Imetelstat for Anemia in Myelodysplastic Syndrome: Effectiveness and Value
Response to Public Comments on Draft Evidence Report

JULY 2, 2024

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#	Comment	Response/Integration
Manufacturers		
Bristol Myers Squibb		
1.	In response to ICER's summary of luspatercept stating that "Luspatercept was recently approved as a first-line treatment for lower-risk MDS patients with anemia, and is particularly effective in patients with ring sideroblasts (RS+, approximately 35% of the MDS population)" BMS would like to clarify that Reblozyl is FDA-approved for first line low-risk MDS treatment regardless of RS status based on the ITT population analysis of the COMMANDS trial.[1,2] The COMMANDS trial was not powered to detect a difference between RS subgroups and caution should be used when comparing unpowered subgroups.	Thank you for your comment. We rewrote the sentence to clarify this point: "Luspatercept was recently approved as a first-line treatment for lower-risk MDS patients with anemia. It is particularly effective…". We also added a clarification that luspatercept is approved for use in RS+ patients who have failed initial ESA therapy. Our evidence rating comparing imetelstat to luspatercept (I Insufficient evidence), reflects our caution when comparing underpowered subgroups without all of the information available for the overall population.
2.	**BMS recommends a re-examination of clinical data inputs.** Regarding "Comparative Clinical Effectiveness," BMS acknowledges the challenges in performing comparisons based on available published data by RS status. Specifically, stratified analyses on safety and modified hematologic response-erythroid (mHI-E) were not conducted, and this brings substantial limitations to the analysis and conclusions.	Thank you for the suggestion. We had hoped to perform the stratified analyses that you highlight. We requested these data from the iMerge trial, but Geron did not provide this information and it is not available in the published data. We have addressed this in the last paragraph of the Uncertainty and Controversies section of the report.

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3.	**BMS suggests modifications are needed regarding the referenced economic data.** Regarding "Patient and Caregiver Perspectives," BMS acknowledges the individual patient experience on luspatercept but recommends further contextualizing the patient quote by including information on out-of-pocket (OOP) costs for the majority of patients and the availability of copay assistance programs. This singular patient quote is not reflective of the overall patient experience in the United States. Currently, 93% of commercially insured and 90% of Medicare patients are paying $0 for their luspatercept prescription ($0 copay). BMS is committed to ensuring the diverse patient voice and perspective is appropriately and meaningfully represented; it is of utmost importance that all eligible patients have access to our medicine. We encourage patients to leverage applicable BMS or third-party copay assistance programs. Through BMS Access Support®, patients can receive information on financial assistance programs that may be available to them.	Thank you for providing the contextual information. However, the section is intended to reflect direct testimony from patients and caregivers. We want to honor their commitment in the meetings they have with us, so we have not altered the "Patient and Caregiver Perspectives" section. You should feel free to articulate the additional information provided on patient out-of-pocket costs in oral comments at the public meeting if you think it would help to inform the discussion. That said, we are unclear about the sources of such information, as the citations listed do not appear to contain these estimates.
4.	Regarding "Long-Term Cost Effectiveness," BMS recommends: Conducting a probabilistic sensitivity analysis. The <0.5% difference in total costs between luspatercept and imetelstat in ICER's cost-effectiveness model is within the uncertainty range that we would typically observe within health economic assessments and warrants further exploration. Including myeloid growth factors as a component of the cost effectiveness model. Myeloid growth factors were used in a substantial proportion of patients in the imetelstat arm of the IMerge trial (35% vs 3% in placebo arm)[3] and were omitted from supportive care costs in the cost-effectiveness model. Due to the important safety concerns and associated costs, BMS feels strongly that this should be included. Conducting the analysis to include the predicted $25,000/month[4], or $300,000/year. Given recently released imetelstat pricing information, a scenario analysis would	Thank you for the suggestions. We have conducted a probabilistic sensitivity analysis, which can be found in our Supplementary Materials Section E4. In addition, myeloid growth factors were already included as a component of the supportive care costs in our cost effectiveness model at the percentages mentioned. Finally, we will be updating our base case using the publicly available wholesale acquisition cost that was released when imetelstat was approved by the FDA.

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	negate the negligible total cost savings of imetelstat as reported in ICERs budget impact and cost-effectiveness models. We also encourage ICER to consider the increased final price of imetelstat which was communicated verbally during Geron's Conference Call following the FDA-approval of imetelstat.	

