Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma

Draft Evidence Report

February 11, 2021

Prepared for

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About ICER

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:
http://icerorg.wpengine.com/wp-content/uploads/2020/10/ICER_MM_Key_Stakeholders_092720.pdf

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List of Acronyms and Abbreviations Used in this Report

95%CI	**95% Confidence Interval**
ADC	**Antibody drug conjugate**
AE	**Adverse event**
AHRQ	**Agency for Healthcare Research and Quality**
AIC	**Academic in confidence**
BCMA	**B-cell maturation antigen**
BP	**Bendamustine + prednisone**
CAR	**Chimeric antigen receptor**
CR	**Complete response**
CRAB	**Calcium, renal, anemia, and bone**
CRS	**Cytokine release syndrome**
D/C	**Discontinuation**
DCEP	**Dexamethasone + cyclophosphamide + etoposide + cisplatin**
DOR	**Duration of response**
EMD	**Extramedullary disease**
EORTC	**European Organization for Research and Treatment of Cancer**
EPd	**Elotuzumab + pomalidomide + dexamethasone**
HR	**Hazard ratio**
HRQoL	**Health-related quality of life**
IMiD	**Immunomodulatory drug**
IQR	**Interquartile range**
ISS	**Idiopathic subglottic stenosis**
ITT	**Intention to treat**
KCd	**Carfilzomib + cyclophosphamide + dexamethasone**
Kg	**Kilogram**
KPd	**Carfilzomib + pomalidomide + dexamethasone**
Mg	**Milligram**
MM	**Multiple Myeloma**
MRD	**Minimal residual disease**
n	**Number**
N	**Total number**
N/A	**Not applicable**
NE	**Not estimable**
NICE	**National Institute for Health and Care Excellence**
NR	**Not reported**
NT	**Neurotoxicity**
OR	**Odds ratio**
ORR	**Overall response rate**
OS	**Overall survival**
OSDI	**Ocular Surface Disease Index**
PCd	**Pomalidomide + cyclophosphamide + dexamethasone**
PFS	**Progression free survival**
PI	**Proteasome inhibitor**
QLQ-C30	**Quality of Life Questionnaire C30**
RRMM	**Relapsed or refractory multiple myeloma**
SEER	**Survey, Epidemiology, and End Results Program**
TCRMM	**Triple-class refractory multiple myeloma**
TTNT	**Time to next treatment**

Executive Summary

Multiple myeloma (MM) is a hematologic cancer of plasma cells. It is estimated that approximately 150,000 Americans are currently living with MM. The last 15 years have seen a proliferation of new, approved therapies for MM, resulting in improved survival, increasing from 37% of MM patients surviving 5 years in 2000 to 56% in 2017.[1]

The mainstays of current MM treatment include immunomodulatory agents (thalidomide, lenalidomide or pomalidomide), proteasome inhibitors (bortezomib, carfilzomib or ixazomib) and anti-CD38 monoclonal antibodies (daratumumab or isatuximab).[2] While numerous combinations of these agents can lead to remission, most patients will relapse. These patients with relapsed or refractory multiple myeloma (RRMM) often cycle through different combinations of agents, which may increase both their clinical and economic burden. When a patient's disease is no longer responsive to agents in each of these three classes of medications, the disease is referred to as "triple-class refractory" MM (TCRMM).[3] TCRMM patients have limited treatment options and limited survival.[4]

In this report, 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 mafodotin was studied in heavily pre-treated (6-7 previous lines of therapy) quad- and penta-refractory patients (usually defined as refractory to 4 or 5 agents across all 3 drug classes noted above). Idecabtagene vicleucel ("ide-cel", Bristol Myers Squibb and bluebird bio) and ciltacabtagene autoleucel ("cilta-cel", Janssen and Legend biotech) are investigational chimeric antigen receptor (CAR) T-cell therapies, requiring a patient's own lymphocytes to be 1) obtained via leukapheresis, 2) modified in the lab with a gene to encode an anti-BCMA antibody, 3) expanded, and 4) reinfused back into the patient. Ide-cel and cilta-cel were studied in patients who were mostly TCRMM, previously exposed to a median of 6 previous lines of therapy.

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. A rolling biologic license application for cilta-cel was submitted to the FDA in December 2020. Belantamab mafodotin received FDA approval in August 2020 for RRMM patients who have been exposed to 4 or more previous lines of therapy.

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.

