is low*

Patients with Lower-Risk MDS Who Are Transfusion Dependent Despite ESAs

Compared with best supportive care, the net benefit of imetelstat is promising, but inconclusive (P/I). There are clear benefits in the reduction in the need for 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.

Patients with Lower-Risk MDS Who are Transfusion Dependent Despite ESAs Who Are RS Positive

Compared with luspatercept, we rate the evidence for imetelstat as insufficient (I). There is no evidence suggesting greater reductions in 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.

Table 3.7. Evidence Ratings

Population	Treatment	Comparator	Evidence Rating
Lower Risk MDS without del(5q) subtype	Imetelstat	Placebo/Best Supportive care	P/I
RS+ Subgroup	Imetelstat	Luspatercept	I

MDS: myelodysplastic syndrome, RS+: ring sideroblast positive

4. Long-Term Cost Effectiveness

4.1. Methods Overview

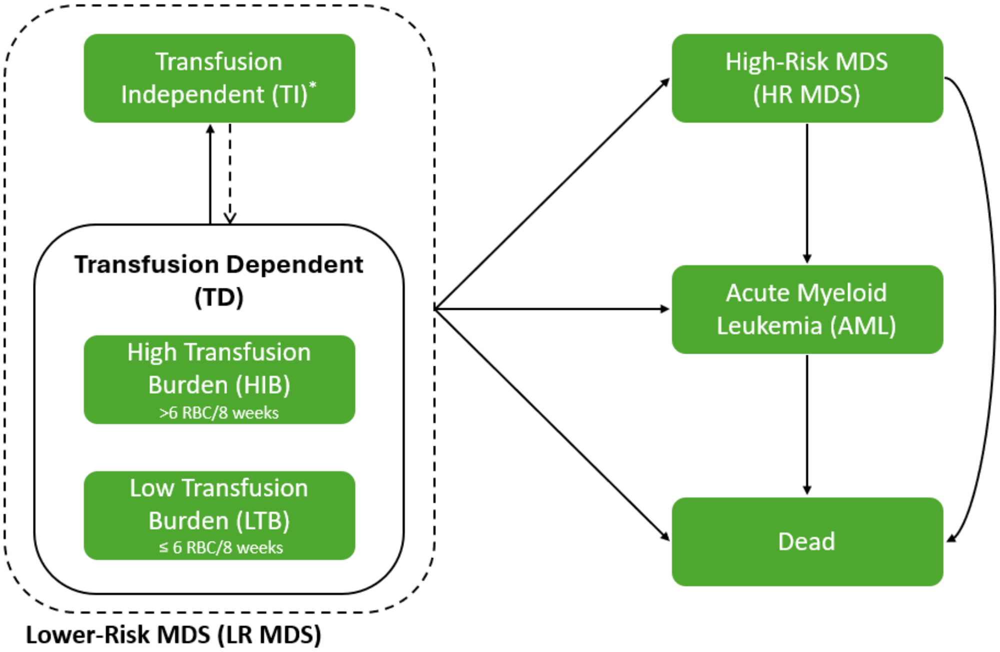
We developed a *de novo* decision analytic model for this evaluation, informed by the two key clinical trials and prior relevant economic models. Costs and outcomes were discounted at 3% per year, and a lifetime time horizon of 28 years was used.

The model focused on an intention-to-treat analysis, with a hypothetical cohort of 1) all imetelstat eligible MDS patients who were treated with imetelstat with best supportive care, or best supportive care alone, and 2) ring sideroblast positive patients who were treated with imetelstat with best supportive care, luspatercept with best supportive care, or received best supportive care alone. Best supportive care consisted of red blood cells (RBC) and platelet transfusions, myeloid growth factors (MGF), and iron chelation therapy. The model cycle length was four weeks, based on what was observed in prior published economic models and available clinical data. [29-31]

The Markov model structure consisted of six health states: transfusion dependent with low transfusion burden (LTB) (receiving ≤6 red blood cell units/8 weeks), transfusion dependent with high transfusion burden (HTB) (receiving >6 red blood cell units/8 weeks), transfusion independent (TI), high risk MDS (HR-MDS), acute myeloid leukemia (AML), and death (Figure 4.1). All individuals entered the model in one of the transfusion dependent states and could transition to transfusion independent if they achieved a response to treatment defined as achieving transfusion independence for at least eight consecutive weeks. Patients could also transition to HR-MDS and AML if their disease progressed. The primary modeled treatment effect for imetelstat and luspatercept was to decrease the transfusion burden in lower-risk MDS. We assumed that neither drug has an impact on the progression to high risk MDS or AML, or a direct effect on overall survival due to a lack of data indicating such correlations.

Patients remained in the model until they died. All patients could transition to death from all causes from any of the alive health states.

Figure 4.1. Model Structure



* Response to treatment defined as achieving transfusion independence for ≥ 8 consecutive weeks informed by interim trial results. Response is a one-time movement after the first four-week cycle. A transition back to transfusion dependent from independent represents a loss of response.

Changes to the economic evaluation between the draft Evidence Report and the revised Evidence Report included:

- Updated cost-effectiveness results based on a publicly available, manufacturer-reported price for imetelstat. The annual price increased from the $250,000 placeholder price to $365,197 following the labeled dose of 7.1mg/kg (equivalent to 7.5 mg/kg of imetelstat sodium used in trials).[16]
- Corrections to the disaggregated undiscounted and discounted results reported for the indirect, "non-zero" approach to the modified societal perspective analysis reported in the Supplementary Materials Section E4. The incremental cost-effectiveness ratios reported in the draft Evidence Report, however, were correctly displayed.

4.2. Key Model Assumptions and Inputs

Our model includes several assumptions stated in Table 4.1.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Response and transition to transfusion independence were defined as achieving transfusion independence for at least eight consecutive weeks.	This was the primary endpoint in the clinical trials. According to the updated IWG 2018 definition of hematological improvement-erythroid (HI-E), eight weeks was not a clinically meaningful end point as it is not long enough to capture quality of life changes.[15] However, due to a lack of data for the 16-week endpoint we used IMerge's definition of response and defining transfusion independence as eight consecutive weeks or longer for our base case. This assumption might lead to an overestimate of treatment effect. We explored a 16-week endpoint in a scenario analysis.
Patients who achieved transfusion independence for at least eight weeks transitioned to the transfusion independent state after the first four-week cycle.	Patients only contributed to responder rates if they maintained transfusion independence for at least 8 weeks. However, patients who respond begin becoming transfusion independent early after treatment initiation.[18] We therefore transitioned patients before the eight weeks to better capture when transfusion independence started.
Treatment was assumed to have an indirect effect on death, and no effect on disease progression to high risk MDS or AML.	There was insufficient data on long-term outcomes to inform direct treatment effect on disease progression and survival for any interventions in this model. The primary modeled treatment effect was to decrease the transfusion burden through transitions to transfusion independence. Our model included an indirect treatment effect by applying a hazard ratio for mortality to transfusion independent individuals.
Patients discontinued treatment if they had no response by 24-weeks, lost response or progressed.	From the clinical experts we consulted there was no clear reason to keep a patient on a treatment if they were not responding. It was assumed that when a patient lost response, they no longer received benefits from treatment and should thus come off.
Patients did not move between high and low transfusion burden states.	There was a lack of data to inform these transitions and patients were kept at their baseline distributions in low and high transfusion dependent states throughout the model. This might have resulted in missing part of the treatment effect and ultimately led to an underestimation of the treatment benefit. We explored this assumption using data on minor response hematological improvement of 50% reduction in red blood cell units over 16 weeks.

Assumption	Rationale
Baseline characteristics, adverse event frequencies, and average dose intensities were the same in the ring sideroblast positive subgroup as the overall population in IMerge with ring sideroblast positive and negative patients.	There was lack of data for these measures in IMerge for the ring sideroblast positive subgroup specifically. As a result we used data from the overall population (two-thirds of patients in IMerge were RS+).

HI-E: Hematological Improvement-Erythroid

Interventions & Comparators

The list of interventions and comparators was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The intervention included imetelstat (Rytelo™, Geron Corporation) with best supportive care. The comparators included luspatercept (Reblozyl®, Bristol Myers Squibb) along with best supportive care in RS+ patients only, and best supportive care alone in RS+ and RS- patients.

Clinical Inputs

We used results from the IMerge trial for imetelstat with best supportive care and best supportive care alone. We used results from the MEDALIST trial for luspatercept.

Transition Probabilities

We used publicly available data from IMerge to model transitions for imetelstat and best supportive care in the overall analysis. Individuals transitioned to transfusion independence after the first four-week cycle, based on the proportion observed to respond in the trial. The transition back to transfusion dependence in patients who lost response was based on the duration of RBC-TI curves for each intervention. For the RS+ analysis, we used BSC response rates for the RS+ BSC population in IMerge to model the transition to transfusion independence. Relative risks from an indirect treatment comparison of the IMerge and MEDALIST trials were used to estimate the transition to transfusion independence for imetelstat and luspatercept (Table 4.2). We did not have duration of response curves for the imetelstat and best supportive care treatments in RS+ patients and used hazard rates from an exponential survival model estimated using the median response duration times. For luspatercept this transition was based on an exponential model fit to the published duration of response curve. Due to lack of data, we did not model the transitions between high and low transfusion burdens, and we kept the baseline proportions of high transfusion burden and low transfusion burden in our base-case; as patients lost response they returned to their respective burden level at baseline.

Although trial results have not shown an effect on survival, RBC transfusions have been shown to be an independent risk factor for mortality, increasing non-leukemic deaths from infection, bleeding and cardiovascular issues when compared to transfusion independent patients.[32] As a result we included a hazard ratio for mortality for transfusion independent patients in our base case, capturing an indirect treatment effect on mortality. We explored a scenario analysis where we did not apply this hazard ratio to examine outcomes when transfusion independence had no impact on survival in section 4.3. Further details regarding mortality and transitions to HR MDS and AML can be found in Supplemental Materials Section E2.

Table 4.2. Transition Probabilities for Treatment Response

<table>
<tr><th colspan="4">Overall</th></tr>
<tr><th>Parameter</th><th>Imetelstat
(IMerge)</th><th colspan="2">Best Supportive Care
(IMerge)</th></tr>
<tr><td>8-week RBC-TI for Low Transfusion Burden (%)</td><td>45.2</td><td colspan="2">21.2</td></tr>
<tr><td>8-week RBC-TI for High Transfusion Burden (%)</td><td>33.9</td><td colspan="2">7.4</td></tr>
<tr><td>TI Duration (transition probability from TI to TD)</td><td>0.048</td><td colspan="2">Log-normal
μ: 2.604
σ: 0.607</td></tr>
<tr><th colspan="4">Ring Sideroblast Positive</th></tr>
<tr><th>Parameter</th><th>Imetelstat
(IMerge)</th><th>Luspatercept
(MEDALIST)</th><th>Best Supportive Care
(IMerge)</th></tr>
<tr><td>8-week RBC-TI</td><td>RR to Best Supportive Care: 2.48 (1.3, 5.73)</td><td>RR to Best Supportive Care: 2.92 (1.77, 5.41)</td><td>19%</td></tr>
<tr><td>TI Duration (transition probability)</td><td>0.058</td><td>0.069</td><td>0.151</td></tr>
</table>

KM: Kaplan-Meier, RBC: Red Blood Cell, RR: Relative Risk, TI: Transfusion Independent, TD: Transfusion Dependent, λ: Hazard Rate

Discontinuation

We used discontinuation data in the results from IMerge for imetelstat, and data from MEDALIST for luspatercept to inform discontinuation due to treatment-emergent adverse events, with 16% and 8% discontinuing respectively. In addition, we assumed patients who did not respond by 24 weeks, those who responded then lost response, and those who progressed to HR-MDS or AML also discontinued. Patients who discontinued imetelstat or luspatercept and remained in lower risk received best supportive care.

Adverse Events

The adverse events included in our model were grade 3-4 thrombocytopenia, neutropenia, anemia, and leukopenia (Table 4.3). We included disutilities for adverse events, which were applied in the first cycle and lasted two weeks.

Table 4.3. Adverse Events (Grade 3-4)

Parameter	Imetelstat (%)	Best Supportive Care (%)	Luspatercept (%)	Treatment Cost	Disutility
Thrombocytopenia	62	8	0	$9,974†	0.0096[33]
Neutropenia	68	3	3.3	$6,423†	0.0134[33]
Anemia	19	7	6.5	$5,759†	0.0028[34]
Leukopenia	8	0	0*	$4,541†	0.0077[35]

* Not available, assumed to be 0. MEDALIST reported serious adverse events with ≥ 2% incidence.

† CMS MS-DRG: Thrombocytopenia (DRG 813), Neutropenia (DRG 810), Anemia (DRG 812), Leukopenia (DRG 816)

Health State Utilities

Health state utilities were derived from publicly available literature as utilities from IMerge were exploratory endpoints only and are not publicly available. We used consistent health state utility values across all treatments evaluated. Utilities used in the model can be found in Table 4.4, with additional details in the Supplemental Materials Section E2.

Table 4.4. Health State Utilities Format

Health State Utilities		
Parameter	**Score**	**Source**
Transfusion Dependent with High Transfusion Burden	0.60	Szende et al. 2009[36]
Transfusion Dependent with Low Transfusion Burden	0.77	Szende et al. 2009[36]
Transfusion Independent	0.84	Szende et al. 2009[36]
High-Risk MDS	0.67	Crespo et al. 2013[37]
AML	0.53	Pan et al. 2010[38]

AML: Acute Myeloid Leukemia, MDS: Myelodysplastic Syndromes

Cost Inputs

All costs used in the model were updated to 2024 US dollars.

For imetelstat, we used the available wholesale acquisition cost of $9,884 for a 188 mg vial from REDBOOK.[39] The acquisition costs displayed in Table 4.5. were calculated using the labeled dose of 7.1mg/kg. The average dose used in the model included dose reductions observed in the pivotal trial, i.e. 95% from week 4 to 12, and 86% from week 12 onward. Further details can be found in the Supplementary Materials Section E2.

For luspatercept, we used the available wholesale acquisition costs from REDBOOK[39] of $3,876 per 25mg vial, and a 9% discount from SSR Health using the four quarter moving average Q3 2022 to Q3 2023.[40] Assumptions regarding dose titration were based on data from the MEDALIST trial, and are described in further detail the Supplement, Section E2. Weighted average acquisition costs after all up-titrations are detailed in Table 4.5.; as a result, drug costs in the first 12 weeks are lower than what is displayed.

We used the median body weight of 75 kg measured in IMerge for both drugs as they used weight-based dosing. Drug acquisition costs are detailed in Table 4.5, and non-drug costs related to MDS are detailed in the Supplementary Materials Table E2.5. Further details on drug utilization to estimate costs, costs for HR MDS and AML, and outpatient service costs can be found in the Supplementary Materials Section E2.

Adverse event unit costs were based on Medicare reimbursable rates for hospitalizations and are detailed in Table 4.3. These costs were applied to all patients who experienced the adverse event of interest under the assumption that all patients with a grade 3-4 event are hospitalized.

Table 4.5. Drug Costs

Drug	Acquisition Cost per Dose	Acquisition Cost per Year
Imetelstat	$27,996	$365,197
Luspatercept	$15,921	$276,919

4.3. Results

Base-Case Results

Total discounted costs, quality adjusted life years (QALYs), equal-value life years (evLYs) and life years (LYs) are detailed in Table 4.6. for the overall population, and in Table 4.7. for the RS+ population. Over the lifetime time horizon imetelstat with best supportive care resulted in higher total costs of approximately $200,000 and incremental gains in QALYs and evLYs of approximately 0.17 and 0.19, respectively, compared to best supportive care alone in the overall population. Imetelstat also resulted in a lower total number of RBC units transfused, with an incremental decrease of approximately 10 units over the lifetime.

In the RS+ population, imetelstat with best supportive care had total costs of approximately $200,000 higher than best supportive care alone and gains in QALYs and evLYs of 0.18 and 0.16, respectively. Imetelstat also resulted in reduced red blood cell transfusions by approximately 13 transfusions over the lifetime horizon. When compared to luspatercept with best supportive care, imetelstat was more costly by approximately $70,000 over the lifetime horizon, with approximately equal number of QALYs, evLYs and RBC units transfused.

The resultant incremental cost-effectiveness ratios in the overall population were $1,197,000 per QALY gained, and $1,029,000 per evLY gained for imetelstat + BSC compared to BSC alone. When compared to luspatercept + BSC in the RS+ population, imetelstat + BSC was more costly and less effective. Additional details for both populations are presented in Table 4.8.