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#	Comment	Response/Integration
Patient/Patient Groups		
Partnership to Improve Patient Care		
1.	**ICER oversimplifies health states, including undervaluing the effect of treatment.** The model assumes that if a patient stops responding to treatment during any cycle in the model, then that patient returns to the transfusion dependance state in which they began - either low or high burden transfusion dependence states, versus contemplating that the patient could have moved from high dependence to low dependence. The model similarly assumes that those who do not respond to treatment in the high transfusion dependance state cannot move to the low transfusion dependance state. This simplification likely underestimates the value of the interventions being evaluated, as it is possible that patients could move and stay in a low dependence state, which would be valuable to the patient. ICER should take a more nuanced view on this topic and capture movement from high to low dependence states.	Thank you for your comment. We understand that a patient's transfusion burden can change with treatment or over time, either increasing in burden from low to high or vice versa. Publicly available data for these transitions were not sufficiently detailed to allow for inclusion in our base case. We requested additional data from the manufacturer but did not receive any. We do explore a scenario in which a transition from high to low burden transfusion dependence is informed by the published data on a minor hematological improvement of 50% reduction in red blood cell units at 16 weeks. The results from this scenario show a small improvement in incremental outcomes for Imetelstat.
2.	**ICER's model should include non-drug costs for ongoing treatment of MDS.** As portrayed, the ICER model does not seem to include non-drug costs for ongoing treatment of MDS in either transfusion independent or transfusion dependent health states other than the cost of adverse events. The methods section for the cost-effectiveness model doesn't refer to any costs being applied to time spent in the first three states of the model. It details the estimated cost of each drug being evaluated, drug utilization, best supportive care costs, and health state costs for high risk MDS and acute myelogenous lymphoma. It does not however describe how health state costs for the states of high burden and low burden transfusion independence and transfusion dependence are calculated. Even if we assume that best supportive care costs would be applied to all patients in these three states equally, this does not accurately represent benefit of treatment. The goal of the drugs under evaluation is to keep patients in transfusion independent states instead of transfusion	Thank you. Our cost-effectiveness model does include non-drug costs, captured as costs associated with best supportive care. These included costs for red blood cell and platelet transfusions, iron chelation, and myeloid growth factors. The best supportive care costs were differentially applied to the three lower-risk MDS states and have been detailed in the Supplementary Materials Section E2. Cost benefits of lower transfusion burdens and transfusion independence are captured through differences in the number of transfusions.

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	dependent states. Transfusion independent states are not only better for patients, but they are significantly less costly, which should be captured in the model. Estimates from the literature suggest that marginal differences in overall direct healthcare costs differ between transfusion dependent and transfusion independent lower-risk MDS patients by between $54,264 per year and $157,198 per year.	
3.	**ICER uses a health care perspective for its base case when it should be using the societal perspective.** MDS is a disease that creates significant caregiver burden. The value of a treatment that could reduce this burden should be reflected in any value assessment for these treatments. When the impact on caregivers and social care costs is high, as in MDS, the societal perspective is always the most appropriate base care. Many leaders in HTA, like the National Institute for Health and Care Excellence (NICE) have already taken the step of caregiver utility in its cost-effectiveness models for diseases such as Alzheimer's, MS and Parkinson's disease. It is also the recommended perspective for cost-effectiveness models of the second panel on cost-effectiveness, and ISPOR. PIPC encourages ICER to replace a purely health care perspective with a broader societal perspective for its base case analysis.	Thank you. ICER reports are intended to inform population-based medical policy and pricing decisions within the US health care system, which includes employers, other plan sponsors, insurers, and risk-bearing provider groups in both private and public health insurance systems that are not responsible for making trade-off decisions that involve broader societal resources. That being said, we recognize the importance of the potential societal benefits of emerging therapies, and will consider a societal perspective as a co-base case analysis when the societal costs of a disease are substantial relative to total costs, and when treatment is expected to impact these costs in important ways. This review also represents the first instance in which we have used a "non-zero" approach to estimate societal impacts in the absence of direct data—namely, productivity, patient time in treatment, caregiver time, and patient consumption costs. Inclusion of these impacts had a modest impact on our cost-effectiveness estimates and did not change our conclusions (see page 33 in the main report and Supplementary Section E4 for further details).

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4.	**ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.** Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions, and people with disabilities. There is widespread recognition that the use of the QALY is discriminatory, reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments. The recent nondiscrimination regulations governing Section 504 of the Rehabilitation Act also bar the use of discriminatory measures such as QALYs in decisions impacting access to care among entities receiving federal financial assistance. We share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities. It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions for patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, older adults, and certain communities of color. With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.	We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of ICER's assessment of the value of new and emerging therapies. Specifically, many of the considerations and nuances you mention are addressed separately as part of the Benefits Beyond Health and Special Ethical Priorities section. Throughout our assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. In other words, if a treatment adds a year of life to a patient population – whether treating individuals with Alzheimer's disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the evLY removes the potential for bias between diseases in life extension. Regarding the claim that the evLY "does not account for any health improvements in extended life years", this is not true—health improvements are simply valued at the same level regardless of disability or severity of disease. Improvements in quality of life before life extension are also captured by the evLY. The evLY is not discriminatory and neither the evLY nor the QALY diminishes the improvements that patients experience.

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5.	ICER continues to fail to capture actual value of treatment to patients by oversimplifying health states, utilizing a health care perspective as its base case, and relying on the discriminatory QALY. PIPC urges ICER to revisit some of its dated modeling constructs and work to more accurately capture value to the patient population in question.	Thank you for your comment. Please see responses to the individual issues mentioned in our previous comments.

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