

Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Triple Class Refractory Multiple Myeloma

Revised Background and Scope

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Background

Multiple Myeloma (MM) is a hematologic cancer of plasma cells. Uncontrolled proliferation of plasma cells may have multiple consequences, including:

- Bone pain and fractures due to lytic lesions from plasma cell proliferation in the marrow.
- Increased total or monoclonal protein, which can have direct toxic effects on the kidney, resulting in worsening renal function.
- Hypercalcemia.
- Anemia, due in part to plasma cells suppressing other hematopoietic cell lines and kidney disease.

MM is a relatively rare cancer, with an annual incidence of approximately 7 in 100,000 Americans. It is estimated that 32,270 new cases of MM were diagnosed in 2020 and 140,000 Americans were living with MM in 2017.¹ It is primarily a disease of older adults, with a median age at diagnosis of 69. African-Americans appear to be at approximately twice the risk of white Americans, while Asian-Americans appear to be at lower risk.¹ The rates of MM have been stable without evidence of increasing incidence over six decades.² The direct medical costs of MM are substantial. A recent analysis of commercial and Medicare claims found that average costs exceeded \$250,000 over a 21-month period, and that 60% of these costs were medication-related.³

The last 15 years have seen a proliferation of new, approved therapies for MM, resulting in substantial improvements in survival.⁴ In 2000, data from the Survey, Epidemiology, and End

Results Program (SEER) suggested that 36% of MM patients achieved 5-year survival while in 2017, SEER models indicated that 56% of MM patients will survive 5 years.¹

Unfortunately, currently-approved therapies are not curative for the vast majority of MM patients. While modern combination treatments and autologous stem cell transplant can often lead to effective control with decreased signs and symptoms of MM, over time, most patients will *relapse*, showing signs and symptoms of renewed, active disease. Some patients will not respond to initial combination treatment (*refractory*). These patients with relapsed or refractory multiple myeloma often cycle through different combinations of agents, which may increase both their clinical and economic burden. MM patients whose disease has progressed through three common classes of anti-myeloma medications (monoclonal antibodies such as daratumumab, immunomodulatory drugs such as lenalidomide, and proteasome inhibitors such as bortezomib) are termed “triple class refractory” and represent the population that may potentially benefit from the three medications in this review.

Three new treatments, idecabtagene vicleucel (commonly called ‘ide-cel’, Bristol Myers Squibb and bluebird bio), ciltacabtagene autoleucel (commonly called ‘cilta-cel’, Janssen and Legend Biotech) and belantamab mafodotin-blmf (Blenrep™, GlaxoSmithKline) are proposed as the focus for this review. All three treatments target the B-cell maturation antigen (BCMA), which is overexpressed on plasma cells, but appear to be minimally expressed on other cells. In addition, BCMA appears to be essential for the survival of long-lived plasma cells, making BCMA an attractive therapeutic target.⁵ Blenrep is an antibody-drug conjugate, with a monoclonal antibody specific for BCMA that is linked to a cytotoxic drug. Blenrep is given as an intravenous infusion every 3 weeks. Ide-cel and cilta-cel are chimeric antigen receptor T (CAR-T) cell therapies, requiring a patient’s own T lymphocytes to be obtained and transduced in the lab with a gene to encode an anti-BCMA antibody. These genetically modified CAR-T cells are expanded and then infused back into the patient intravenously. A biologic license application for ide-cel was submitted to the FDA in July 2020, with a regulatory decision expected in the first half of 2021. The biologic license application for cilta-cel is expected to be submitted before the end of 2020.

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, manufacturers, payers, and researchers. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public.

Patients and patient groups highlighted the burdens of the disease and of the current treatments. The bone pain and fatigue of poorly-controlled MM can be debilitating. Equally frustrating can be the side effects of the medications that suppress MM. One patient noted how he hates how he feels when he takes steroids, but recognizes he needs the medication to keep his disease under

control. Patients were excited about new treatment options, especially if these options could lead to a durable, long-term response that could avoid the need for continuous therapy. Patients mentioned how they were grateful for current treatment options, but struggled with the burdens of these treatments, with one patient stating, “visiting the doctor every month gets old.” Patients also stressed that although current treatments may prolong survival, at least some of the time gained is burdened by treatment side effects or treatment-related decrements in quality of life, with one patient noting, “being tied to two IV pumps sucks the life out of you.” Several patients noted the potentially significant cost burden of the proposed treatments and voiced concerns that these costs may limit their availability. These concerns add to the significant economic uncertainty that MM patients already struggle with; data from the Cancer Support Community’s Multiple Myeloma Specialty Registry indicate that nearly two-thirds of MM patients are concerned about the cost of their cancer care and 42% are often or always upset about the cost of their myeloma care.