Table 4.6. Results for the Base-Case for Imetelstat Compared to Best Supportive Care in the Overall Population

Treatment	Intervention Cost	Total Cost	Total RBC Units	QALYs	evLYs	Life Years
Imetelstat + BSC	$1,030,000	$1,150,000	149	2.83	2.86	4.07
Best Supportive Care	$846,000	$951,000	159	2.67	2.67	3.90

evLYs: equal-value life years, QALY: quality-adjusted life year, RBC: red blood cell

Table 4.7. Results for the Base-Case for Imetelstat Compared to Luspatercept and Best Supportive Care in Ring Sideroblast + Population

Treatment	Intervention Cost	Total Cost	Total RBC Units	QALYs	evLYs†	Life Years
Imetelstat + BSC	$1,024,000	$1,144,000	150	2.84	2.87	4.08
Luspatercept + BSC	$964,000	$1,073,000	150	2.86	2.88	4.08
Best Supportive Care	$839,000	$945,000	163	2.69	2.69	3.92

evLYs: equal value of life years, QALY: quality-adjusted life year, RBC: red blood cell

† evLYs were calculated relative to best supportive care

Table 4.8. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Imetelstat + BSC(Overall)	**Best Supportive Care (Overall)**	$1,197,000	$1,029,000	$1,162,000
Imetelstat + BSC (RS+)	**Luspatercept + BSC (RS+)**	More costly, less effective	More costly, less effective	More costly, less effective
	Best Supportive Care (RS+)	$ 1,297,000	$1,115,000	$1,269,000

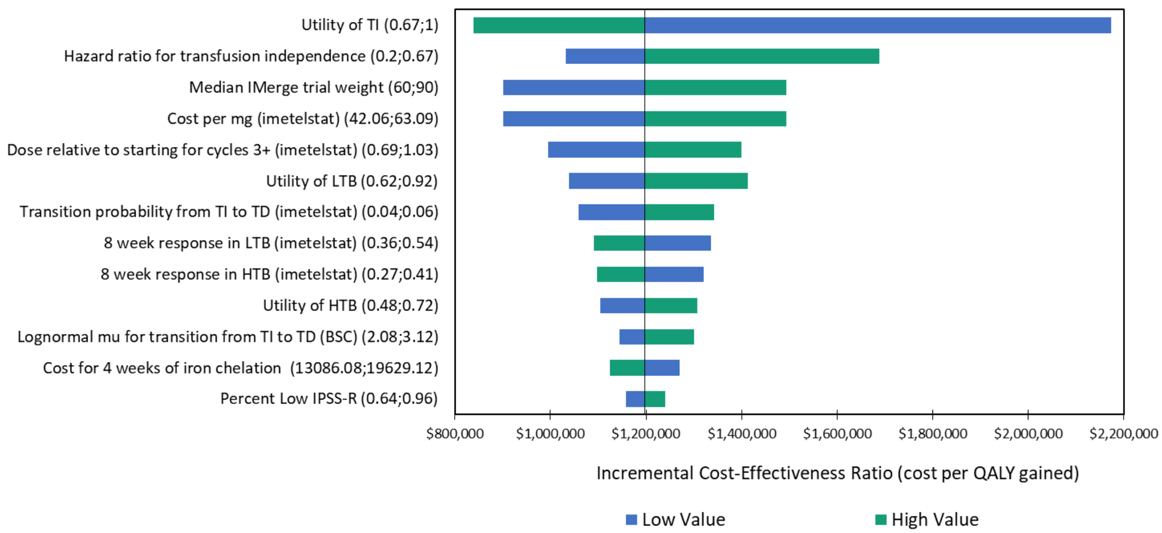
evLYs: equal value of life years gained, QALY: quality-adjusted life year

Sensitivity Analyses

One-way sensitivity analyses were conducted to identify the impact of parameter uncertainty and key drivers of model outcomes. Figure 4.2 presents the results for imetelstat compared to best supportive care in the overall population from the health care sector perspective. The most influential inputs were the utility values for transfusion independence and the low-transfusion burden health states, imetelstat price, and average dose for imetelstat, mortality hazard ratio for transfusion independence, response rates and duration of response for imetelstat, and iron chelation costs. Details of the analysis and results for the RS+ population can be found in the Supplementary Materials Section E3.

Probabilistic sensitivity analyses were conducted by jointly varying all parameters over 1000 simulations, then calculating the proportion of simulations that were cost-effective at various commonly used willingness-to-pay thresholds (Table 4.9 and 4.10). Imetelstat had a 0% probability of being cost effective across all thresholds evaluated vs. best supportive care in the overall population. Results for the RS+ analysis can be found in the Supplementary Materials Section E3.

Figure 4.2. Tornado Diagram for Imetelstat Compared to Best Supportive Care in the Overall Population



TI: Transfusion Independent, TD: Transfusion Dependent, LTB: Low Transfusion Burden, HTB: High Transfusion Burden, mg: milligram

Table 4.9. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Imetelstat versus Best Supportive Care

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Imetelstat + BSC (Overall Population)	0%	0%	0%	0%

QALY: quality-adjusted life year

Table 4.10. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Imetelstat versus Best Supportive Care

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Imetelstat + BSC (Overall Population)	0%	0%	0%	0%

evLYs: equal value of life years gained

Scenario Analyses

We conducted scenario analyses to examine uncertainty and potential variation in the findings. The scenarios are presented below, and findings are presented in Tables 4.11 and 4.12. Findings were not materially different from those observed in the base case aside from scenario 4. When we removed the effect transfusion independence had on mortality this reduced the treatment effect observed and increased the incremental cost-effectiveness ratios from $1,197,000 to $3,784,000 per QALY in the overall analysis. Additional details can be found in Supplementary Materials Section E4.

1. Modified societal perspective using an indirect, “non-zero” approach as described in the Supplementary Materials Section E4.
2. Definition of response changed in overall analysis from 8 to 16 consecutive weeks of transfusion independence.
3. Transition from high to low burden transfusion dependence for overall analysis based on minor hematological improvement of 50% reduction in red blood cell units in 16 weeks.
4. Removed mortality hazard ratio for TI, so treatment has no indirect effect on mortality.

Table 4.11. Scenario Analysis Results

Treatment (Population)	Intervention Cost	Total Cost	QALYs	evLYs	Life Years
Scenario 1: Modified Societal Perspective					
Imetelstat + BSC (Overall)	$1,030,000	$1,159,000	2.83	2.86	4.07
BSC (Overall)	$846,000	$968,000	2.67	2.67	3.90
Scenario 2: 16-week Transfusion Independence					
Imetelstat + BSC (Overall)	$1,022,000	$1,142,000	2.80	2.82	4.04
BSC (Overall)	$846,000	$951,000	2.67	2.67	3.90
Scenario 3: Minor HI-E Response					
Imetelstat + BSC (Overall)	$1,029,000	$1,149,000	2.87	2.90	4.07
BSC (Overall)	$845,000	$950,000	2.70	2.70	3.90
Scenario 4: No Indirect Mortality Effect					
Imetelstat + BSC (Overall)	$985,000	$1,101,000	2.70	2.70	3.89
BSC (Overall)	$843,000	$948,000	2.66	2.66	3.89
Imetelstat + BSC (RS+)	$978,000	$1,094,000	2.70	2.70	3.89
Luspatercept + BSC (RS+)	$920,000	$1,025,000	2.72	2.72	3.89
BSC (RS+)	$833,000	$938,000	2.66	2.66	3.89

evLY: equal-value of life-year, QALY: quality-adjusted life-year, HI-E: hematological improvement-erythroid, BSC: best supportive care, RS+: ring sideroblast positive

Table 4.12. Scenario Analysis Results (Overall Population)

Treatment	Base Case Results	Scenario 1: Modified Societal Perspective	Scenario 2: 16-Week Transfusion Independence	Scenario 3: Minor HI-E Response	Scenario 4: No Indirect Mortality Effect
	Incremental Cost-Effectiveness Ratio ($/QALY)				
Imetelstat + BSC vs. BSC alone	$1,197,000	$1,151,000	$1,466,000	$1,135,000	$3,784,000
	Incremental Cost-Effectiveness Ratio ($/evLY)				
Imetelstat + BSC vs. BSC alone	$1,029,000	$989,000	$1,257,000	$991,000	$3,784,000

evLY: equal-value of life-year, QALY: quality-adjusted life-year, BSC: best supportive care, HI-E: hematological improvement-erythroid

Threshold Analyses

Threshold analyses were conducted for imetelstat to calculate the price needed to meet commonly accepted cost-effectiveness thresholds for QALY and evLYs and are shown below (Table 4.8 and 4.9). Note that these were only calculated for imetelstat plus best supportive care versus best supportive care alone in the overall population, as imetelstat was slightly less effective than luspatercept in the RS+ population (precluding threshold calculations) and is not likely to be differentially priced based on RS status. Annual prices were calculated with the starting dose of 7.1mg/kg and a body weight of 75kg every 4 weeks.

Table 4.13. QALY-Based Threshold Analysis Results

	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Imetelstat (Overall)	$82,500	$ 94,800	$ 107,000	$ 119,000

QALY: quality-adjusted life-year

Table 4.14. evLY-Based Threshold Analysis Results

	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Imetelstat (Overall)	$84,500	$ 98,900	$113,000	$ 128,000

evLYs: equal value of life years

Uncertainty and Controversies

Given the limited amount of publicly available data to inform the cost-effectiveness analysis, we were unable to model patient transitions between high and low transfusion burden in the overall analysis. We assumed patients stayed in high and low burden states based on their initial proportions at baseline, although there is expected to be movement between the two groups due to the disease trajectory as well as the treatment effect. We explored a reduction in transfusion burden using minor hematological improvement-erythroid response statistics in a scenario analysis, however we did not have any data to model any increase due to the disease trajectory. Statistics on the number of units transfused for the transfusion dependent patients were only provided for the overall imetelstat population and not by transfusion burden or ring sideroblast status. Transfusions contributed a significant amount to overall costs based on average numbers of five and seven transfusions for low and high burden respectively, but these estimates are uncertain because of limited data on the distribution of transfusion volume.

Additionally, we lacked significant data for the RS+ subgroup analysis. We did not have baseline characteristics specific to this subgroup, and so assumed characteristics of the overall imetelstat population instead. We also did not have information about adverse events for the subgroup and had to apply discontinuation due to treatment emergent adverse events, and adverse event rates in general, from the overall population. For treatment duration we only had median times for the imetelstat and BSC populations, and therefore were required to assume a constant rate of loss of response. In addition, response rates for the RS+ population were for the whole group, and not by transfusion burden; we therefore were forced to collapse the high and low transfusion burden health states into one transfusion dependent state. Finally, we had to assume dosing of imetelstat for the RS+ subgroup was the same as the dose intensity curve published for the overall imetelstat population due to lack of data.

The utility values used were from a mix of patients with some from outside of the US, including the UK, Germany and France.[36] Utility differences between countries tend to be substantial yet have not been explained, which may introduce uncertainty about the generalizability of these utilities to the US patient population.[41] However, we believe these values likely align more to the patient population in the US than the US based values reported in the same paper. The US sample who participated in the TTO survey were recruited from a patient organization who may have milder disease when compared to the overall patient population.[36] Another limitation with these values comes from the surveys given to patients in the study, that described the transfusion states broadly including fatigue and tiredness and not just level of transfusion dependence. Although we would like to evaluate the difference in transfusion burden, these values covered a variety of other health issues and cannot be interpreted solely as a difference due to a reduction in transfusion burden.[42] This will likely overestimate the treatment effect, especially since only a limited impact on fatigue was observed in the trial. Despite the high transfusion burden utility of 0.60 being lower than the one used for HR MDS of 0.67, we believe this can be explained by HR MDS populations having a mix of LTB, HTB and transfusion independent patients.

4.4 Summary and Comment

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 imetelstat is currently not cost-effective at the wholesale acquisition cost of $9,884/188mg, exceeding commonly used price thresholds. In the ring sideroblast subgroup, imetelstat was shown to be more costly but also less effective when compared to luspatercept.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There is substantial unmet need despite currently available treatments.	There are currently no approved therapies for patients with lower risk MDS who are transfusion dependent despite ESA therapy who are RS negative. In addition, patients who are RS positive who fail luspatercept may benefit from imetelstat, though we have no data in this population of patients. To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below. Note that these estimates represent shortfalls for patients undergoing treatment primarily for MDS-induced anemia rather than for the overall burden of MDS. evLY shortfalls: • Absolute shortfall: 8.72 • Proportional shortfall: 74% QALY shortfalls: • Absolute shortfall: 8.20 • Proportional shortfall: 73% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively, that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.	Does not apply.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.	Yes, if long term transfusion independence is achieved.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.	Does not apply.

ICER did not calculate the Health Improvement Distribution Index (HIDI) because of sparse epidemiologic data. MDS has a higher prevalence in relatively advantaged communities (non-Hispanic White men). It is a disease of older people with a median age of diagnosis of 77 years.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the intervention(s) are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. The HBPB for imetelstat ranges between $94,800 to $113,000, at discounts between 69.1% to 74.0% from the WAC. Note that, while the base case model evaluation considered dose reductions experienced in the IMerge trial as a component of pricing over a lifetime horizon, the benchmarks presented here are based on the recommended starting dose of imetelstat for the purpose of full transparency.

Table 6.1. Annual Cost-Effectiveness Threshold Prices for Imetelstat

Annual Prices Using…	Annual WAC	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from WAC to Reach Threshold Prices
Imetelstat				
QALYs Gained	$365,197	$94,800	$107,000	70.7% - 74.0%
evLYs Gained		$98,900	$113,000	69.1% - 72.9%

evLY: equal value life year, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of imetelstat for adult patients with MDS. Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used an annual WAC of $323,027 in year one and $314,069 in years two to five for a 7.1mg/kg dose (based on an annual price of $365,197 adjusted for dose reduction) and the three threshold prices (at $50,000, $100,000, and $150,000 per evLYG) for imetelstat in our estimate of budget impact.

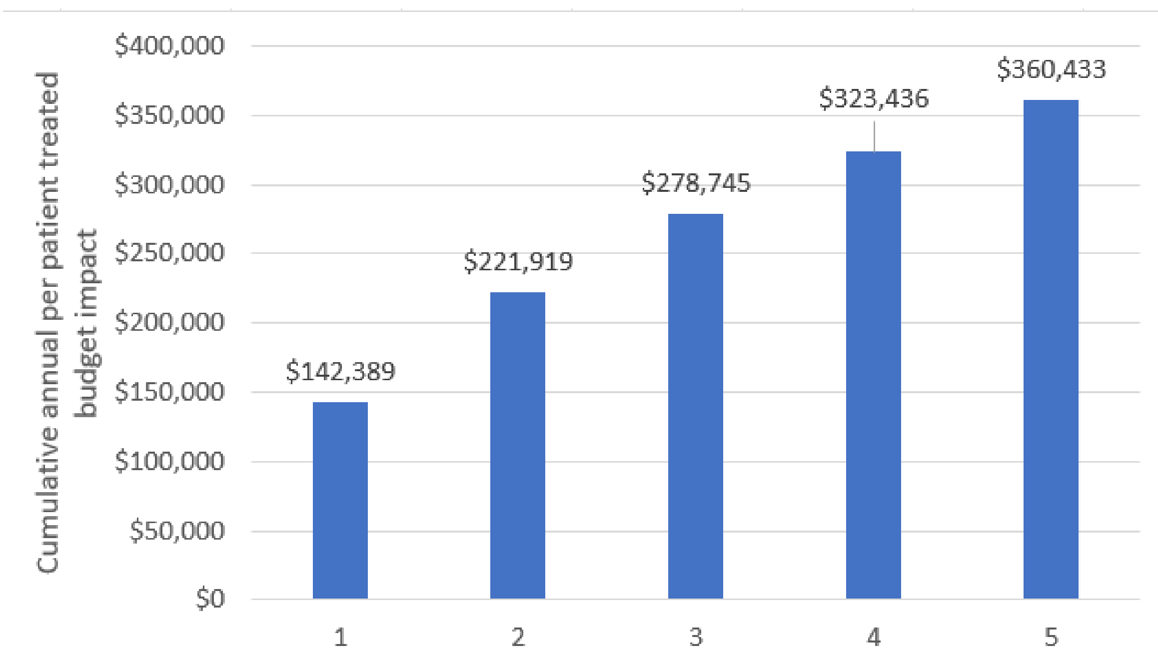
This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment with imetelstat. In line with the cost-effectiveness analyses, we estimated the potential budgetary impact of imetelstat separately for the comparison of imetelstat plus best supportive care to best supportive care alone (for the overall population), and the comparison of imetelstat plus best supportive care to luspatercept plus best supportive care (for patients who are RS+). To estimate the size of the potential candidate population for imetelstat with best supportive care compared to best supportive care alone, we applied a prevalence estimate of 115,000[3], an incidence estimate of four per 100,000, 0.004%[10], and a death rate of 0.25% within two years[43] to the overall US population (average projected population from 2024-2028: 346 million). This resulted in a total population of 95,212 patients with MDS over five years. We limited the potential eligible patient population to patients with lower-risk MDS (two-thirds of all MDS patients, 66.6%)[43], who are transfusion dependent (40%)[6], without the del(5q) subtype (90%)[8], and patients who are ineligible or refractory to ESAs (70%). The estimate of 70% of patients being ineligible or refractory to ESAs was based on data suggesting that 20-40% of patients with LR-MDS respond to treatment with ESAs[43]. Our estimate for the percentage of patients being ineligible or refractory to ESAs was further supported by systematic review findings of a 37% ESA response rate in LR-MDS patients[44]. Applying these sources resulted in estimates of 15,996 eligible patients in the US over five years. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 3,199 patients per year.

