Summary

KEY FINDINGS

	idecabtagene vicleucel ("ide-cel," Abecma®, Bristol-Myers Squibb and bluebird bio)	Ciltacabtagene autoleucel ("cilta-cel," Janssen and Legend Biotech)	Belantamab mafodotin-blmf ("belantamab," Blenrep™, GlaxoSmithKline)
Evidence Rating	B+	B+	P/I
Estimated Annual Price	$419,500	Cilta-cel's manufacturers have not yet announced an estimated or actual price.	$8,277 per vial
Annual Health-Benefit Price Benchmark	**evLYG threshold:** $206,000-$265,000 **QALY threshold:** $192,000-$245,000 These prices were calculated with the assumption that there would be a second charge for individuals requiring retreatment.	**evLYG threshold:** $244,000-$312,000 **QALY threshold:** $230,000-$292,000 These prices were calculated with the assumption that a second dose will require payment.	evLYG threshold: $8,400-$9,500 per vial QALY threshold: $8,300-$9,300 per vial
Change from Annual Price Required to Reach Threshold Price	37-54% discount	**26%-45% discount**	None

"Many people with multiple myeloma develop resistance to existing treatments, so these three new therapies with new mechanisms of action represent a very important expansion of the clinical options available to patients and oncologists. Data are extremely limited at this time for the two CAR-Ts, and important evidence gaps remain to be filled, but having a new innovative approach become available for patients with multiple myeloma is something to celebrate. Shadowing these new treatments are concerns that the pricing for the first approved CAR-T agent in multiple myeloma exceeds a reasonable level for its given benefit. Manufacturers should restrain their pricing and work with payers to ensure that payment mechanisms and overall benefit coverage can help patients from all walks of life get affordable access to these treatments. Belantamab appears to deliver more modest overall clinical benefit, but clinical experts believe it too will have a role in therapy. At its current pricing, belantamab appears to meet commonly cited thresholds for cost-effectiveness, but our independent appraisal committee determined that its long-term value for money was 'low' due to questions about the magnitude of overall survival benefit and certain favorable assumptions within the economic model."

– ICER President, Steven D. Pearson, MD, MSc

Summary

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with multiple myeloma are introduced in a way that will help reduce health inequities.
- Manufacturers should seek to set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments.
- Payers should use the FDA label as the guide to coverage policy and engage clinical experts and diverse patient representatives in considering how to address coverage issues for which there is limited or no evidence at the current time.
- Medicare should consider new reimbursement strategies, including enhanced new technology add-on payments or demonstration projects that carve out pricing and payment for cell and gene therapy, to improve the chances that hospitals and clinics can provide the necessary services to deliver these novel therapies to patients safely.
- The clinical research community should move rapidly to address key gaps in evidence for treatments for multiple myeloma.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Multiple myeloma (MM) is a hematologic cancer of plasma cells, currently estimated to afflict approximately 150,000 Americans. The mainstays of current MM treatment include immunomodulatory agents, proteasome inhibitors and anti-CD38 monoclonal antibodies. Most patients eventually relapse; these patients with relapsed or refractory multiple myeloma (RRMM) often cycle through different combinations of agents. When a patient's disease is no longer responsive to agents in each of the three classes, the disease is referred to as "triple-class refractory" MM (TCRMM).

ICER reviewed three new treatments targeting the B-cell maturation antigen (BCMA) for heavily pre-treated patients with RRMM who have cycled through numerous previous lines of therapy. Belantamab mafodotin blmf (Blenrep®, GlaxoSmithKline) is an antibody drug conjugate, with a monoclonal antibody to BCMA linked to a cytotoxic drug. Belantamab was studied in patients with heavily pre-treated (6-7 previous lines of therapy) TCRMM (majority quad- and penta-refractory, usually defined as refractory to 4 or 5 agents across all 3 drug classes outlined above). Idecabtagene vicleucel ("ide-cel", Abecma®, Bristol Myers Squibb and bluebird bio) and ciltacabtagene autoleucel ("cilta-cel", Janssen and Legend biotech) are chimeric antigen receptor (CAR) T-cell therapies, involving engineering a patient's own T cells to target BCMA, and were studied in patients who were mostly TCRMM (majority triple- or quad-refractory patients).