Clinical experts conveyed the importance of additional therapeutic options for the population of relapsed or refractory MM patients who are at a minimum “triple class refractory.” Current treatment options for this population are quite limited and often have suboptimal efficacy/toxicity profiles. While both Blenrep and the CAR-T cell therapies have been associated with substantial toxicities (e.g., ocular toxicities with Blenrep and cytokine release syndrome with CAR-T cell therapy) there is also great interest in understanding the potential for these therapies to deliver durable response as well as extensions in progression-free and overall survival.

There was substantial heterogeneity among clinical experts on what the current therapeutic options are for “triple class refractory” MM and in fact how the designation is applied in clinical practice. Some experts felt that “triple class refractory” defines patients whose disease has progressed on any medication in each of the three major classes of medications (anti CD38 monoclonal antibodies, immunomodulators and proteasome inhibitors). Others felt this classification should be reserved for those patients whose disease has progressed on the most efficacious agent in each of the three classes. Stakeholders also pointed out that the FDA indication for Blenrep represents a population with somewhat more advanced disease than either of the CAR-Ts under evaluation, and so relevant comparator regimens will differ. Our approach is further discussed in the “Comparators” section below.

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 the treatments under review.

Report Aim

This project will evaluate the health and economic outcomes of ide-cel, cilta-cel, and belantamab mafodotin for “triple class refractory” MM. 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.

Applicable Framework Adaptations

We will apply ICER’s standard Value Assessment Framework for all therapies under review. Our preliminary review of the current state of the evidence and conversations with several clinical experts and patient groups indicate that while CAR-T therapies appear to extend progression-free survival more than currently-approved therapies, their curative potential is currently unknown.

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 available clinical trials as well as high-quality systematic reviews; high-quality 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 of focus for the review is patients who have at a minimum triple-class refractory MM, defined as disease that has progressed while on an anti-CD38 antibody (e.g. daratumumab), immunomodulatory drugs (e.g. lenalidomide), and a proteasome inhibitor (e.g., bortezomib). As mentioned above, the indication for Blenrep involves a population subset with somewhat more advanced disease (at least four prior lines of treatment) than those in the current CAR-T trials (at least three prior lines). We will therefore not make any explicit comparisons between Blenrep and the CAR-T therapies, and we will summarize evidence on relevant comparator therapies to match these population differences (see below).

Data permitting, we will consider evidence across relevant subgroups, such as patients with genetic factors that put them at particularly high risk as well as subgroups defined by race.

Interventions

The full list of interventions is as follows:

- Idecabtagene vicleucel
- Ciltacabtagene autoleucel
- Belantamab mafodotin

Comparators

We will use the characteristics of patients enrolled in each of the pivotal studies of the drugs under consideration to guide the most appropriate comparator treatments (i.e., the regimens patients would have received if the drugs under consideration were not an option). Since the Blenrep study focused on a more refractory population, we anticipate that comparator evidence for Blenrep will differ from that for CAR-T therapy.

Data permitting, we intend to compare the selected interventions to commonly used regimens in triple-class refractory populations as well as to palliative care (no active anti-cancer therapy). Potential comparator regimens include:

- Carfilzomib + cyclophosphamide + dexamethasone (KCd)
- Pomalidomide + cyclophosphamide + dexamethasone (PCd)
- Carfilzomib + pomalidomide + dexamethasone (KPd)
- Elotuzumab + pomalidomide + dexamethasone (EPd)

Due to differences in the intervention populations, selection of comparator evidence will be guided by whether data are available for more or less heavily-pretreated subgroups in available RCTs and observational studies; regimens that would be considered for patients whose disease is refractory to only one medication in a given class versus all medications in that class; and other factors. For example, regimens containing pomalidomide may be appropriate for disease that is refractory to lenalidomide, while KCd may be considered for disease that is also refractory to pomalidomide.