To estimate the size of the potential candidate population for imetelstat plus best supportive care to luspatercept plus best supportive care, we further limited the potential eligible patient population calculated above to patients who are ring sideroblast positive (35%)[7]. Applying these sources results in estimates of 5,598 eligible patients over five years, with 1,120 patients (20%) initiating treatment per year.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient treated potential budget impact for imetelstat plus best supportive care compared to best supportive care alone for the overall population. At imetelstat's annual price of $323,027 in year one and $314,069 in years two to five for a 7.1mg/kg dose (based on an annual price of $365,197 adjusted for dose reduction), the average annual budget impact per patient was $142,389 in year one with cumulative net annual costs increasing to $360,433 in year five. While the year over year costs of treatment and non-treatment costs for both imetelstat plus best supportive care and best supportive care alone decrease from years 1 to 5, the cumulative incremental annual costs increase due to our assumptions for treatment uptake (i.e., 20% of patients assumed to start treatment each year over 5 years).

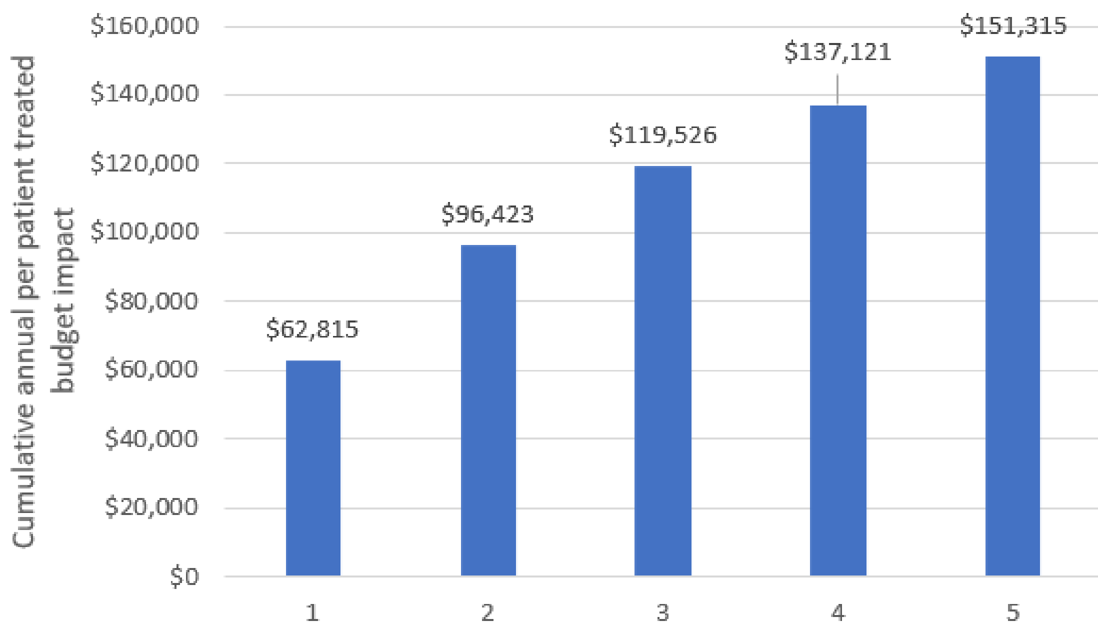
Figure 7.1. Cumulative Annual Per-Patient Treated Budget Impact of Imetelstat Plus Best Supportive Care Compared to Best Supportive Care Alone (for the Overall Population)



Results showed that compared to best supportive care alone, 100% of patients eligible for treatment with imetelstat in the overall population could be treated over the span of five years without crossing the ICER potential budget impact threshold of $735 million per year. At prices to reach $50,000, $100,000, and $150,000 per evLYG ($84,539, $98,873, and $113,206 respectively), all eligible patients could be treated over five years.

Figure 7.2 illustrates the cumulative annual per patient treated potential budget impact for imetelstat plus best supportive care compared to luspatercept plus best supportive care for patients who are RS+. The cumulative net annual costs were $62,815 in year one with cumulative net annual costs increasing to $151,315 by year five.

Figure 7.2. Cumulative Annual Per-Patient Treated Budget Impact of Imetelstat plus Best Supportive Care Compared to Luspatercept Plus Best Supportive Care (for patients who are RS+)



Consequently, 100% of patients eligible for treatment could be treated without crossing the ICER potential budget impact threshold of $735 million per year.

The purpose of an ICER affordability and access alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Hematologic Improvement-Erythroid (HI-E) 2006 International Working Group: A measure of improvement in cytopenias in lower-risk MDS. "Improvement" by this metric is defined as increasing hemoglobin levels by at least 1.5 g/dL for at least 8 weeks and reducing transfusions by at least four units of red blood cells over 8 weeks.[5,15]

Hematologic Improvement-Erythroid (HI-E) 2018 International Working Group: The definition of HI-E was revised in 2018. "Improvement" by the revised metric is defined as achieving 16-weeks of transfusion independence and a 50% or greater reduction in transfusion burden.[5,15]

International Prognostic Scoring System (IPSS): IPSS is a scoring system used to assign a risk score and risk group based on three prognostic indicators of a given patient with MDS: the percent of blast cells in the bone marrow, the type of chromosomal changes (cytogenetics), and the number of cytopenias (anemia, neutropenia, or thrombocytopenia. A patient can be categorized into one of four risk groups: low, intermediate-1, intermediate-2, or high risk.[45]

International Prognostic Scoring System-Revised (IPSS-R): The IPSS-R is a revised version of the IPSS covering more detailed information on the same prognostic indicators: percent of blast cells in the bone marrow, types of chromosomal changes (cytogenetics), and biomarkers of anemia, neutropenia, and thrombocytopenia (hemoglobin levels, platelet count, and absolute neutrophil count, respectively). Patients can be categorized into one of five risk groups: very low, low, intermediate, high, and very high.[45]

Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue): A measurement of 13 items related to fatigue and its impact on daily life and functioning. Scores range from 0 to 52 with a higher score indicating better fatigue-related quality of life. A change of 5 points is considered a minimal clinically important change in fatigue for patients with MDS.[46]

Lower-Risk Myelodysplastic Syndrome: Defined as MDS that is "low" or "intermediate-1" by IPSS criteria, or MDS that is "very low" to "intermediate" risk as identified by the IPSS-R criteria.

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[47] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[48,49] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

A2. Potential Cost-Saving Measures in MDS

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for MDS as the economic model would capture such impacts. Rather, we are seeking services used in the current management of MDS beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with MDS that could be reduced, eliminated, or made more efficient. To date, we have not received any suggested cost-saving measures.

A3. Patient Input on Clinical Trial Design

We solicited this information from the manufacturer of imetelstat and did not receive any feedback on this topic.

B. Patient Perspectives: Supplemental Information

B1. Methods

We reached out to both the Cancer Support Community and the MDS Foundation to gain insights into the impact MDS has on patients and their caregivers. To provide MDS caregiver perspectives, the Cancer Support Community shared insights from their *Cancer Experience Registry*. They also provided feedback on ICER's methods and suggestions for better incorporating the patient perspective into the report, including periodically revisiting value assessments as real-world evidence evolves. The MDS Foundation shared their MDS Global Survey Report, spoke with us at length, and helped to arrange a focus group including three individuals living with MDS and three caregivers. We described the findings in section two of the evidence report.

C. Clinical Guidelines

The guidelines were consistent in their recommendations for managing anemia in patients with MDS:

1. RBC transfusions with iron chelation as needed to prevent secondary hemochromatosis
2. ESAs to reduce the burden of transfusions in those with erythropoietin levels that are not elevated (<500 units per liter)
3. In patients with del(5q): Lenalidomide
4. Higher risk patients: Hypomethylating agents (HMAs) with azacitidine preferred over decitabine

NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes[50]

The following applies to patients with symptomatic anemia and lower risk MDS. If patients have the del(5q) subtype, lenalidomide is the preferred treatment. If no del(5q) mutations, but elevated ringed sideroblasts, then luspatercept is the preferred treatment. If no del(5q) mutations and few ringed sideroblasts, then ESAs are first line if the serum EPO level is ≤ 500 mU/mL; if serum EPO is > 500, then consider lenalidomide.

Myelodysplastic Syndromes: ESMO Clinical Practice Guidelines For Diagnosis, Treatment And Follow-Up[51]

The following applies to patients with symptomatic anemia and lower risk MDS. If patients require ≤ 2 units of RBCs per month and their serum EPO level is ≤ 500, then ESAs are recommended. If not and the del(5q) subtype is present, then lenalidomide is the preferred treatment. If no del(5q) mutation, then participation in a clinical trial of azacytidine, luspatercept, lenalidomide or other experimental therapy is suggested.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, and Setting) elements.

Population

The population for this review was adults with lower-risk myelodysplastic syndromes without the del(5q) mutation who are transfusion-dependent and ineligible for or refractory to ESAs.

Interventions

The included intervention is as follows:

- Imetelstat (Geron Corporation) in addition to best supportive care

Comparators

We compared the intervention to the following:

- Luspatercept-aamt (Reblozyl®; Bristol Myers Squibb) plus best supportive care
- Best supportive care (repletion of iron, B12, folate; iron chelation; transfusions)

Outcomes

The outcomes of interest are described in the list below:

- Patient-Important Outcomes
    - Fatigue
    - Transfusion independence
    - Duration of transfusion independence
    - Time to onset of transfusion independence
    - Health-related quality of life
    - Activities of daily living (ADL), measures of functional ability, and work productivity for those still employed
    - Progression-free survival
    - Progression to AML
    - Overall survival

    - Adverse events including
        - Cytopenias (thrombocytopenia, neutropenia, etc.)
        - Bleeding events
        - Infections
        - Liver injury
- Other Outcomes
    - Hemoglobin levels
    - Cytogenetic response rate
    - MDS response (complete or partial response)
    - Reduction in central bone marrow ring sideroblasts

Timing

Evidence on intervention effectiveness were derived from studies of any duration.

Settings

All relevant settings were considered.

Table D1.1 PRISMA 2020 Checklist[52]

Section and Topic	Item	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.

Section and Topic	Item	Checklist item
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.

Section and Topic	Item	Checklist item
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for MDS followed established best research methods.[53,54] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[52] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

Table D1.2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews Search Strategy

1	exp myelodysplastic syndrome/
2	("myelodysplastic syndrome" or "myelodysplastic syndromes" or "mds" or "mds (myelodysplastic syndrome)" or "myelodysplastic disease" or "myelodysplastic disorder" or "myelodysplastic neoplasm" or "myelodysplasia" or "myelodysplasia, h*ematopoietic" or "myelodysplasias, h*ematopoietic" or "h*ematopoietic myelodysplasia" or "h*ematopoietic myelodysplasias" or "dysmyelopoietic syndrome" or "dysmyelopoietic syndromes" or "syndrome, dysmyelopoietic" or "syndrome, myelodysplastic" or "syndromes, dysmyelopoietic" or "syndromes, myelodysplastic" or "bone marrow dysplasia").ti,ab.
3	1 or 2
4	("imetelstat" or "telomerase inhibitor" or "JNJ-63935937" or "JNJ63935937" or "JNJ 63935937" or "GRN 163L" or "GRN163L" or "GRN-163L").ti,ab.
5	("luspatercept" or "reblozyl" or "luspatercept-aamt" or "ACE-536" or "ACE536" or "ACE 536" or "RAP-536" or "RAP536" or "RAP 536" or "Modified Activin Receptor Type IIb-Fc Fusion Protein" or "Liblozep" or "bms 986347" or "bms986346" or "bms-986347").ti,ab.
6	3 and (4 or 5)
7	6 NOT (animals not (humans and animals)).sh.
8	7 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).pt
9	limit 8 to English language

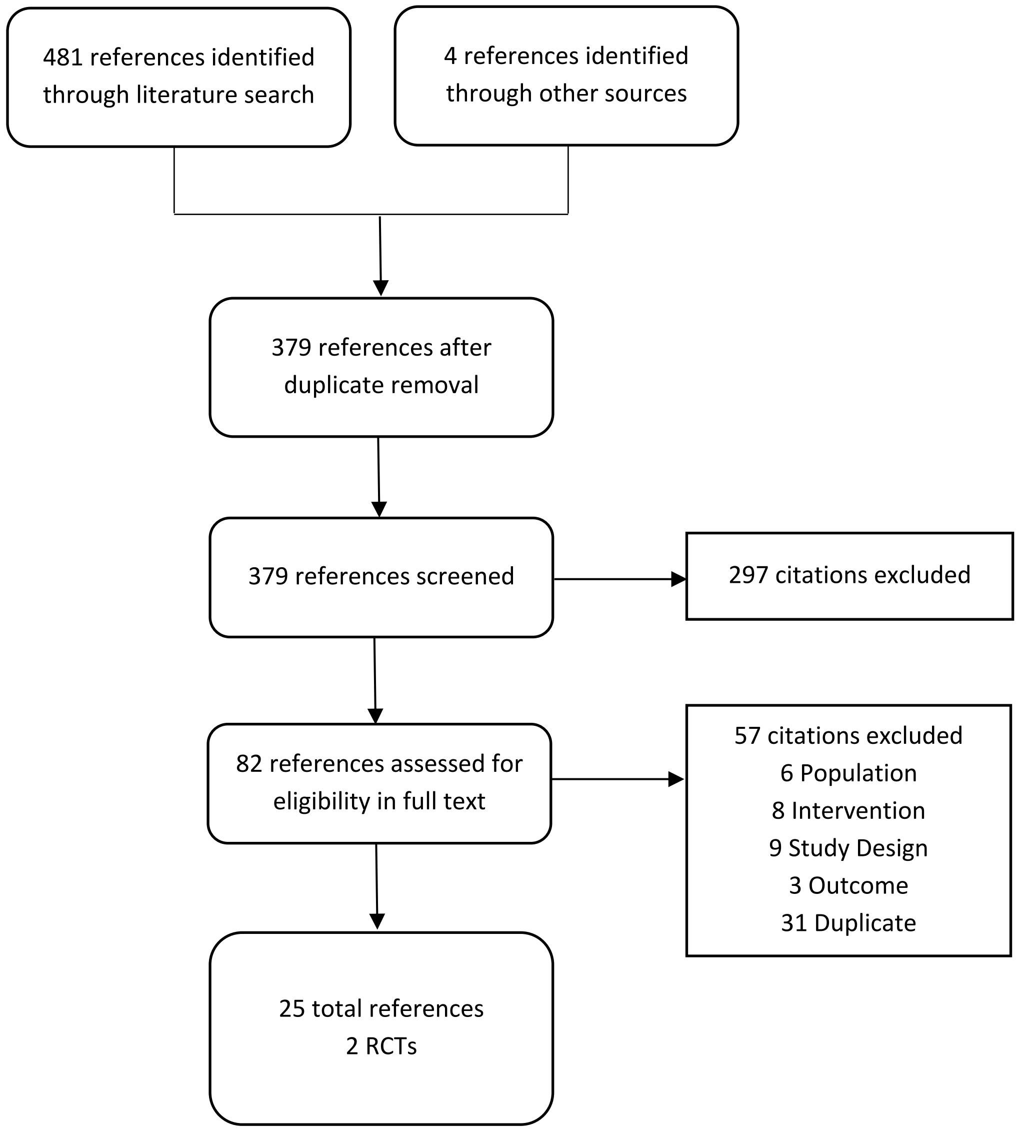
Date of latest search: June 06, 2024

Table D1.3. EMBASE Search Strategy

1	'myelodysplastic syndrome'/exp
2	('myelodysplastic syndrome' or 'myelodysplastic syndromes' or 'mds' or 'mds (myelodysplastic syndrome)' or 'myelodysplastic disease' or 'myelodysplastic disorder' or 'myelodysplastic neoplasm' or 'myelodysplasia' or 'myelodysplasia, hematopoietic' or 'myelodysplasia, haematopoietic' or 'myelodysplasias, hematopoietic' or 'myelodysplasias, haematopoietic' or 'hematopoietic myelodysplasia' or 'hematopoietic myelodysplasias' or 'haematopoietic myelodysplasia' or 'haematopoietic myelodysplasias' or 'dysmyelopoietic syndrome' or 'dysmyelopoietic syndromes' or 'syndrome, dysmyelopoietic' or 'syndrome, myelodysplastic' or 'syndromes, dysmyelopoietic' or 'syndromes, myelodysplastic' or 'bone marrow dysplasia'):ti,ab
3	#1 OR #2
4	('imetelstat' or 'telomerase inhibitor' or 'JNJ-63935937' or 'JNJ63935937' or 'JNJ 63935937' or 'GRN 163L' or 'GRN163L' or 'GRN-163L'):ti,ab
5	('luspatercept' or 'reblozyl' or 'luspatercept-aamt' or 'ACE-536' or 'ACE536' or 'ACE 536' or 'RAP-536' or 'RAP536' or 'RAP 536' or 'Modified Activin Receptor Type IIb-Fc Fusion Protein' or 'Liblozep' or 'bms 986347' or 'bms986346'):ti,ab
6	#3 AND (#4 OR #5)
7	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
8	#6 NOT #7
9	#8 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
10	#9 AND [english]/lim
11	#10 NOT [medline]/lim

Date of latest search: June 06, 2024

Figure D1.1. PRISMA Flow Chart: Results of Literature Search for Imetelstat and Luspatercept



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge™ (Saint Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to imetelstat. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Data Extraction

Data were extracted into Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[54,55] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias: The study is judged to be at low risk of bias for all domains for this result.

Some concerns: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

High risk of bias: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

We examined the risk of bias for the following outcomes: 8-week transfusion independence and FACIT-Fatigue. See Table D1.4 below.

