Imetelstat for Anemia in Myelodysplastic Syndrome

Revised Background and Scope

February 1, 2024

Background

Myelodysplastic syndromes (MDS) are an uncommon 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] 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 common and bothersome symptom of these effects is severe fatigue, although they may also cause bleeding, night sweats, bone pain, fever, weight loss, and recurrent infections.[2]

Between 60,000 and 170,000 people are 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.[4] The economic burden of MDS is substantial, as the total annual cost may escalate to around $220,000 for lower-risk MDS patients.[5]

Diagnosis of MDS typically involves a bone marrow biopsy and molecular genetic testing.[6] 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 (erythroblasts with perinuclear ring of blue granules on Prussian blue staining). Additionally, MDS is classified as lower or higher risk for progression to AML.[7]

First line therapy for anemia in MDS is typically the use of erythropoesis stimulating agents (ESAs). However, some patients do not respond and others stop responding after a period of time. Luspatercept was recently approved as a first-line treatment for low-risk MDS patients with anemia, and is particularly effective in patients with the ring sideroblast phenotype. Lenalidomide is an option for patients with the del(5q) phenotype; these patients were excluded from the clinical trials of imetelstat, the intervention of focus for this review.[7,8]

Imetelstat (Geron Corporation) is a first-in-class, oligonucleotide telomerase inhibitor which 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 is under review as a treatment for transfusion-dependent anemia in low-risk MDS patients without the del(5q) mutation, with a Food and Drug Administration (FDA) decision expected in June 2024.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of imetelstat for the treatment of transfusion-dependent anemia in patients with myelodysplastic syndrome. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction,

and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

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

Interventions

The full list of interventions is as follows:

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

Comparators

Data permitting, we intend to compare all the agents to each other and to to following:

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

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 will be derived from studies of any duration.

Settings

All relevant settings will be considered.

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 would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
There is substantial unmet need despite currently available treatments.
This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.
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.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on March 28, 2024. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments (e.g., luspatercept, best supportive care). The model structure will be based in part on a literature review of prior published models of myelodysplastic syndrome.[9-11] Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Patient and caregiver productivity impacts and other indirect costs will be considered in a separate modified societal perspective analysis. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of imetelstat on productivity (patient and caregiver). The modified societal perspective analysis will be considered as a co-base case when direct data on indirect costs are available, the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. The target population will consist of adults with lower-risk myelodysplastic syndrome without the del(5q) mutation who are transfusion dependent despite best supportive care. The model will likely consist of health states that include transfusion dependent, transfusion independent, high-risk MDS, acute myeloid leukemia (AML), and death. A cohort of patients will transition between states during predetermined cycles (of four weeks) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will likely be estimated using data from key clinical trials for the intervention and comparators as well as publicly available literature on myelodysplastic syndrome including impacts on anemia, transfusions, and disease progression. If a network meta-analysis is performed, relative effects for the interventions versus included comparators will be used.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of duration of transfusion independence, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be

applied to each health state, including quality of life decrements for anemia, transfusions, AML impacts, and serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per year of transfusion independence.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

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 additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by imetelstat, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of myelodysplastic syndrome beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

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