Stakeholder input also suggested the combination of the nuclear export inhibitor selinexor (Xpovio®, Karyopharm) and dexamethasone, which also carries an indication for heavily pretreated relapsed or refractory MM. However, we received input from clinical experts suggesting that its use has been extremely limited due to its toxicity profile and single-agent activity, and oncologists are more likely to use one of the regimens listed above in this population prior to selinexor.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
 - Overall survival (OS)
 - Quality of life
 - Complete response rate
 - Progression-free survival (PFS)
 - Durability of response
 - Pain and function
 - Treatment burden
 - Bone fractures
 - Adverse events including:
 - cytokine response syndrome
 - fatigue/sleep disturbance
 - infection
 - peripheral neuropathy
 - ocular toxicity
 - anemia
 - gastrointestinal toxicity
 - thromboembolism
 - death
- Other Outcomes
 - Overall response rate
 - Partial response rate
 - Minimal residual disease
 - Blood and urine markers of disease

Timing

Evidence on intervention effectiveness and harm will be derived from studies of any duration.

Settings

All relevant settings will be considered.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits 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. Potential Other Benefits or Disadvantages and Contextual Considerations

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.

Scope of Comparative Value Analyses

As a complement to the evidence review and where data allow, we will develop a *de novo* economic model to assess the lifetime cost-effectiveness of the interventions of interest as compared to relevant comparator treatments, including active agents and palliative care. The model structure will be based in part on a literature review of prior published models of “triple class

refractory” MM. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case if 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 quality-adjusted life year (QALY), and/or when the result crosses the threshold of \$100,000-\$150,000 per QALY gained. The target population will consist of patients with “triple class refractory” MM. The comparative value analysis will use an intention-to-treat approach.

A detailed economic model analysis plan is forthcoming with proposed methodology, model structure, parameters, and assumptions. The model may include an up-front decision tree (for the multiple stages inherent in CAR-T interventions) and lifetime semi-Markov partitioned survival model. Specific to CAR-T interventions, the decision tree will capture phases of bridging chemotherapy, leukapheresis, manufacturing and expansion of engineered T-cells as well as their infusion through the first assessment of response per the trial protocols. Lifetime survival and outcomes will be modeled through a series of semi-Markov partitioned survival models using the direct extrapolation of progression-free survival and overall survival data (where available). Health states may include alive and progression free, alive with subsequent relapse, and dead. Patients will transition between health states during predetermined cycles (e.g., one month) over a lifetime horizon.

Model inputs will be informed by existing clinical and economic evidence. Key model inputs include probability of response, duration of response, event-free survival, overall survival, occurrence of adverse events, quality of life utility values, and health care costs. Probabilities, costs, and other inputs will differ between treatments to reflect varying effectiveness between interventions; however, health state utility values will be consistent across interventions. Treatment effectiveness will be estimated using best available evidence.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and direct medical costs. Costs will include costs associated with infusion, treatment acquisition, administration and monitoring, adverse events, and relevant health care utilization. Health outcomes for each intervention will include life-years gained, QALYs gained, equal value of life years gained ([evLYG](#)), and progression-free time. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. There will be no comparisons between active interventions. Pairwise comparisons will only be made between an intervention and its respective comparator (i.e., common regimens used in triple class refractory and more advanced disease), and results will be expressed in terms of the marginal costs per QALY, evLYG, and life-year gained, as well as cost per responder. Costs and outcomes will be discounted by 3% per year. Uncertainty will be assessed through one-way and probabilistic

sensitivity analyses. In addition to sensitivity analyses, scenario analyses will be conducted, including a modified societal perspective that will include productivity changes and other indirect costs (e.g., caregiver impact) if available data allow. Data permitting, we will consider estimating costs and health outcomes among relevant subgroups, such as patients with genetic factors that put them at particularly high risk as well as subgroups defined by race.

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

As described in its Value Assessment Framework for 2020-2023, ICER will include 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 the treatments considered in this review, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of relapsed or refractory multiple myeloma beyond the potential offsets that arise from a new intervention. We did not receive any suggestions of such services during the public comment period on the draft scope. During future public comment periods, 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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