Table D1.4. Risk of Bias Assessment

Trial	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Proportion of Participants Achieving 8-week Transfusion Independence						
IMerge Phase III	Low	Low	Low	Low	Low	**Low**
MEDALIST	Low	Low	Low	Low	Low	**Low**
Proportion of Participants with a Sustained Meaningful Improvement in FACIT-Fatigue*						
IMerge Phase III	Low	Low	Low	Some concern	Low	**Some concern**

* The MEDALIST trial did not assess FACIT-Fatigue

† The judgement of "some concern" was based on the possibility that participant knowledge of the intervention through marked differences in the rate of cytopenias in the imetelstat versus placebo arm could influence participants' assessment of the outcome.
FACIT: Functional Assessment of Chronic Illness Therapy, NA: not applicable, TI: transfusion independence

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[56] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5 below.[56] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.5 below. Representation for each demographic category was evaluated relative to the disease prevalence, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.6 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.7.

Table D1.5. Demographic Characteristics and Categories

Demographic Characteristics	Categories
Race and Ethnicity	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
Sex	• Female • Male
Age	• Older adults (≥65 years)

Table D1.6. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.7. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

* American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

For this review, both trials were multinational (i.e., enrolled patients from the US and other countries). We were unable to obtain US subgroup data on both of these trials, thus, these trials were rated on race/ethnicity using the full sample (including both US and non-US participants).

Incidence estimates for sex and racial/ethnic populations were derived from the SEER*Explorer, an interactive website for SEER cancer statistics.[10] Because specific incidence data for the Asian population alone was not available, we relied on the incidence data provided for both Asian and Pacific Islander populations combined from the SEER*Explorer. Data relevant to the incidence estimate for adults ≥65 years old who are living with MDS was obtained from the Global Burden of Disease Database.[57]

Results

Table D1.8. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older adults)
IMERGE (Imetelstat)	Fair	Good	NE
MEDALIST (Luspatercept)	Poor	Good	Good

NE: Not Estimated, NR: Not Reported.

Table D1.8. presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for both IMerge and MEDALIST trials. Details on each of the demographic categories are provided below. Additional details on the CDR tool are provided in ICER's updated Value Assessment Framework (VAF).

Race and Ethnicity: A higher prevalence of MDS diagnosis is observed in White adults (85% of those with MDS) compared to other racial/ethnic groups. Both trials, IMerge and MEDALIST, predominantly enrolled White adults living with MDS (69% to 80%). Although there was good representation of White and Asian populations in the IMerge trial, this trial enrolled very few Black or African American (1.7% of trial participants vs. 11% of MDS patients) and Hispanic adults (6% of trial participants vs. 14% of MDS patients), resulting in a rating of "fair". The MEDALIST trial did not adequately represent Black or African American (0.4% of trial participants) and Hispanic adults (3% of trial participants) and did not report data on the proportion of Asian adults enrolled, resulting in a rating of "poor".

Sex: MDS is more common in males (62%) than females (38%). Around two-thirds of the enrolled participants in the IMerge and MEDALIST trials were male, leading to a rating of "good" for both trials.

Age: There is a higher prevalence of MDS in older adults (86% of those with MDS). The IMerge trial did not report the proportion of older adults aged 65 or above enrolled, thus we were not able to evaluate the representation of age for that trial. The majority of the MEDALIST trial participants were older adults (81%), leading to a rating of "good".

Table D1.9. Race and Ethnicity

	White	Black/ African American	Asian	Hispanic/ Latino	Total Score	Diversity Rating	AIAN	NHPI
Prevalence	84.94%	10.54%	4.10%*	14.33%			1.33%	NR
IMerge	80.34%	1.69%	5.62%	6.18%	--	--	0.00%	0.00%
PDRR	0.95	0.16	1.37	0.43	--	--	--	--
Score	3	1	3	1	8	Fair	--	--
MEDALIST	69.00%	0.40%	NR	3.10%	--	--	NR	NR
PDRR	0.81	0.04	NC	0.22	--	--	--	--
Score	3	1	0	1	5	Poor	--	--

AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio
* Incidence data for both Asian and Pacific Islanders combined.

Table D1.10. Sex and Age

	Sex				Age		
	Male	Female	Score	Rating	Older Adults (≥65 years)	Score	Rating
Prevalence	62.20%	37.80%	--	--	85.77%	--	--
IMerge	62.36%	37.64%	--	--	NR	--	--
PDRR	1	1	--	--	NC	--	--
Score	3	3	6	Good	NC	NC	NC
MEDALIST	62.90%	37.10%	--	--	81.10%	--	--
PDRR	1.01	0.98	--	--	0.95	--	--
Score	3	3	6	Good	3	3	Good

NC: Not Calculated, PDRR: Participant to Disease-prevalence Representation Ratio

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[58,59]

Assessment of Bias

We evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using ClinicalTrials.gov. Search terms included "imetelstat," "luspatercept", and "myelodysplastic syndrome." We scanned the site to identify studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized narratively in the body of the review and in evidence tables (see Supplement Section D3). Key differences between the studies in terms of the study design, patient characteristics, outcomes, and study quality were discussed in the text of the report. Additional methods and results are described in Supplement Section D2 and Section 3.2 of the main report.

Indirect Treatment Comparison Methods

We conducted an indirect treatment comparison of imetelstat and luspatercept for the economic analysis purpose. First, we assessed the feasibility by evaluating differences in study population, study design, and outcome assessments of IMerge and MEDALIST trials. We compared the ring sideroblast positive subgroup of the IMerge Phase III trial to the overall ring sideroblast positive population of the MEDALIST trial. The outcome of interest was 8-week transfusion independence, with data during 52 weeks retrieved from the IMerge trial and 48 weeks from the MEDALIST trial. This analysis was conducted in a Bayesian framework using the gemtc package in R.[60] The primary input was the number of patients achieved the outcome of interest and the total sample size. For our primary results, we used a fixed-effects model. We expected a priori that the fixed-effect model would be more appropriate since there is only one trial in each connection. However, the deviance information criteria (DIC) and other residual deviance (resdev) statistics were similar for the fixed and random effects models. See Supplement Table D3.3 for more details.

Figure D1.2. Network Diagram

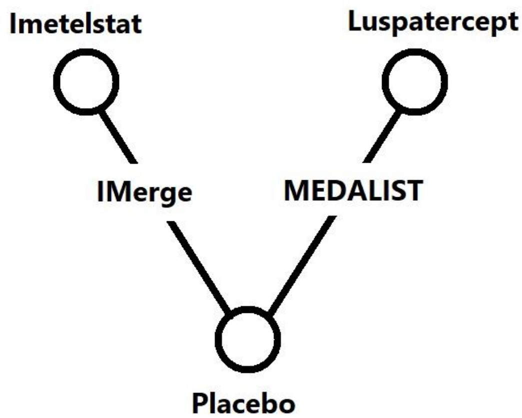


Table D1.11. Indirect Treatment Comparison Data Inputs for 8-week Transfusion Independence

Study	Arms	Responders	Sample Size	Proportion of Patients Achieving the Primary Endpoint
IMerge	Imetelstat	33	73	45%
IMerge	Placebo	7	37	19%
MEDALIST	Luspatercept	69	153	45%
MEDALIST	Placebo	12	76	16%

IMerge data represents only the subset of included trial participants who were RS+ (110 out of 178).

Table D1.12. Model Fit Statistics

Model Type	Dbar	DIC	Unconstrained Datapoints	I^2
Fixed Effects	4.043	8.069	4	26%
Random Effects	4.044	8.073	4	26%

Dbar: posterior mean residual deviance, DIC: deviance information criterion, I^2: heterogeneity statistics

D2. Additional Clinical Evidence

The main report discusses primary sources of data and key evidence to inform our review of imetelstat for the treatment of anemia in MDS. This supplementary section provides an overview of additional trial characteristics, baseline data, and relevant secondary endpoints from both the IMerge Phase III and MEDALIST Phase III trials, along with safety findings from the IMerge Phase II trial that were not included in the main clinical section.

Additional Evidence Base

We identified ten references including two peer-reviewed publications describing the IMerge trial[9,18,23,26,61-66], and 12 references with one peer-reviewed publication describing the MEDALIST trial[19,21,22,24,25,28,67-72]. We also included data from two briefing documents from the Food and Drug Administration (FDA) Advisory Committee meeting for imetelstat, which took place on March 14, 2024.[5,73]

Imetelstat

In this section, we discuss the design of part one of the IMerge trial, which was a Phase II, single-arm, open-label study. The Phase II trial enrolled adults with a confirmed diagnosis of MDS according to the WHO 2016 criteria, had low to intermediate-1 risk as per IPSS criteria, were relapsed or refractory to ESA treatment, and transfusion-dependent with at least four RBC transfusions over eight weeks. Adults with a history of hematopoietic stem cell transplantation or clinically significant cardiovascular diseases were excluded from the trial. The trial observed a higher hematologic response rate in a subset of 13 patients who were non-del(5q) and naïve to an HMA or lenalidomide among the initial cohort of 32 individuals enrolled. Subsequently, the trial refined its inclusion criteria to enroll participants without a del(5q) mutation and those without prior treatment with an HMA or lenalidomide only, defined as the "target population".[64]

The trial administered imetelstat intravenously every four weeks to the 57 enrolled participants, which included 38 individuals meeting the criteria of the target population. A majority of the participants were older adults, with a median age of 71 years and approximately two-thirds of them had "low" risk MDS according to the IPSS-R criteria. Participants received a median of seven units of RBC transfusions per eight weeks, with 90% of the enrolled patients previously using ESAs.[64] See Supplement Table D3.2 for more detailed baseline characteristics.

Luspatercept

We described the design of the MEDALIST Phase III trial for luspatercept in the main report. See Supplement Table D3.2 for more detailed baseline characteristics.

Additional Clinical Benefits

Overall Population in Scope

Imetelstat

Below we describe additional secondary endpoints of the IMerge Phase III trial, comparing the efficacy of imetelstat to placebo.

Transfusion Independence

In addition to the primary efficacy findings of the IMerge Phase III trial described in the main report, participants also achieved transfusion independence for periods longer than eight weeks. Transfusion independence for 24 consecutive weeks was achieved by 28% in the imetelstat arm compared to 3% in the placebo arm (p=0.0001). Additionally, 18% of participants in the imetelstat arm achieved 1-year transfusion independence compared to 2% of the placebo arm (p=0.0023).[18] As for the duration of transfusion independence, the median duration was comparably low in both imetelstat and placebo arms when considering the entire enrolled population regardless of achievement of the primary endpoint (5 vs. 4 weeks, respectively).[73] Overall, patients treated with imetelstat experienced slightly greater reductions in transfusion units over the course of treatment compared to those in the placebo group (-4.3 vs. -3.6 units, p=0.042).[5]

Hematologic Improvement-Erythroid

Hematologic improvement-erythroid (HI-E) is a measure of the production and function of red blood cells. IMerge measured both the 2006 and 2018 version of this outcome. HI-E as per the 2006 IWG is defined as an increase of ≥1.5 g/dL in hemoglobin lasting ≥8 weeks and reduced transfusion burden by ≥4 units over 8 weeks. HI-E as per the 2018 IWG is defined as 16 weeks of transfusion independence and a 50% or greater reduction in transfusion burden. More patients in the imetelstat arm achieved HI-E by both definitions compared to placebo (2006 HI-E: 64% vs. 52% and 2018 HI-E: 42% vs. 13%).[18] More participants in the imetelstat arm achieved at least a 1.5 g/dL increase in hemoglobin over 8 weeks compared to placebo (34% vs. 10%), and at least a 50% reduction in transfusion burden (43% vs. 15%)[5] See Supplement Section A1 and Supplement Table D3.3 for more details on the components of HI-E.

Patient-Reported Outcomes: FACIT-Fatigue

Similar proportions of participants sustained meaningful deteriorations in FACIT-Fatigue across the two arms, indicating no impact of imetelstat on worsening fatigue (43% vs. 45%).[9]

Ring Sideroblasts Positive Population

Luspatercept

Below we describe additional secondary endpoints of the MEDALIST trial, such as transfusion independence for 16 weeks or longer, the duration of transfusion independence, hematologic improvement, and survival-related clinical outcomes.

Transfusion Independence

In the MEDALIST trial, participants achieved transfusion dependence for periods longer than the primary endpoint duration of 8 weeks. During the 48-week trial period, 28% of participants in the luspatercept arm achieved 16 weeks of consecutive transfusion independence compared to 7% in the placebo arm. Among participants who achieved the primary endpoint, the median duration of transfusion independence was 31 weeks in the luspatercept arm compared to 19 weeks in the placebo group at 48 weeks of follow-up.[19] In a separate analysis, the median cumulative duration of RBC-TI response of 8 weeks or more with luspatercept was approximately 81 weeks compared to 21 weeks in the placebo group.[24]

Hematologic Improvement-Erythroid (HI-E)

The MEDALIST trial measured HI-E as per 2006 IWG definitions of an increase of ≥1.5 g/dL in hemoglobin lasting ≥8 weeks and reduced transfusion burden by ≥4 units over 8 weeks. More participants in the luspatercept arm achieved HI-E at 24 weeks of treatment compared to placebo (53% vs. 12%). The rate of HI-E remained consistent at 48 weeks of treatment as well (59% vs. 17%).[19]. Substantially more participants in the luspatercept arm also achieved at least a 1.5 g/dL increase in hemoglobin over 8 weeks compared to placebo (70% vs. 5%), and at least a 50% reduction in transfusion burden (54% vs. 21%)[5] See Supplement Section A1 and Supplement Table D3.3 for more detail on the components of HI-E.

Patient-Reported Outcomes

The MEDALIST trial did not measure FACIT-Fatigue scores. Patient-reported quality of life was primarily evaluated using the EORTC QLQ-C30 questionnaire which includes global health status/QoL, physical functioning, emotional functioning, fatigue, and dyspnea. Additionally, Quality of Life assessment in MDS questionnaire (QOL-E) version 3.0 was used as an exploratory endpoint, which includes domains such as physical well-being, functional well-being, social and family life, sexual well-being, fatigue, and MDS-specific disturbances. Up to week 25, there were no clinically meaningful differences in mean change from baseline within or between the luspatercept and placebo groups across all domains of both EORTC QLQ-C30 and QOL-E questionnaires. Of note, the analysis lacked the statistical power to detect significant differences.[22] See Supplement Table D3.3 for more details.

Overall Survival and Progression Free Survival

Data on overall survival and progression-free survival are immature.[69] To date, the mortality rates are similar in the two arms.[19] See Supplement Table D3.3 for more details.

Additional Harms

Imetelstat

The safety profile of imetelstat from the IMerge Phase III trial is mainly described in the main report. In the trial, a notable portion of patients receiving imetelstat experienced dose reduction due to adverse events (49%) compared to those receiving placebo (7%), with dose delay occurring in 69% vs. 24% of participants, respectively. Neutropenia and thrombocytopenia were managed with dose reductions in 33% and 23% of participants and with dose delays in 51% and 47% of participants, respectively. Growth factors and platelet transfusions were administered to manage neutropenia and thrombocytopenia in 35% and 18% of patients receiving imetelstat, respectively.[5,23] Although imetelstat showed significantly higher rates of neutropenia and thrombocytopenia, their clinical consequences such as infections, febrile neutropenia, and bleeding events did not reflect the same discrepancy, as described in the main report. See Supplement Table D3.4 for more details.

In the IMerge Phase II trial, all but one participant experienced at least one adverse event and 88% experienced at least one grade 3/4 adverse event with 75% found to be related to imetelstat by investigator assessment.[5] The most frequently reported grade 3/4 events were neutropenia and thrombocytopenia occurring in 60% and 54% of participants, respectively. A majority of these events resolved to grade 2 or lower within 4 weeks. Febrile neutropenia and grade 3/4 bleeding events were each reported in two participants, but none were related to imetelstat. Overall, 75% of participants discontinued the trial with 25% of participants discontinuing due to adverse events and 5% due to progression to higher risk disease (n=1) or further to AML (n=2). There were two deaths at the time of the primary analysis.[64] See Supplement Table D3.4 for more details.

Luspatercept

The safety profile of luspatercept is described from the MEDALIST trial in the main report. See Supplement Table D3.4 for more details.