Clinical Analyses

Patients spoke about the burden of symptoms from both MM and its available treatments. Common symptoms of disease include fatigue, which can be overwhelming, and bony pain. Symptoms of the current treatments vary by medication, but frequently mentioned bothersome side effects include neuropathy as well as insomnia and psychosis from dexamethasone. Patients also noted substantial financial burden with annual out-of-pocket costs exceeding $10,000 leading one patient to remark that one had to be a "mathematician" to navigate the costs of being a myeloma patient.

Response rates and survival statistics are presented in Table 1. The CAR T-cell therapies (ide-cel and cilta-cel) appear to be superior to currently available treatment regimens for TCRMM, as estimated from the recent MAMMOTH observational study. In contrast, belantamab appears to be equivalent or slightly superior to the most relevant comparative set from MAMMOTH.

Table 1. Complete Response at One and Two Years

Response Rates and Median PFS for Anti-BCMA Therapies

Intervention	Study	Follow-Up Duration	As Treated ORR	ITT ORR	Median PFS or OS*	Toxicity
CAR T Population (Triple- or Quad- Refractory, 3+ prior lines of treatment)						
Ide-cel	KarMMa	13.3 months	73%	63%	As-treated PFS = 8.6 months	51% CRS Grade 2+
Cilta-cel	CARTITUDE-1	18 months	98%	75%	As-treated PFS >19 months	44% CRS Grade 2+ 6% Treatment-related deaths
Usual Care	MAMMOTH	10.6 months	–	31%	PFS = 3.4 months	Variable
Belantamab Population (Triple-, Quad- or Penta- Refractory MM, 4+ prior lines of treatment)						
Belantamab	DREAMM-2	13 months	–	32%	ITT OS = 13.8 months	18-46% Meaningful to moderate reversible visual decline (duration 22-33 days)
Usual Care	MAMMOTH subcohort†	10.6 months	–	28%	Triple/quad OS = 9.2 months Penta OS = 5.6 months	Variable

BCVA: Best Corrected Visual Acuity, CRS: cytokine release syndrome, ITT: intention-to-treat, ORR: overall response rate, OS: overall survival, PFS: progression free survival

* Ide-cel and cilta-cel PFS is as-treated. All other PFS and OS data are ITT

† MAMMOTH comparator subcohort was defined by weighting the MAMMOTH triple/quad- and penta- refractory cohort proportions to the DREAMM-2 triple/quad- and penta-refractory proportions

Clinical Analyses

Toxicities were common with both CAR T-cell therapies and belantamab. For CAR T-cell therapies, Grade 2+ cytokine release syndrome (usually requiring hospitalization) occurred in 51% of patients who received ide-cel and 44% of patients who received cilta-cel. In addition, 6% of patients who received cilta-cel died of treatment-related complications. For belantamab, 18-46% experienced meaningful to moderate decline in vision lasting 22-33 days.

Table 2. ICER Evidence Ratings for Anti-BCMA Therapies

Treatment	Comparator	Evidence Rating
Triple- or Quad- Refractory MM (3+ prior lines of treatment)		
Ide-cel	Usual Care	B+: Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
Cilta-cel	Usual Care	B+: Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
Ide-cel	Cilta-cel	I: Any situation in which the level of certainty in the evidence is low
Triple-, Quad- or Penta- Refractory MM (4+ prior lines of treatment)		
Belantamab	Usual Care	P/I*: Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit

MM: multiple myeloma.*Compared to current treatments, belantamab appears to be comparable to slightly superior. There is a small but nonzero likelihood of slight net harm. Current evidence does not support belantamab being substantially superior to current treatments.

Economic Analyses

LONG-TERM COST EFFECTIVENESS

ICER also performed cost-effectiveness modeling and analyses of the new therapies. The base-case findings from our analysis suggest that CAR-T therapies provide clinical benefit in terms of gains in both quality-adjusted and overall survival over current treatment options for triple- or quad-refractory MM patients exposed to three or more lines of therapy.