D3. Evidence Tables

Table D3.1. Study Design

Trial	Study Design	Arms & Dosage	Key Inclusion & Exclusion Criteria	Key Outcomes
IMerge Phase II/III: Study to Evaluate Imetelstat (GRN163L) in Subjects With International Prognostic Scoring System (IPSS) Low or Intermediate-1 Risk MDS[74] NCT02598661	Part 1 Phase II, open-label, single-arm (N = 57) Part 2 Phase III, double-blind, randomized trial (N = 178)	Part 1 Imetelstat (7.5* mg/kg IV Q4W) Part 2 **Arm 1**: Imetelstat (7.5* mg/kg IV Q4W) **Arm 2**: Placebo (IV Q4W)	Inclusion Criteria: • Adults 18 years or older • Diagnosis of MDS per WHO criteria • IPSS low or intermediate-1 risk MDS • RBC transfusion dependent: ≥4 units/8-weeks • ECOG performance status 0-2 • Relapsed/refractory to ESA Exclusion Criteria: • Prior history of haematopoietic SCT • Part 2: Prior treatment with an HMA • Part 2: Prior treatment with lenalidomide • Part 2: del(5q) subtype	Primary: • RBC Transfusion independence (RBC-TI) for ≥8 consecutive weeks Key Secondary: • RBC-TI for ≥24 consecutive weeks • Duration of RBC-TI • Hematologic improvement-erythroid • Progression to AML
MEDALIST: A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk MDS[75] NCT02631070	Phase III, double-blind, randomized trial (N = 229)	**Arm 1**: Luspatercept (1.0mg/kg SQ Q3W) **Arm 2**: Placebo (SQ Q3W)	Inclusion Criteria: • Adults 18 years or older • Diagnosis of MDS (WHO/FAB classification) with ring sideroblasts • IPSS-R: very low, low, or intermediate risk • RBC transfusion burden: ≥2 units/8-weeks • ECOG performance status 0-2 • Refractory/intolerant/ineligible to ESAs Exclusion Criteria: • Prior allogenic or autologous SCT • Prior treatment with luspatercept/sotatercept • del(5q) subtype • Secondary MDS or diagnosis of AML	Primary: • RBC-TI for ≥8 consecutive weeks Key Secondary: • RBC-TI for ≥12 consecutive weeks • Duration of RBC-TI • Hematologic improvement-erythroid • Progression to AML • Safety

ECOG: Eastern Cooperative Oncology Group, ESA: erythropoiesis-stimulating agent, FAB: French American British, HMA: hypomethylating agent, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-Revised, IV: intravenous, MDS: myelodysplastic syndrome, mg/kg: milligram per kilogram, N: total number, Q3W: once every 3 weeks, Q4W: once every 4 weeks, RBC-TI: red blood cell transfusion independence, SCT: stem cell transplant, SQ: subcutaneous, WHO: World Health Organization

* 7.5 mg/kg of imetelstat sodium used in trials is equivalent to the 7.1 mg/kg label-recommended dose of imetelstat[16]

Table D3.2. Baseline Characteristics

Drug		Imetelstat				Luspatercept	
Trial		IMerge Phase II[64,73]		IMerge Phase III[5,18,26,66]		MEDALIST[19,28,68,71,75]	
Arm		Imetelstat Overall	Imetelstat Non-del(5q)	Imetelstat	Placebo	Luspatercept	Placebo
N		57	38	118	60	153	76
Demographics – n/N (%) unless otherwise specified							
Age – years	Median (range)	71 (46-83)	72 (46-83)	72 (44-87)	73 (39-85)	71 (40-95)	72 (26-91)
	Mean (SD)	NR	NR	NR	NR	70.5 (8.7)	70.7 (10.9)
Sex	Male	32/57 (56%)	25 (66%)	71 (60%)	40 (67%)	94 (61%)	50 (66%)
	Female	25/57 (44%)	13 (34%)	47 (40%)	20 (33%)	59 (39%)	26 (34%)
Race	White	NR	NR	95 (81%)	48 (80%)	107 (70%)	51 (67%)
	Black/African American	NR	NR	1 (1%)	2 (3%)	1 (1%)	0
	Asian	NR	NR	8 (7%)	2 (3%)	NR	NR
	Other	NR	NR	1 (1%)	1 (2%)	1 (1%)	1 (1%)
	Unknown	NR	NR	1 (1%)	1 (2%)	NR	NR
	Not Reported	NR	NR	12 (10%)	6 (10%)	44 (29)	24 (32)
Ethnicity	Hispanic/Latino	NR	NR	6 (5%)	5 (8%)	3 (2%)	4 (5%)
	Non-Hispanic/Latino	NR	NR	100 (85%)	48 (80%)	115 (75%)	52 (68%)
	Unknown/Not Reported	NR	NR	12 (11%)	7 (12%)	35 (23%)	20 (26%)
Geographic Region	North America	NR	NR	13 (11%)	12 (20%)	31 (20%)	19 (25%)
	European Union	NR	NR	80 (68%)	38 (63%)	122 (80%)	57 (75%)
	Rest of World	NR	NR	25 (21%)	10 (17%)	0 (0%)	0 (0%)
Disease-Related Information – n/N (%) unless otherwise specified							
Time since diagnosis	Median years (range)	NR	NR	3.5 (0.1-26.7)	2.8 (0.2-25.7)	3.7 (0.3, 35.1)*	3 (0.3, 16.1)*
ECOG Score	0	52/57 (91%)	34 (59%)	42 (35.6%)	21 (35.0%)	54 (35%)	33 (43%)
	1			70 (59.3%)	39 (65.0%)	91 (59%)	32 (42%)
	2	NR	NR	6 (5.1%)	0 (0%)	8 (5%	11 (14%)
Ring Sideroblast Status	RS+	NR	NR	73 (62%)	37 (62%)	153 (100%)	76 (100%)
	RS-	NR	NR	44 (37%)	23 (38%)	0 (0%)	0 (0%)
WHO 2001 Classification	RARS or RCMS-RS	35/57 (61%)	27 (71%)	NR	NR	NR	NR
	RA, RCMD, RAEB-1	22/57 (39%)	11 (29%)	NR	NR	NR	NR
WHO 2008 Classification	RARS	NR	NR	NR	NR	7 (5%)	2 (3%)
	RCMD	NR	NR	NR	NR	145 (95%)	74 (97%)
IPSS Risk Category	Low	36 (63%)	24 (63%)	80 (68%)	39 (65%)	NR	NR

Drug		Imetelstat				Luspatercept	
Trial		IMerge Phase II[64,73]		IMerge Phase III[5,18,26,66]		MEDALIST[19,28,68,71,75]	
Arm		Imetelstat Overall	Imetelstat Non-del(5q)	Imetelstat	Placebo	Luspatercept	Placebo
N		57	38	118	60	153	76
	Intermediate-1	21 (37%)	14 (37%)	38 (32%)	21 (35%)	NR	NR
IPSS-Revised Risk Category	Very low	3 (5%)	2 (5%)	3 (2.5%)	2 (3.3%)	18 (12%)	6 (8%)
	Low	37 (65%)	25 (66%)	87 (74%)	46 (77%)	109 (71%)	57 (75%)
	Intermediate	9 (16%)	7 (18%)	20 (17%)	8 (13%)	25 (16%)	13 (17%)
	High	NR	NR	1 (1%)	0	1 (1%)	0
	Missing	NR	NR	7 (6%)	4 (7%)	NR	NR
Hemoglobin – g/dL	Median (range)	7.8	NR	7.9 (5.3-10.1)	7.8 (6.1-9.2)	7.6 (6-10)	7.6 (5-9)
Prior RBC transfusion burden – units/8 weeks	Median (range)	7 (4-14)	8 (4-14)	6 (4-33)	6 (4-13)	5 (1-15)	5 (2-20)
	N with <4	NR	NR	0	0	46 (30%)	20 (26%)
	N with ≥4 to ≤6	53/57 (93%)	35/38 (92%)	62 (53%)	33 (55%)	41 (27%)	23 (30%)
	N with >6			56 (48%)	27 (45%)	66 (43%)	33 (43%)
Serum erythropoietin level – mU/mL	median (range)	NR	NR	175 (6-4460)	277 (17-5514)	157 (12-2454)	131 (29-2760)
	mean (SD)	NR	NR	361 (556)	472 (764)	NR	NR
	N with ≤500	NR	NR	87 (74%)	36 (60%)	131 (75%)	65 (76%)
	N with >500	22/55 (40%)	12/37 (32%)	26 (22%)	22 (37%)	21 (14%)	11 (14%)
Mutations	Mutated SF3B1	NR	NR	NR	NR	138/148 (93%)	64/74 (86%)
	Non-del(5q)	38/57 (67%)	38 (100%)	NR	NR	NR	NR
Baseline cytopenias	Neutropenia	NR	NR	NR	NR	15 (10%)	10 (13%)
	Thrombocytopenia	NR	NR	NR	NR	8 (5%)	6 (8%)
Prior Treatments – n/N (%)							
Prior ESA		51/57 (90%)	34 (89%)	108 (92%)	52 (87%)	148 (97%)	70 (92%)
Prior ESA with G-CSF		NR	NR	NR	NR	51 (33%)	22 (29%)
Prior iron chelation therapy		NR	NR	NR	NR	71 (46%)	40 (53%)
Prior luspatercept		NR	NR	7 (6%)	4 (7%)	NR	NR

ECOG: Eastern Cooperative Oncology Group, ESA: erythropoiesis-stimulating agent, G-CSF: granulocyte-colony stimulating factor, g/dL: gram per deciliter, IPSS: International Prognostic Scoring System, IPSS-R International Prognostic Scoring System: Revised, mU/mL: milliunit per milliliter, N: total number, n: number, NR: not reported, RA: refractory anemia, RAEB-1: refractory anemia with excess blasts type 1, RARS: refractory anemia with ring sideroblasts, RCMD: refractory cytopenias with multilineage dysplasia, RS+: ring sideroblast positive, RS-: ring sideroblast negative, SD: standard deviation, WHO: World Health Organization

* Interquartile range

Table D3.3. Key Efficacy Outcomes

Drug	Imetelstat		Luspatercept			
Trial	IMerge Phase III[5,9,18,62,73]		MEDALIST[19,21,22,24,69,75]			
Follow-up	18 months		48 weeks		24 weeks	
Arm	Imetelstat	Placebo	Luspatercept	Placebo	Luspatercept	Placebo
N	118	60	153	76	153	76
Transfusion Independence Outcomes – n/N (%) unless otherwise stated						
8-week RBC-TI	47 (40%)	9 (15%)	69 (45%)	12 (16%)	58 (38%)	10 (13%)
12-week RBC-TI	NR	NR	51 (33%)	9 (12%)	43 (28%)	6 (8%)
16-week RBC-TI	37 (31%)	4 (7%)	43 (28%)	5 (7%)	29 (19%)	3 (4%)
24-week RBC-TI	33 (28%)	2 (3%)	NR	NR	NR	NR
1-year RBC-TI	21 (18%)	1 (2%)	NR	NR	NR	NR
Duration of RBC-TI in 8-week TI responders – median weeks (range)	51.6 (26.9-83.9)	13.3 (8.0-24.9)	30.6	18.6	30.6	13.6
Duration of RBC-TI in all participants – median weeks (range)	5.0 (4.0-0.7)	3.9 (3.6-4.0)	NR	NR	NR	NR
Time to 8-wk RBC-TI – mean weeks (SD)	NR	NR	40.3 (61.0)	57.2 (79.2)	17.2 (29.4)	26.0 (31.8)
Hematologic Outcomes – n/N (%)						
HI-E (IWG 2018)	50 (42%)	8 (13%)	NR	NR	NR	NR
Major response: 16-week TI	37 (31%)	4 (7%)	NR	NR	NR	NR
≥50% reduction in transfusion burden	51 (43%)	9 (15%)	NR	NR	NR	NR
HI-E (IWG 2006)	75 (64%)	31 (52%)	90 (59%)	13 (17%)	81 (53%)	9 (12%)
≥1.5 g/dL increase in Hb lasting ≥8 weeks	40 (34%)	6 (10%)	32/46 (70%)	1/20 (5%)	29/46 (63%)	1/20 (5%)
Transfusion reduction by ≥4 units/8 weeks	71 (60%)	30 (50%)	58/107 (54%)	12/56 (21%)	52/107 (49%)	8/56 (14%)
Transfusion Burden Outcomes						
CFB in RBC transfusion burden during best 8-week interval – mean (range)	-4.3 (-24, 15)	-3.6 (-11, 2)	NR	NR	NR	NR
Disease Progression Outcomes – n/N (%)						
Progression to higher-risk MDS	5 (4%)	4 (7%)	NR	NR	1 (1%)	1 (1%)
Progression to AML	2 (1.7%)	1 (1.7%)	4 (2.6%)	3 (4%)	3 (2%)	1 (1%)
FACIT-Fatigue Outcomes – n/N (%) unless otherwise stated						
Sustained meaningful improvement*	59 (50%)	23/57 (40%)	NR	NR	NR	NR
Time to sustained improvement	28.3	65.0	NR	NR	NR	NR

Drug	Imetelstat		Luspatercept			
Trial	IMerge Phase III[5,9,18,62,73]		MEDALIST[19,21,22,24,69,75]			
Follow-up	18 months		48 weeks		24 weeks	
Arm	Imetelstat	Placebo	Luspatercept	Placebo	Luspatercept	Placebo
N	118	60	153	76	153	76
– median weeks						
Sustained meaningful deterioration*	51 (43%)	26/57 (46%)	NR	NR	NR	NR
FACT-An and QUALMS: Symptom-specific derived scores‡ – LSM (95%CI)						
Dyspnea	NR	NR	0.53 (0.2, 0.8)	-0.40 (-0.8, 0.0)	NR	NR
Physical burden	NR	NR	-0.41 (-3.2, 2.4)	-6.8 (-10.5, -3.0)	NR	NR
QUALMS: Total Composite Score	NR	NR	-0.55 (-2.9, 1.8)	-5.21 (-8.3, -2.1)	NR	NR
QULAMS: Physical burden	NR	NR	-0.41 (-3.2, 2.4)	-6.75 (-10.5, -3.0)	NR	NR
Other HRQoL Scores - Mean change from baseline in score unless otherwise stated						
EORTC QLQ-C30: Global Health†	NR	NR	NR	NR	-1.82	0.16
EORTC QLQ-C30: Physical Functioning†	NR	NR	NR	NR	-2.3	4.81
EORTC QLQ-C30: Emotional Functioning†	NR	NR	NR	NR	-2.07	-2.36
EORTC QLQ-C30: Fatigue†	NR	NR	NR	NR	4.08	-5.56
EORTC QLQ-C30: Dyspnea†	NR	NR	NR	NR	3.46	-4.32
EQ-5D-5L index – mean score	0.75	0.69	NR	NR	NR	NR
EQ-5D-5L VAS – mean score	70.6	63.8	NR	NR	NR	NR
Other Outcomes – n/N (%) unless otherwise stated						
CFB mean daily dose iron chelation therapy – least squares mean (SE)	NR	NR	N=78 -149 (46.1)	N=12 -124 (92.2)	N=128 10 (29.3)	N=68 51 (35.9)
≥50% reduction in central bone marrow RS	29/71 (41%)	3/31 (10%)	NR	NR	NR	NR
Overall Survival – median (95%CI)	NR	NR	46.0 (42.0, NA)	NA (43.1, NA)	NR	NR
Progression-free survival – median (95%CI)	Not reached	Not reached	NA (223.6, NA)	NA (NA, NA)	NR	NR
HCRU Outcomes – n/N (%) unless otherwise stated						
Overall outpatient health care encounters	NR (36.4%)	NR (40.0%)	NR	NR	NR	NR
Length of hospital stay, days	6	25.5	NR	NR	NR	NR

AML: acute myeloid leukemia, CFB: change from baseline, EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-5D-5L: EuroQol-5 Dimensions-5 Levels, FACIT: Functional Assessment of Chronic Illness Therapy, FACT-An: Functional Assessment of Cancer Therapy-Anemia, HCRU: health care resource utilization, HI-E: hematologic improvement-erythroid, IWG: International Working Group, LSM: least-squares mean, MDS: myelodysplastic syndrome, n: number, N: total number, NA: not applicable, NR: not reported, QUALMS: Quality of Life in Myelodysplasia Scale, RBC-TI: red blood cell transfusion independence, SE: standard error, VAS: visual analogue scale

* Sustained meaningful improvement/deterioration in FACIT-Fatigue is defined as an increase/decrease of ≥3 points for ≥2 consecutive cycles

† Positive score is better for EORTC QLQ-C30 Global health and functioning domains, whereas negative score is better for other domains (i.e., fatigue)

‡ Higher scores indicate improvement. Only domains with statistically significant treatment differences reported ($p<0.05$).

Table D3.4. Safety

Drug		Imetelstat				Luspatercept	
Trial		IMerge Phase II[5,63,64]		IMerge Phase III[5,18,23,26]		MEDALIST[19,25,71]	
Arm		Imetelstat Overall	Imetelstat Non-del(5q)	Imetelstat	Placebo	Luspatercept	Placebo
N		57	38	118	59	153	76
Median Follow-up, months		**16 months**	**16 months**	**18.5 months**		**24 weeks**	
Adverse Events, n (%)	Overall	56 (98%)	37 (94%)	117 (99%)	59 (100%)	150 (98%)	70 (92%)
	Serious	27 (47%)	NR	38 (32%)	13 (22%)	48 (31%)	23 (30%)
	Grade 3/4	50 (88%)	31 (82%)	107 (91%)	28 (48%)	65 (42%)	34 (45%)
Treatment-related Adverse Events, n (%)	Overall	50 (88%)	1 (2.6%)	97 (82%)	NR	NR	NR
	Serious	27 (47%)	NR	6 (5%)	NR	NR	NR
	Grade ≥3	43 (75%)	NR	85 (72%)	6 (10%)	NR	NR
Discontinuation, n (%)	Overall	43 (77%)	26 (68%)	91 (77%)	45 (76%)	83 (54%)	70 (92%)
	Lack of efficacy	16 (28%)	12 (32%)	28 (24%)	25 (42%)	13 (8%)	6 (8%)
	Adverse event-related	14 (25%)	8 (21%)	17 (14%)	0	13 (8%)	6 (8%)
	Treatment-related	9 (16%)	NR	11 (9%)	0	NR	NR
	Disease progression	3 (5%)	2 (5%)	7 (6%)	5 (9%)	1 (1%)	1 (1%)
Mortality, n (%)	Overall	2 (4%)	NR	19 (16%)	8 (13%)	12 (8%)	9 (12%)
	AE-related	NR	NR	1 (<1%)	1 (1.7%)	5 (3%)	4 (5%)
	Treatment-related	NR	NR	0	0	0	0
Disease Progression, n(%)	Higher-risk MDS	1 (1.8%)	NR	7 (6%)	5 (8%)	1 (1%)	1 (1%)
	AML	2 (3.5%)	NR	2 (2%)	1 (2%)	3 (2%)	1 (1%)
Dose changes, n (%)	Any infusion or dose modification	NR	NR	87 (63.7)	18 (30.5)	NR	NR
	Dose delay due to AE	NR	NR	81 (68.6)	14 (23.7)	NR	NR
	Dose reduction due to AE	NR	NR	58 (49.2)	4 (6.8)	7 (4.6%)	0
Cytopenia-Related Safety							
Neutropenia (Grade 3/4)	n (%)	34 (60%)	21 (55%)	80 (68%)	2 (3%)	NR	NR
	no. events	NR	NR	279	6	NR	NR
	no. events (%) resolving to Grade ≤2 within 4 weeks	NR	NR (90%)	226 (81.0%)	3 (50.0%)	NR	NR
	no. events (%) resolving ≥4 weeks	NR	NR	40 (14.3%)	2 (33.3%)	NR	NR
	unresolved (ongoing)	NR	NR	13 (4.7%)	1 (16.7%)	NR	NR

Drug		Imetelstat				Luspatercept	
Trial		IMerge Phase II[5,63,64]		IMerge Phase III[5,18,23,26]		MEDALIST[19,25,71]	
Arm		Imetelstat Overall	Imetelstat Non-del(5q)	Imetelstat	Placebo	Luspatercept	Placebo
N		57	38	118	59	153	76
Cytopenia-Related Safety (continued)							
Neutropenia (Grade 3/4)	Median duration (range) weeks	NR	1.7 (NR)	1.86 (0-15.9)	2.21 (1.0-4.6)	NR	NR
	no. (%) of dose reductions	NR	NR	39/58 (67%)	NR	NR	NR
	no. (%) of dose delays	NR	NR	60/81 (74%)	NR	NR	NR
	led to discontinuation	NR	NR	6 (5%)	0	NR	NR
	growth factor support	NR	NR	41 (35%)	NR	NR	NR
Thrombocytopen-ia (Grade 3/4)	n (%)	31 (54%)	23 (61%)	73 (62%)	5 (8%)	0	0
	no. events	NR	NR	212	9	N/A	N/A
	no. events (%) resolving to Grade ≤2 within 4 weeks	NR	NR (88%)	183 (86.3%)	4 (44.4%)	N/A	N/A
	no. events (%) resolving ≥4 weeks	NR	NR	17 (8%)	1 (11.1%)	N/A	N/A
	unresolved (ongoing)	NR	NR	12 (5.7%)	4 (44.4%)	N/A	N/A
	Median duration (range) weeks	NR	1.1 (NR)	1.43 (0.1-12.6)	2.00 (0.3-11.6)	N/A	N/A
	no. (%) of dose reductions	NR	NR	27 (23%)	NR	N/A	N/A
	no. (%) of dose delays	NR	NR	55 (47%)	NR	N/A	N/A
	led to discontinuation	NR	NR	4 (3%)	0	N/A	N/A
	platelet transfusions	NR	NR	21 (18%)	NR	N/A	N/A
Clinical Consequences Cytopenias – n (%)							
Febrile Neutropenia	Overall	NR	2 (5%)	NR	NR	NR	NR
	Grade ≥3	NR	NR	1 (1%)	0	NR	NR
Bleeding Events	Overall	NR	4 (10%)	25 (21%)	7 (12%)	NR	NR
	Grade ≥3	NR	2 (5%)	3 (2.5%)	1 (1.7%)	NR	NR
Infections	Overall	NR	NR	50 (42%)	20 (34%)	82 (54%)	31 (41%)
	Grade ≥3	NR	NR	13 (11%)	8 (14%)	NR	NR
	Concurrent with neutropenia	NR	NR	3 (2.5%)*	NR	4/9 (44%)	3/7 (42.9%)

Drug		Imetelstat				Luspatercept	
Trial		IMerge Phase II[5,63,64]		IMerge Phase III[5,18,23,26]		MEDALIST[19,25,71]	
Arm		Imetelstat Overall	Imetelstat Non-del(5q)	Imetelstat	Placebo	Luspatercept	Placebo
N		57	38	118	59	153	76
Adverse Events of Special Interest – n (%)							
Thromboembolic/ thrombophlebitis	Any Grade	NR	NR	NR	NR	4 (3%)	3 (4%)
Thrombocytopen-ia	Any Grade	35 (61%)	25 (66%)	89 (75%)	6 (10%)	NR	NR
	Grade 3/4	31 (54%)	23 (61%)	73 (62%)	5/59 (8%)	0	0
Adverse Events of Special Interest (continued) – n (%)							
Neutropenia	Any Grade	38 (67%)	22 (58%)	87 (74%)	4 (7%)	7 (5%)	7 (9%)
	Grade 3/4	34 (60%)	21 (55%)	80 (68%)	2/59 (3%)	5 (3.3%)	6 (8%)
Anemia	Any Grade	13 (23%)	10 (26%)	24 (20%)	6 (10%)	11 (7%)	6 (8%)
	Grade 3/4	11 (19%)	8 (21%)	23 (19%)	4/59 (7%)	10 (6.5%)	5 (6.6%)
Leukopenia	Any Grade	NR	NR	12 (10%)	1 (1.7%)	NR	NR
	Grade 3/4	NR	NR	9 (8%)	0/59 (0%)	NR	NR
Pneumonia	Any Grade	NR	NR	NR	NR	3 (2%)	2 (3%)
	Grade 3/4	NR	NR	NR	NR	NR	NR
Fatigue	Any Grade	NR	NR	NR	NR	41 (27%)	10 (13%)
	Grade 3/4	NR	NR	NR	NR	7 (5%)	2 (3%)
Back pain	Any Grade	9 (16%)	7 (18%)	NR	NR	NR	NR
	Grade 3/4	3 (5%)	2 (5%)	NR	NR	3 (2%)	0
ALT increased	Any Grade	10 (18%)	7 (18%)	14 (12%)	4 (7%)	9 (6%)	3 (4%)
	Grade 3/4	3 (5%)	2 (5%)	3 (3%)	2 (3%)	3 (2%)	0
AST increased	Any Grade	8 (14%)	6 (16%)	NR	NR	NR	NR
	Grade 3/4	3 (5%)	3 (8%)	NR	NR	NR	NR
Bronchitis	Any Grade	6 (11%)	6 (16%)	NR	NR	17 (11%)	1 (1%)
	Grade 3/4	3 (5%)	3 (8%)	NR	NR	1 (1%)	0
Headache	Any Grade	12 (21%)	6 (16%)	15 (13%)	3 (5%)	24 (16%)	5 (7%)
	Grade 3/4	1 (2%)	1 (3%)	1 (1%)	0	1 (1%)	0
Nasopharyngitis	Any Grade	6 (11%)	6 (16%)	NR	NR	NR	NR
	Grade 3/4	0	0	NR	NR	NR	NR
Diarrhea	Any Grade	9 (16%)	6 (16%)	14 (12%)	7 (12%)	34 (22%)	7 (9%)
	Grade 3/4	1 (2%)	0	1 (1%)	1 (2%)	0	0
Constipation	Any Grade	8 (14%)	6 (16%)	9 (8%)	7 (12%)	17 (11%)	7 (9%)

Drug		Imetelstat				Luspatercept	
Trial		IMerge Phase II[5,63,64]		IMerge Phase III[5,18,23,26]		MEDALIST[19,25,71]	
Arm		Imetelstat Overall	Imetelstat Non-del(5q)	Imetelstat	Placebo	Luspatercept	Placebo
N		57	38	118	59	153	76
	Grade 3/4	0	0	0	0	0	0
Peripheral edema	Any Grade	8 (14%)	6 (16%)	13 (11%)	8 (14%)	25 (16	13 (17%)
	Grade 3/4	0	0	0	0	0	1 (1%)
Asthenia	Any Grade	6 (11%)	6 (16%)	22 (19%)	8 (14%)	31 (20%)	9 (12%)
	Grade 3/4	1 (2%)	1 (3%)	0	0	4 (3%)	0
Adverse Events of Special Interest (continued) – n (%)							
Hyperbilirubin-emia	Any Grade	NR	NR	11 (9%)	6 (10%)	NR	NR
	Grade 3/4	NR	NR	1 (1%)	1 (2%)	NR	NR
Pyrexia	Any Grade	NR	NR	9 (8%)	7 (12%)	13 (8.5%)	7 (9.2%)
	Grade 3/4	NR	NR	2 (2%)	0	NR	NR
Nausea	Any Grade	NR	NR	NR	NR	31 (20%)	6 (8%)
	Grade 3/4	NR	NR	NR	NR	1 (1%)	0
Dizziness	Any Grade	NR	NR	NR	NR	30 (20%)	4 (5%)
	Grade 3/4	NR	NR	NR	NR	0	0
Arthralgia	Any Grade	NR	NR	NR	NR	8 (5%)	9 (12%)
	Grade 3/4	NR	NR	NR	NR	1 (1%)	2 (3%)
Dyspnea	Any Grade	NR	NR	NR	NR	23 (15%)	5 (7%)
	Grade 3/4	NR	NR	NR	NR	1 (1%)	0
Cough	Any Grade	NR	NR	NR	NR	27 (18%)	10 (13%)
	Grade 3/4	NR	NR	NR	NR	0	0
Urinary Tract Infection	Any Grade	NR	NR	NR	NR	17 (11%)	4 (5%)
	Grade 3/4	NR	NR	NR	NR	2 (1%)	3 (4%)
Vomiting	Any Grade	NR	NR	NR	NR	10 (6.5%)	5 (6.6%)
Abdominal Pain	Any Grade	NR	NR	NR	NR	7 (4.6%)	4 (5.3%)

AE: adverse event, ALT: alanine aminotransferase, AML: acute myeloid leukemia, AST: aspartate aminotransferase, MDS: myelodysplastic syndrome, n: number, N: total number, no.: number, NR: not reported

* Grade 3/4 neutropenia concurrent with grade 3/4 infections

Table D3.5. Subgroup Findings

Trial		IMerge Phase III[18,26,66]			MEDALIST[19,28]		
Arm		Imetelstat	Placebo	% Difference (95% CI); p-value	Luspatercept	Placebo	% Difference (95%CI)
N		118	60		153	76	
8-Week RBC-Transfusion Independence							
Overall		47/118 (40%)	9/60 (15%)	24.8 (9.9-36.9); p=<0.001	58/153 (38%)	10/76 (13%)	24.6 (14.5, 34.6)
WHO Category	RS+	33/73 (45%)	7/37 (19%)	26.3 (5.9-42.2); p=0.016	69 (45%)	12 (16%)	NA
	RS-	14/44 (32%)	2/23 (9%)	23.1 (-1.3-40.6); p=0.038	NA	NA	NA
Prior Transfusion Burden (IWG 2006)	<4	NR	NR	NR	37/46 (80%)	8/20 (40%)	40.4 (14.5, 63.9)
	4-6 U/8 week	28/62 (45%)	7/33 (21%)	23.9 (1.9-41.4); p=0.027	15/41 (37%)	1/23 (4%)	32.2 (6.8, 55.0)
	>6 U-8 week	19/56 (34%)	2/27 (7%)	26.5 (4.7-41.8); p=0.023	6/66 (9%)	1/33 (3%)	6.1 (-15.5, 27.2)
IPSS Risk Category	very low/low	32/80 (40%)	8/39 (21%)	19.5 (-0.1-35.2); p=0.034	NR	NR	NR
	intermediate	15/38 (40%)	1/21 (5%)	34.7 (8.8-52.4); p=0.004	NR	NR	NR
IPSS-R Risk Category	low	37/87 (42.5%)	9/46 (19.6%)	NR	48/127 (38%)	9/63 (14%)	NR
	intermediate-1	7/20 (35%)	0/8 (0%)	NR	10/25 (40%)	1/13 (8%)	NR
Baseline sEPO	≤500 mU/mL	39/87 (45%)	7/36 (19%)	25.4 (5.3-40.7); p=0.011	54/131 (41%)	10/65 (15%)	25.8 (11.3, 40)
	>500 mU/mL	7/26 (27%)	2/22 (9%)	17.8 (-8.2-40.3); p=0.107	3/21 (14%)	0/11 (0%)	14.3 (-22.6, 48.3)
24-Week RBC-Transfusion Independence							
Overall		33/118 (28%)	2/60 (3%)	24.6 (12.6, 34.2); p=<0.001	NR	NR	NR
WHO Category	RS+	24/73 (33%)	2/37 (5%)	27.5 (10.0, 40.4); p=0.003	NR	NR	NR
	RS-	9/44 (21%)	0/23 (0%)	20.5 (-0.03, 35.8); p=0.019	NR	NR	NR
Prior Transfusion Burden (IWG 2006)	4-6 U/8 week	19/62 (31%)	2/33 (6%)	24 (5.7, 38.7); p=0.006	NR	NR	NR
	>6 U-8 week	14/56 (25%)	0/27 (0%)	25 (6.4, 38.7); p=0.001	NR	NR	NR
IPSS Risk Category	very low/low	23/80 (29%)	2/39 (5%)	23.6 (7.2, 35.8); p=0.003	NR	NR	NR
	intermediate	10/38 (26%)	0/21 (0%)	26.3 (3.46, 43.9); p=0.009	NR	NR	NR
IPSS-R Risk Category	low	26/87 (29.9%)	2/46 (4.3%)	NR	NR	NR	NR
	intermediate-1	5/20 (25%)	0/8 (0%)	NR	NR	NR	NR
Baseline sEPO	≥500 mU/mL	29/87 (33%)	2/36 (6%)	27.8 (10.5, 39.1); p=0.002	NR	NR	NR
	>500 mU/mL	4/26 (15%)	0/22 (0%)	15.4 (-5.8, 35.7); p=0.05	NR	NR	NR
Prior ESA	Yes	31/108 (29%)	2/52 (34%)	24.9 (11.6, 35.0); p<.001	NR	NR	NR
	No	2/10 (20%)	0/8 (0%)	20.0 (-23.5, 55.8); p=0.225	NR	NR	NR

Median Duration of 8-Week RBC Transfusion Independence (95%CI)							
Arm		**Imetelstat**	**Placebo**	**HR (95%CI); p=p-value**	**Luspatercept**	**Placebo**	**% Difference (95%CI)**
N		118	60		153	76	
Overall		51.6 (26.9-83.9)	13.3 (8.0-24.9)	0.23 (0.09-0.57); p<.001	NR	NR	NR
Median Duration of 8-Week RBC Transfusion Independence (95%CI) – *continued*							
Arm		**Imetelstat**	**Placebo**	**HR (95%CI); p=p-value**	**Luspatercept**	**Placebo**	**% Difference (95%CI)**
N		118	60		153	76	
WHO Category	RS+	46.9 (25.9-83.9)	16.9 (8.0-24.9)	0.32 (0.11-0.95); p=0.035	NR	NR	NR
	RS-	51.6 (11.9-NE)	11.2 (10.1-NE)	0.11 (0.01-1.43); p=0.062	NR	NR	NR
Prior Transfusion Burden (IWG 2006)	4-6 U/8 week	51.9 (24.9-122.9)	16.9 (10.1-24.9)	0.35 (0.13-0.96); p=0.035	NR	NR	NR
	>6 U-8 week	39.9 (15.9-NE)	8.4 (8.0-NE)	0.04 (0.003-0.48); p<.001	NR	NR	NR
IPSS Risk Category	low	43.9 (25.0-NE)	15.1 (8.0-24.9)	0.26 (0.10-0.68); p=0.004	NR	NR	NR
	intermediate-1	51.6 (11.9-NE)	10.1 (NE-NE)	0.15 (0.01-2.47); p=0.128	NR	NR	NR
Baseline sEPO	≥500 mU/mL	51.6 (26.9-83.9)	13.3 (8.0-24.9)	0.21 (0.08-0.61); p=0.002	NR	NR	NR
	>500 mU/mL	122.9 (8.14-NE)	14.6 (12.3-NE)	0.34 (0.03-3.85); p=0.364	NR	NR	NR
Prior ESA	Yes	43.9 (26.9-80.0)	13.3 (8.0-24.9)	0.26 (0.10-0.72); p=0.006	NR	NR	NR
	No	122.9 (8.14-NE)	14.6 (12.3-NE)	0.34 (0.03-3.85); p=0.364	NR	NR	NR

95%CI: 95 percent confidence interval, ESA: erythropoiesis stimulating agent, HR: hazard ratio, IPSS: International Prognostic Scoring System, IWG: International Working Group, NE: not estimable, RBC: red blood cell, RS+: ring sideroblasts positive, RS-: ring sideroblast negative, U: units, WHO: World Health Organization, mU/mL: milliunit per milliliter, p: p-value, sEPO: serum erythropoietin