The incremental cost-effectiveness ratios for ide-cel versus the triple- or quad-refractory MM comparator market basket were approximately $319,000 per QALY gained $250,000 per LY gained, $280,000 per evLYG gained, and $35,000 per additional PFS month gained. Threshold pricing suggests ide-cel would meet the $100,000 per QALY threshold at a price of

Economic Analyses

around $200,000 or a >50% discount from the current list price. Cilta-cel would meet this threshold at a price of around $230,000, but this finding is preliminary and an optimistic estimate given the extremely limited evidence currently available. Base-case findings for belantamab suggest current list pricing is within commonly cited cost-effectiveness thresholds when compared to a triple-, quad-, or penta-refractory MM market basket. However, given uncertainties with the PFS-OS relationship and other parameters in the belantamab model, updated data should be generated and incorporated into future modeling analyses. Small changes in any of the key drivers changed belantamab model findings to a significant extent. Key drivers across all model findings included comparator market basket prices, progression-free survival for the active interventions, and utility of PFS (on or off treatment).

POTENTIAL OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

Several potential benefits and contextual considerations not fully captured in the economic modeling include the limited treatment options for patients with TCRMM. Since anti-BCMA treatments represent a novel mechanism of action, these treatments may provide efficacy for patients who currently have few alternatives. However, CAR-T therapies are complex and high-cost with significant side effects. Treatments with these characteristics have been underutilized by disadvantaged populations, suggesting that disparities may be worsened.

VOTING RESULTS

During the public meeting, the Midwest CEPAC panelists voted unanimously (15-0) that the evidence is adequate to demonstrate that ide-cel provides a net health benefit over usual care. A majority (13-2) found the evidence adequate to demonstrate cilta-cel provides a net health benefit over usual care. Finally, a majority (10-5) found the evidence was not adequate to demonstrate a net health benefit of belantamab over usual care. The panel also voted unanimously (15-0) that the evidence was not adequate to demonstrate a net health benefit of ide-cel compared to cilta-cel.

During their deliberations, panel members also weighed the therapies' other potential benefits, disadvantages, and contextual considerations. For both treatments, voting highlighted the following as particularly important for payers and other policymakers to note:

- The acuity of need for treatment based on the severity of the condition being treated;
- The patients' ability to achieve major life goals related to education, work, or family life;
- The caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life; and
- The patients' ability to manage and sustain treatment given the complexity of regimen.

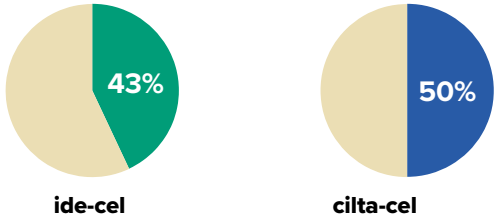
A majority of panelists found that ide-cel represents "low" long-term value for money. ICER did not conduct a long-term value for money vote because cilta-cel's manufacturers have not yet announced a price for the therapy. Finally, a majority of panelists found that belantamab represents "low" long-term value for money.

Economic Analyses

POTENTIAL BUDGET IMPACT

Approximately 43% (ide-cel) and 50% (cilta-cel) of eligible triple- or quad-refractory multiple myeloma patients could be treated within five years before crossing the ICER potential budget impact threshold of $819 million per year. Testimony from clinical experts at the public meeting suggested that the ideal clinical uptake of the CAR-Ts would include the chance for nearly every eligible patient to receive one or the other. Given that efforts to reach this clinical target would create a short-term potential budget impact that exceeds ICER's threshold, ICER is issuing an access and affordability alert for ide-cel and cilta-cel.

The purpose of an ICER access and affordability 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, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients. ICER is not issuing an access and affordability alert for belantamab, because all eligible patients could be treated within five years (assuming 20% uptake each year) at the wholesale acquisition cost for belantamab.



Percent of eligible patients with multiple myeloma that could be treated in a given year before crossing the ICER potential budget impact threshold

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).