D4. Ongoing Studies

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion
Imetelstat					
Study to Evaluate Imetelstat in Patients With High-Risk MDS or AML Failing HMA-based Therapy (IMpress) GCP-Service International West GmbH NCT05583552	Phase II single-arm, open-label trial Estimated enrollment: N = 46	**Single-arm**: Imetelstat IV administration	**Inclusions**: - Adults 18 years or older - Diagnosis of MDS or AML (WHO 2016 classification) - ≥1 cytopenia - ≥5% bone marrow blasts - Ineligible for allogeneic SCT - relapsed/refractory to HMAs **Exclusions**: - Prior intensive chemotherapy or hematopoietic SCT	Overall hematologic response rate (IWG 2018 criteria) [4 months]	February 2025
Luspatercept					
Assessment of Effectiveness and Safety of Luspatercept in Patients Suffering From Lower-risk Myelodysplastic Syndrome. (LUSPLUS) GWT-TUD GmbH NCT05181592	Phase IIIb, single-arm, open-label, multi-center study Estimated enrollment: N = 70	**Single-arm:** Luspatercept	**Inclusions**: - Adults 18 years or older - MDS diagnosis (WHO classification) - IPSS-R: very low, low, intermediate-risk MDS - RS≥ 15% of erythroid precursors or ≥5% SF3B1 mutation - ≥5% blasts in bone marrow - Refractory/relapsed/ineligible to prior ESA treatment - RBC transfusions ≥2 units/8 weeks **Exclusions**: - Prior treatment with an HMA, lenalidomide, luspatercept, or sotatercept - Prior allogeneic or autologous SCT - Secondary MDS or AML	RBC transfusion independence (IWG 2018 criteria) [Week 24]	December 2024

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Primary Outcomes	Estimated Completion
Luspatercept (continued)					
A Study to Assess Luspatercept in Lower-risk Myelodysplastic Syndrome Participants (MAXILUS) Bristol-Myers Squibb NCT06045689	Phase IIIb, open-label, non-randomized, parallel assignment study Estimated enrollment: N = 100	**ESA naive** Single-arm Luspatercept **ESA relapsed or refractory** Single-arm Luspatercept	**Inclusions**: - Adults 18 years or older - MDS diagnosis (WHO classification) - IPSS-R: very low, low, intermediate-risk MDS - ECOG score 0, 1, 2 - RBC transfusions according to study criteria **Exclusions**: - Prior allogeneic or autologous SCT - History or diagnosis of AML	RBC transfusion independence for 8 weeks consecutively with mean increase in hemoglobin ≥1 g/dL [Week 24]	January 2026

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

AML: acute myeloid leukemia, ECOG: Eastern Cooperative Oncology Group, ESA: erythropoiesis stimulating agent, HMA: hypomethylating agent, IPSS-R: International Prognostic Scoring System-Revised, IV: intravenous, IWG: International Working Group, MDS: myelodysplastic syndrome, N: total number, RBC: red blood cell, SCT: stem cell transplant, WHO: World Health Organization

D5. Previous Systematic Reviews and Technology Assessments

We identified three health technology assessments (HTA) of imetelstat and luspatercept for the treatment of MDS. The National Institute for Health and Care Excellence (NICE) initiated assessments for imetelstat and luspatercept separately but suspended both. The Canadian Agency for Drugs and Technologies in Health (CADTH) completed one assessment on luspatercept that we describe below. We identified one systematic literature review relevant to our scope, however no results related to imetelstat were publicly available to summarize.

Previous Health Technology Assessments

NICE: Imetelstat for treating relapsed or refractory transfusion-dependent myelodysplastic syndromes (TA10800)

NICE began an appraisal of the clinical and cost effectiveness of imetelstat for the treatment of relapsed or refractory transfusion-dependent MDS. The review was officially suspended in February 2024 while Geron confirms their regulatory filing plans in the United Kingdom.

NICE: Luspatercept for treating anaemia caused by myelodysplastic syndromes (TA844)

NICE intended to complete an appraisal of the clinical and cost effectiveness of luspatercept for the treatment of anemia caused by MDS. However, the manufacturer declined to submit evidence so no appraisal could be completed.

CADTH: Luspatercept (SR0670-000)

CADTH completed a systematic review of the efficacy and safety of luspatercept for the treatment of adults with transfusion-dependent anemia in very low- to intermediate-risk MDS with ring sideroblasts who had failed or were not suitable for ESA-based therapy in 2021. Their review was based on the MEDALIST trial findings demonstrating superiority of luspatercept to placebo in achieving the trial's primary endpoint of achieving 8 consecutive weeks of transfusion independence. Uncertainty on the superiority of luspatercept to placebo remained for key secondary and health-related quality of life endpoints. The review highlighted concerns of thromboembolic events, hypertension, hepatic and renal harms, and neoplasms associated with luspatercept. CADTH recommended reimbursement of luspatercept under the following conditions: restriction to only those failing or ineligible for erythropoietin-based therapy, renewal based on RBC transfusion independence for 16 consecutive weeks during the first 24 weeks (not 8-weeks), prescribed by an MDS specialist, and a reduction in the price of 85% to achieve an ICER of $50,000 per QALY compared to best supportive care.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	Time seeking medical care.*
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	Patient and caregiver formal labor time*
	Cost of unpaid lost productivity due to illness	NA	X	Patient unpaid productivity*
	Cost of uncompensated household production	NA	X	Patient household production*
Consumption	Future consumption unrelated to health	NA	X	Patient consumption*
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[76]

* Analysis based on ICER's indirect "non-zero" approach. Please see ICER's reference case for further information.

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[77]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus for the economic evaluation included patients with lower risk transfusion dependent MDS without the del(5q) subtype who were refractory or ineligible to ESAs. There were two analytic populations: 1) Overall population which included all imetelstat eligible MDS patients, and 2) RS+ which included ring sideroblast positive patients. Baseline population characteristics were obtained from the IMerge Phase III clinical trial. [18] IPSS-Revised percentages were calculated based on the number of people for whom IPSS-R information was available in IMerge. This population contained a mix of ring sideroblast positive (RS+) and negative (RS-) patients. While luspatercept was only used to treat patients who were ring sideroblast positive, we lacked baseline population characteristics by ring sideroblast subgroups from IMerge.

Table E1.2. Base-Case Model Cohort Characteristics

Baseline Characteristic	Value
Median Age (years)	72
Percent Female (%)	38
Transfusion Burden	
≤6 RBC units/8wks (%)	53
>6 RBC units/8wks (%)	47
IPSS-Revised	
Very Low (%)	3
Low (%)	80
Intermediate Risk-1 (%)	17

WHO: World Health Organization, RBC: red blood cell, wks: weeks, IPSS: International Prognostic Scoring System, sEPO: serum erythropoietin concentration

E2. Model Inputs and Assumptions

Model Inputs

Transition Probabilities

In the overall analysis patients started in the low and high transfusion dependent states following the baseline proportions in Table E1.2. These proportions were kept through the duration of the model in the base case. In the RS+ analysis everyone began transfusion dependent and were not differentiated by burden. We assumed the IPSS-R distribution was even between low and high transfusion burdens.

Given the short duration of the trials, only three patients in IMerge progressed to AML, and 12 experienced any disease progression. We therefore informed transitions on disease progression to high-risk MDS and AML based on parametric models fit on digitized survival curves found in literature (Table E2.1). IPSS-R progression models the probability of progressing one IPSS-R risk category in lower-risk MDS. For example, if a patient was in low risk, they would move to intermediate-1.

Table E2.1. Transition Probabilities to HR-MDS and AML

Parameter	Value	Source
Transition to AML (IPSS-R Very Low)	0.001	Greenberg et al. 2012[78]
Transition to AML (IPSS-R Low)	0.002	Greenberg et al. 2012[78]
Transition to AML (IPSS-R Intermediate)	LogNormal μ: 6.914 σ: 2.480	Greenberg et al. 2012[78]
Transition to AML (IPSS-R High)	LogNormal μ: 5.630 σ: 2.222	Greenberg et al. 2012[78]
Transition to AML (IPSS-R Very High)	LogNormal μ: 4.921 σ: 1.994	Greenberg et al. 2012[78]
IPSS-R progression	0.004	Buckstein et al. 2022[79]

AML: Acute Myeloid Leukemia, IPSS-R: Revised International Prognostic Scoring System

Mortality

Published trial data were not mature enough to obtain direct mortality effects of imetelstat or luspatercept. We used mortality information based on IPSS-R, AML, and transfusion dependence from the literature and all-cause mortality from life tables (Table E2.2). We applied the same mortality rates to all treatments as there was not sufficient evidence that these treatments directly impact survival. We adjusted the mortality rates for patients in the transfusion independent state by applying a mortality hazard ratio to the IPSS-R risk stratified mortality rates, under the assumption that these rates were estimated in transfusion dependent patients; this yielded an indirect effect on mortality between treatments. For each cycle we applied the higher transition probability from the modeled curves or age-specific life tables.

Table E2.2. Mortality

Parameter	Value	Source
Mortality (IPSS-R Very Low)	LogNormal μ: 5.929 σ: 0.883	Greenberg et al. 2012[78]
Mortality (IPSS-R Low)	0.012	Greenberg et al. 2012[78]
Mortality (IPSS-R Intermediate)	0.019	Greenberg et al. 2012[78]
Mortality (IPSS-R High)	0.032	Greenberg et al. 2012[78]
Mortality (IPSS-R Very High)	0.061	Greenberg et al. 2012[78]
Mortality (AML)	0.118	Oran et al. [80]
Mortality Hazard Ratio for Transfusion Independence	0.382 (0.201 – 0.666)	Lemos et al. 2021[32]
All-Cause Mortality		U.S. Life Tables

AML: Acute Myeloid Leukemia, IPSS-R: Revised International Prognostic Scoring System

Utilities

Utilities from Szende et al.[36] were used for transfusion dependent and independent health states, obtained from the time trade-off (TTO) method in face-to-face interviews with patients from France, Germany, the UK and the US.s. These utilities were used in previous economic analyses reviewed by CADTH[31] for luspatercept in lower risk MDS and by Pan et al. [38] for decitabine in high-risk MDS. In the RS+ analysis we used a weighted average of the LTB and HTB utilities based on our baseline proportions for the transfusion dependent health state. For high risk MDS, we used a utility value estimated by Crespo et al. [37] who mapped European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) scores to EQ-5D values. For AML we used a utility calculated by Pan et al.[38], who mapped a published European Organization for the Research and Treatment of Cancer core 30-item questionnaire 13 to the EQ-5D utility scale using a published algorithm. This utility was specifically for patients who progressed to AML from MDS, as they are expected to be less healthy than patients diagnosed directly with AML.

Prior published economic models for transfusion dependent MDS include a disutility for iron chelation with deferoxamine as it is administered as a subcutaneous injection.[31] In our base case we assumed that iron chelation therapy was already included in the utilities for transfusion dependent states and did not add an additional disutility.

Economic Inputs

Drug Utilization

The following inputs were used to model drug utilization (Table E2.3). The average dose for patients on imetelstat was based on the relative dose intensity per cycle plot from IMerge with everyone starting at 7.5mg/kg (equvalient to 7.1mg/kg Rytelo™), dropping to 95% of the initial dose for cycles

2 and 3, and to 86% for the remaining cycles.[18] For luspatercept, patients started with an initial dose of 1.0 mg/kg every 3 weeks; this was the maximum dose for 22.9% of patients in the luspatercept + BSC arm of the MEDALIST trial. The dose was increased at 6 weeks to 1.33mg/kg for the remaining patients who did not respond, with 18.3% of patients receiving this as their maximum dose. It was then further increased to 1.75 mg/kg, for the remaining 58.8% of patients at 12 weeks. The dose used in the model was a weighted average of the maximum dose following the 6- and 12-week timepoints for up titrations.

Table E2.3. Drug Utilization

Generic Name	Imetelstat	Luspatercept
Brand Name	Rytelo™	Reblozyl®
Manufacturer	Geron Corporation	Bristol Myers Squibb
Route of Administration	IV	SQ
Dosing	4.4 to 7.1 mg/kg every 4 weeks	1.0 to 1.75 mg/kg every 3 weeks

IV: Intravenous Infusion, SQ: Subcutaneous Injection, mg: milligram, kg: kilogram

Health State Costs

Average prices containing all medical and outpatient pharmacy costs were sourced from published literature on US-based studies and used for HR MDS and AML (Table E2.4). HR-MDS cost estimates were obtained from Bell et al.,[81] who looked at resource utilization and costs among patients with HR-MDS from January 1, 2008, and December 31, 2015. AML cost estimates were obtained from Kota et al.[82] who looked at resource utilization and costs for patients with HR-MDS who progressed to AML between January 1, 2008, and June 30, 2019.

Table E2.4. Average Costs for HR-MDS and AML

State	Costs per Month	Source
HR-MDS Year 1	$20,529	Bell et al. 2019[81]
HR-MDS Year 2+	$15,365	Bell et al. 2019[81]
AML	$40,326	Kota et al. 2023[82]

HR-MDS: High Risk Myelodysplastic Syndromes, AML: Acute Myeloid Leukemia

Best Supportive Care Costs

Costs associated with best supportive care consisted of RBC and platelet transfusions, myeloid growth factors and iron chelation therapy and can be found in Table E2.5.

Average RBC and platelet costs contained all costs associated with transfusing the maximum of 2 units. [83] We assumed the average number of RBC units transfused in 8 weeks in the low burden population and high burden population were 5 and 7 respectively for the overall population analysis. In the RS+ population we used the median transfusion burden of 6 RBC units/8weeks as reported in IMerge.[18] We used a monthly iron chelation cost of $16,324. This was calculated assuming 90% of patients received deferasirox orally, and the remaining 10% received deferoxamine mesylate subcutaneously. [84] We used a 20 mg/kg/day dose of deferasirox at $600 per 1500mg, and 2000 mg/day of deferoxamine mesylate at 51.80 per 2000 mg, 6 days per week. Price estimates for both drugs were based on the wholesale acquisition cost of the lowest cost generic from REDBOOK.[39] A cost for 60mcg of filgrastim (Neupogen®) was also obtained from REDBOOK and applied to patients who received growth factors subcutaneously. [84] Administrative costs associated with each treatment were also applied (Table E2.5).

Platelet costs were applied to 18% of imetelstat patients and 2% of patients on best supportive care alone, and growth factors were applied to 35% of patients on imetelstat and 3% on best supportive care following data from IMerge. [18] Iron chelation costs were applied to all transfusion dependent patients independent of treatment.

Table E2.5. Best Supportive Care Costs

	Value ($)	Source
Transfusion Costs		
Average RBCs, each unit	946	Cogle et al. 2016 [83]
Platelets, each unit	778	Cogle et al. 2016 [83]
Other		
Growth Factors 60mcg	33	REDBOOK[39]
Iron Chelation, average monthly cost	16,324	REDBOOK[39]

RBC: Red Blood Cell, mcg: microgram

Outpatient Services

Costs associated with outpatient services are detailed in Table E2.6.

Table E2.6. Outpatient Service Costs

	Value ($)	Source
Physician office visit (First 40 minutes)	177	CMS Fee Schedule
Physician office visit (Additional 30 minutes)	32	CMS Fee Schedule
Subcutaneous injection	14	CMS Fee Schedule
IV Administration Cost (First Hour)	62	CMS Fee Schedule
IV Administration Cost (Subsequent hours)	20	CMS Fee Schedule

Adverse Event Costs

Adverse event costs were obtained from CMS MS-DRG following codes 813, 810, 816 and 812 for thrombocytopenia, neutropenia, leukopenia, and anemia respectively.

Productivity Costs

We obtained estimates on employment from the Cancer Experience Registry (CER) at the Cancer Support Community.[85] Of patients who completed the Work Productivity and Activity Impairment (WPAI) questionnaire, 13% were employed, 14% were unemployed due to disability and 69% were retired. In the absence of direct data to inform a societal perspective analysis that includes the impact of treatment on productivity for patients with MDS and their caregivers, we used an indirect approach. To inform estimates for the indirect approach, we used the published relationship between patient utility scores and US-based patient time use data[86] to derive the anticipated impacts of the treatment on productivity due to the disease and its management for the patient. Since no parallel relationship between patient utility scores and caregiver productivity impacts for the US setting, we assumed that caregiver time spent is proportional to 75% of patient formal labor time lost. This estimate is based on the modeled relationship between caregiver time required[87] and patient time lost[88] according to patient utility scores in the United Kingdom setting. Further details on the implementation of this approach are detailed in ICER's reference case.

E3. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. One way sensitivity analyses results are displayed below in Figures E3.1, E3.2, E3.3, and Tables E3.1, E3.2 and E3.3. Tornado plots were broken into incremental costs and incremental QALYs for the RS+ positive comparing imetelstat to luspatercept due to quadrant jumping in the ICERs. Probabilistic sensitivity analysis was also conducted for the RS+ analysis, where we found Imetelstat to be cost-effective in 7.0%, 6.0%, 6.1%, and 6.1% of the simulations compared to luspatercept at willingness to pay threshold of $50,000, $100,000, $150,000, and $200,000 per QALY, respectively. Mean total costs, QALY and evLYs can be found in Tables E3.4, and E3.5.

Table E3.1. Tornado Diagram Inputs and Results for Imetelstat versus Best Supportive Care in the Overall Population

	Lower Incremental CE Ratio ($)	Upper Incremental CE Ratio ($)	Lower Input*	Upper Input*
Utility of TI	839,000	2,174,000	0.67	1
Hazard ratio for transfusion independence	1,031,000	1,689,000	0.2	0.67
Median IMerge trial weight	901,000	1,494,000	60	90
Cost per mg (imetelstat)	901,000	1,494,000	42.06	63.09
Dose relative to starting for cycles 3+ (imetelstat)	994,000	1,400,000	0.69	1.03
Utility of LTB	1,039,000	1,413,000	0.62	0.92
Transition probability from TI to TD (imetelstat)	1,060,000	1,342,000	0.04	0.06
8 week response in LTB (imetelstat)	1,090,000	1,336,000	0.36	0.54
8 week response in HTB (imetelstat)	1,098,000	1,322,000	0.27	0.41
Utility of HTB	1,104,000	1,308,000	0.48	0.72
Lognormal mu for transition from TI to TD (BSC)	1,145,000	1,300,000	2.08	3.12

CE: cost-effectiveness, TI: Transfusion Independent, TD: Transfusion Dependent, LTB: Low Transfusion Burden, HTB: High Transfusion Burden, mg: milligram

* Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E3.1. Tornado Diagram for Imetelstat Compared to Best Supportive Care in the RS+ Population

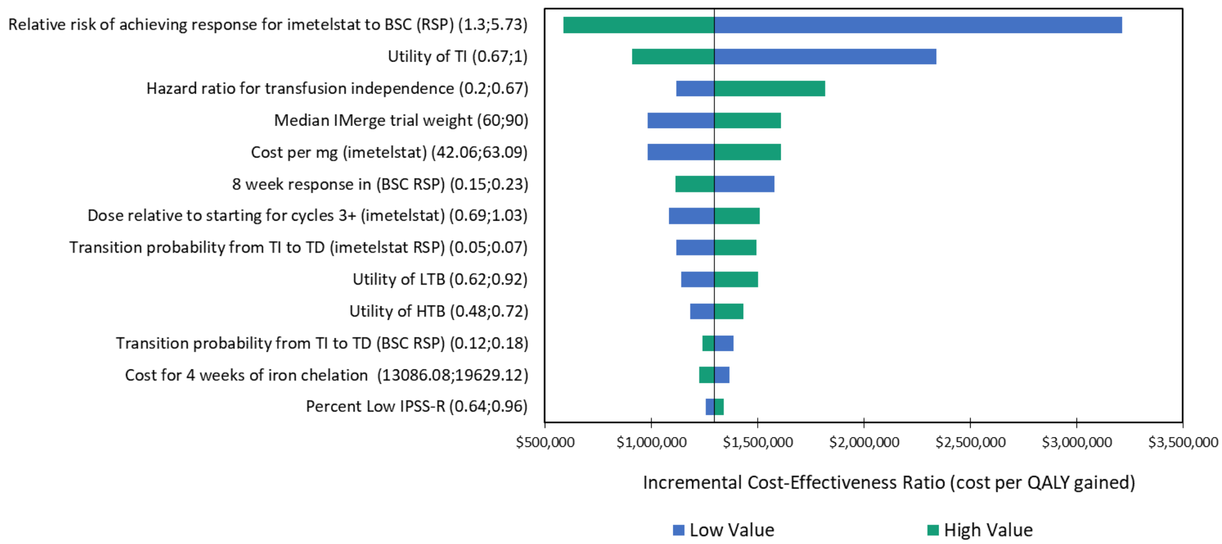


Table E3.2. Tornado Diagram Inputs and Results for Imetelstat versus Best Supportive Care in the RS+ Population

	Lower Incremental CE Ratio ($)	Upper Incremental CE Ratio ($)	Lower Input*	Upper Input*
Relative risk of achieving response for imetelstat to BSC (RSP)	585,000	3,215,000	1.3	5.73
Utility of TI	910,000	2,341,000	0.67	1
Hazard ratio for transfusion independence	1,116,000	1,818,000	0.2	0.67
Median IMerge trial weight	982,000	1,611,000	60	90
Cost per mg (imetelstat)	982,000	1,611,000	42.06	63.09
8-week response in (BSC RSP)	1,115,000	1,581,000	0.15	0.23
Dose relative to starting for cycles 3+ (imetelstat)	1,083,000	1,511,000	0.69	1.03
Transition probability from TI to TD (imetelstat RSP)	1,118,000	1,494,000	0.05	0.07
Utility of LTB	1,140,000	1,503,000	0.62	0.92
Utility of HTB	1,184,000	1,433,000	0.48	0.72
Transition probability from TI to TD (BSC RSP)	1,241,000	1,385,000	0.12	0.18

CE: cost-effectiveness, TI: Transfusion Independent, TD: Transfusion Dependent, LTB: Low Transfusion Burden, HTB: High Transfusion Burden, RSP: Ring Sideroblast Positive, mg: milligram

* Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Figure E3.2. Tornado Diagram for Imetelstat Compared to Luspatercept in the RS+ Population (Incremental Costs)

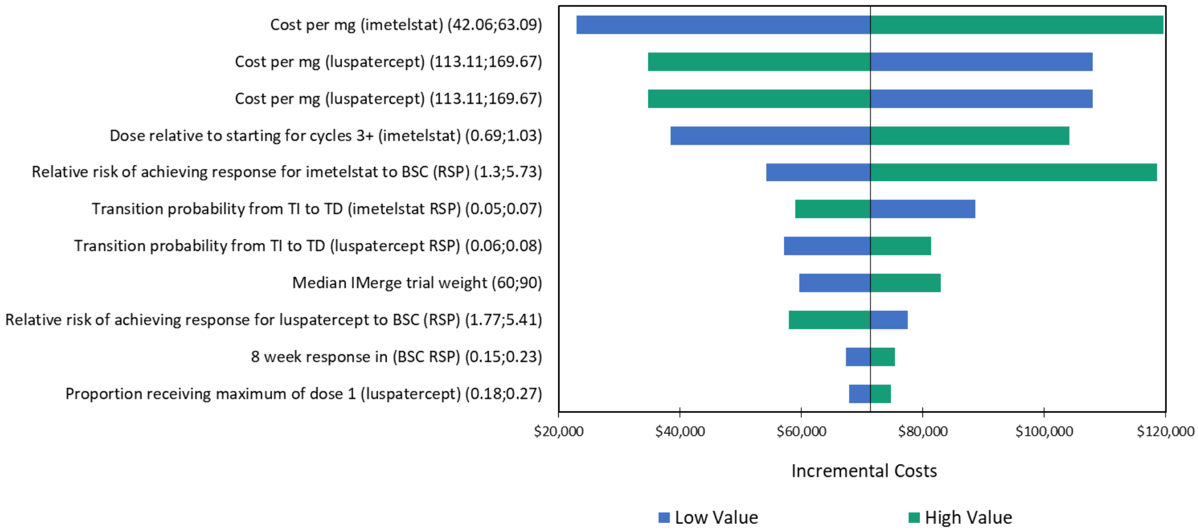


Figure E3.3. Tornado Diagram for Imetelstat Compared to Luspatercept in the RS+ Population (Incremental QALYs)

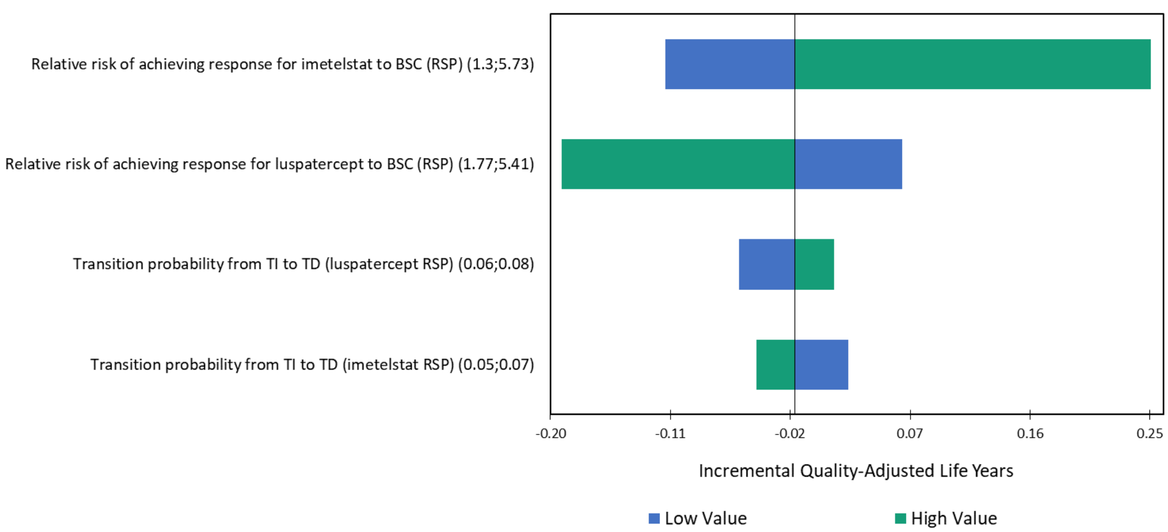


Table E3.3. Tornado Diagram Inputs and Results for Imetelstat versus Luspatercept in the RS+ Population

Incremental Costs				
	Lower Incremental Costs ($)	Upper Incremental Costs ($)	Lower Input*	Upper Input*
Cost per mg (imetelstat)	23,000	120,000	42.06	63.09
Relative risk of achieving response for imetelstat to BSC (RSP)	35,000	108,000	1.3	5.73
Cost per mg (luspatercept)	35,000	108,000	113.11	169.67
Dose relative to starting for cycles 3+ (imetelstat)	38,000	104,000	0.69	1.03
Transition probability from TI to TD (imetelstat RSP)	54,000	119,000	0.05	0.07
Median IMerge trial weight	59,000	89,000	60	90
Transition probability from TI to TD (luspatercept RSP)	57,000	81,000	0.06	0.08
Relative risk of achieving response for luspatercept to BSC (RSP)	60,000	83,000	1.77	5.41
8 week response in (BSC RSP)	58,000	78,000	0.15	0.23
Proportion receiving maximum of dose 1 (luspatercept)	67,000	75,000	0.18	0.27
Incremental Quality Adjusted Life Years				
	Lower Incremental QALYs	Upper Incremental QALYs	Lower Input*	Upper Input*
Relative risk of achieving response for imetelstat to BSC (RSP)	-0.11	0.25	1.3	5.73
Relative risk of achieving response for luspatercept to BSC (RSP)	-0.19	0.06	1.77	5.41
Transition probability from TI to TD (luspatercept RSP)	-0.06	0.01	0.06	0.08
Transition probability from TI to TD (imetelstat RSP)	-0.05	0.02	0.05	0.07

CE: cost-effectiveness, TI: Transfusion Independent, TD: Transfusion Dependent, LTB: Low Transfusion Burden, HTB: High Transfusion Burden, RSP: Ring Sideroblast Positive, QAYLs: Quality Adjusted Life Years

* Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

Table E3.4. Results of Probabilistic Sensitivity Analysis for Imetelstat Compared to Best Supportive Care in the Overall Population

	Mean Total Costs	Mean QALYs	Mean evLYs
Imetelstat + BSC	$1,147,000	2.81	2.84
BSC	$ 952,000	2.65	2.65

evLYs: equal-value life years, QALY: quality-adjusted life year

Table E3.5. Results of Probabilistic Sensitivity Analysis for Imetelstat Compared to Luspatercept and Best Supportive Care in the Ring Sideroblast + Population

	Mean Total Costs	Mean QALYs	Mean evLYs
Imetelstat + BSC	$1,142,000	2.73	2.75
Luspatercept + BSC	$1,073,000	2.84	2.84
BSC	$946,000	2.67	2.67

evLYs: equal-value life years, QALY: quality-adjusted life year

E4. Scenario Analyses

We conducted several scenario analyses to examine the uncertainty and potential variation in the findings.

Scenario Analysis 1

Modified Societal Perspective

Results for the modified societal perspective analysis using the indirect approach for estimating non-health care sector costs (i.e., patient and caregiver productivity impacts net of consumption costs) for the overall population are presented in Tables E4.1 and E4.2.

Table E4.1. Undiscounted Non-Health Care Sector Costs for the Modified Societal Perspective Analysis for Imetelstat + Best Supportive Care Compared to Best Supportive Care Alone in the Overall Population

Treatment	Patient productivity gains†	Patient consumption costs‡	Patient time seeking care‡	Caregiver productivity loss‡	Total Non-Health Care Sector Costs
Imetelstat+BSC	$13,300	$5,200	$10,900	$7,700	$10,400
BSC alone	REF	REF	$10,600	$8,200	$18,900

BSC: Best supportive care, REF: Reference

† Represent cost savings; ‡Represent costs incurred

Table E4.2. Discounted Total Costs for the Modified Societal Perspective Analysis for Imetelstat + Best Supportive Care Compared to Best Supportive Care Alone in the Overall Population

Treatment	Health Care Sector Costs	Non-Health Care Sector Costs	Total Societal Costs
Imetelstat+BSC	$1,150,000	$9,200	$1,159,000
BSC alone	$951,400	$16,900	$968,200

BSC: Best supportive care

Scenario Analysis 2

16-week Transfusion Independence (Overall Analysis)

The proportion of responders were changed in the overall analysis to how many were observed to achieve transfusion independence for at least 16 consecutive weeks in IMerge.[18] According to the IWG 2018 definition of hematological improvement-erythroid, 8 weeks was not a clinically meaningful end point and not long enough to capture changes in quality of life.[15] This scenario analysis will explore the impact of using a longer response definition. For Imetelstat this was 33% and 31% for low and high transfusion burdens respectively. For best supportive care alone, 22% of patients with low transfusion burdens were observed to respond while no patients with a high transfusion burden responded. We assumed the duration of response was the same as when response was defined as 8-weeks.

Scenario Analysis 3

Minor HI-E Response (Overall Analysis)

In this scenario we allowed movement from the high transfusion burden health state to the low transfusion burden health state based on the proportion of patients in IMerge who experienced a 50% reduction red blood cell units in 16 weeks from the high transfusion burden subgroup.[18] For imetelstat and best supportive care, 13% and 10% of high transfusion burden patients achieved this minor response, respectively. Similar to a major response of transfusion independence, patients were moved after the first cycle.

Scenario Analysis 4

No Indirect Mortality Effect

In this scenario we looked at a conservative approach to modeling the treatment effect and removed the hazard ratio for transfusion independence. This removed the indirect treatment effect on survival observed in imetelstat and luspatercept compared to best supportive care through the increase of transfusion independence. This scenario was conducted in both the overall and RS+

analyses. Overall analysis results are detailed in Table 4.11 and 4.12 of the main report, and RS+ results can be found below in table E4.3. The incremental cost effectiveness ratio for evLYs was the same as QALY due to all treatments having the same LYs and was not reported. As this scenario reduced the treatment effect, we observed a large increase in the ICER from 800k to almost 2 million in the RS+ population.

Table E4.3. Scenario Analysis Results (RS+ Population)

Treatment	Base Case Results	Scenario 4: No Indirect Mortality Effect
	Incremental Cost-Effectiveness Ratio ($/QALY)	
Imetelstat + BSC vs. BSC alone	$1,297,000	$3,920,000
Imetelstat + BSC vs. Luspatercept + BSC	More costly, less effective	More costly, less effective

QALY: quality-adjusted life-year, BSC: best supportive care, HI-E: hematological improvement-erythroid

E5. Heterogeneity and Subgroups

Subgroups of interest include ring sideroblast positive as luspatercept is only used to treat patients who are ring sideroblast positive.

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

Prior economic models published on MDS used a variety of model schematics.[29-31,83,89] The majority of models found evaluated therapies for high-risk MDS and are difficult compare to our results as they dealt with a different patient population. However we did generate similar lifetime QALYs outcomes for luspatercept compared to a previously published report by CADTH (2.84 in our assessment versus 2.98 in the CADTH-adjusted analysis).[31]

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with imetelstat.

The potential budget impact analysis included the estimated number of people in the US who are likely to be eligible for imetelstat. To estimate the size of the potential candidate population for imetelstat with best supportive care compared to best supportive care alone, we applied a prevalence estimate of 115,000[3], an incidence estimate of four per 100,000, 0.004%[10], and a death rate of 0.25% within two years[43] to the overall US population (average projected population from 2024-2028: 346 million). This resulted in a total population of 95,212 patients with MDS over five years. We limited the potential eligible patient population to patients with lower-risk MDS (two-thirds of all MDS patients, 66.6%)[43], who are transfusion dependent (40%)[6], without the del(5q) subtype (90%)[8], and patients who are ineligible or refractory to ESAs (70%). The estimate of 70% of patients being ineligible or refractory to ESAs was based on data suggesting that 20-40% of patients with LR-MDS respond to treatment with ESAs[43]. Our estimate for the percentage of patients being ineligible or refractory to ESAs was further supported by systematic review findings of a 37% ESA response rate in LR-MDS patients[44]. Applying these sources resulted in estimates of 15,996 eligible patients in the US over five years. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 3,199 patients per year.

To estimate the size of the potential candidate population for imetelstat plus best supportive care to luspatercept plus best supportive care, we further limited the potential eligible patient population calculated above to patients who are ring sideroblast positive (35%)[7]. Applying these sources resulted in estimates of 5,598 eligible patients over five years, with 1,120 patients (20%) initiating treatment per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[90,91] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2023-2024, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $735 million per year for new drugs.