The CAR T-cell therapies (ide-cel and cilta-cel) appear to be superior to currently available treatment regimens for TCRMM. Patients receiving ide-cel had an overall response rate (ORR, inclusive of both partial and complete response) of 63% when expressed on an intention-to-treat (ITT) basis, and a median progression-free survival (PFS) of 8.6 months among those receiving an infusion (i.e., "as treated").[5] ITT analyses are preferred for the reporting of most clinical trials, since ITT analyses generally lead to less biased results. Patients receiving cilta-cel had an ITT ORR of 75% at a median of 12.4 months of follow-up and a PFS of >12.4 months, balanced by 6% of patients dying from treatment related complications.[6] In comparison, the recent observational MAMMOTH study showed that TCRMM patients on current therapies had an ORR of 31%, with a median PFS of 3.4 months.[7]

Belantamab mafodotin appears to be equivalent or slightly superior to currently available treatments for quad- and penta-refractory MM patients. Belantamab mafodotin had an ITT ORR of 32% and a median OS of 13.7 months (DREAMM-2 study).[8,9] In comparison, a MAMMOTH sub-cohort matched to the DREAMM-2 cohort showed an ORR of 28% and a median OS of 9.2 months among triple/quad refractory patients and a median OS of 5.6 months for the penta refractory subset of this group.

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, 30% experienced severe decline in vision with Grade 3 decline in Best Corrected Visual Acuity (BCVA).

Table ES1. 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 (Mostly Triple-Class Refractory)						
Ide-cel	KarMMa	13.3 months	73%	63%	As-treated PFS = 8.6 months	51% CRS Grade 2+
Cilta-cel	CARTITUDE-1	12.4 months	97%	75%	As-treated PFS >12.4 months	44% CRS Grade 2+ 6% Treatment-related deaths
Usual Care	MAMMOTH	10.6 months	--	31%	PFS = 3.4 months	Variable
Belantamab Population (Quad- and Penta-Refractory)						
Belantamab mafodotin	DREAMM-2	13 months	--	32%	ITT OS = 13.8 months	30% Severe decline invision (BCVA scale Grade 3+)
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.

Table ES2. ICER Evidence Ratings for Anti-BCMA Therapies

Treatment	Comparator	Evidence Rating
Adults with Triple-class Refractory MM		
Ide-cel	Usual Care	B+
Cilta-cel	Usual Care	B+
Ide-cel	Cilta-cel	I
Adults with Quad- and Penta-Class Refractory MM		
Belantamab	Usual Care	P/I*

MM: multiple myeloma.

*Compared to current treatments, belantamab appears to be comparable with a chance that it may be slightly superior or slightly inferior. Current evidence does not support belantamab being substantially superior to current treatments.

Several important uncertainties remain. First, 9% of the ide-cel patients who were leukapheresed did not receive treatment (14% for cilta-cel) and were not included in the PFS and OS estimates. Since sicker patients who are less likely to do well with any treatment are likely overrepresented in this group, it is likely that accounting for these patients would diminish the benefits seen with ide-cel and cilta-cel; future studies should publish an intention-to-treat analysis incorporating these patients. Second, longer follow-up data for ide-cel and cilta-cel would quantify the median PFS and

OS. Third, additional information is needed for the 6% of deaths related to cilta-cel treatment. Fourth, belantamab appears to have improved OS to a much greater degree than its impact on PFS or ORR, in contrast to prior studies of these relationships in MM. Future studies should determine whether this is a reproducible finding.

ICER also performed cost-effectiveness modeling and analyses of the new therapies. The base-case findings from our analysis suggest the CAR-T therapies provide clinical benefit in terms of gains in life expectancy and quality-adjusted life years (QALYs) over current treatment options for TCRMM patients. Threshold pricing suggests ide-cel should be priced in the $170,000 range to meet the $100,000 per QALY threshold, whereas cilta-cel should be priced in the $420,000 range to meet the same threshold. However, cilta-cel cost-effectiveness findings should be viewed as an optimistic estimate given the extremely limited clinical evidence available and immature PFS/OS follow-up. Base-case findings for belantamab suggest current pricing is in line with meeting the $100,000 per QALY threshold. However, further evidence on the relationship between PFS and OS should be generated and incorporated into future modeling analyses.

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. Historically, treatments with these characteristics are underutilized by historically disadvantaged populations, suggesting these treatments may worsen disparities.

In conclusion, the evidence suggests that ide-cel and cilta-cel improves outcomes for triple-class refractory MM patients, with higher rates of response and longer survival than treatment with current therapies. Belantamab appears to be equivalent or slightly superior to current treatments for quad- and penta- refractory MM patients; however, due to uncertainties regarding PFS, OS and the development of severe visual impairment the current evidence base cannot rule out a small possibility of net harm from this treatment.

1. Background

Multiple Myeloma (MM) is a hematologic cancer of plasma cells.[1] Uncontrolled proliferation of plasma cells can lead to a variety of clinical presentations, 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 most often diagnosed through a bone marrow biopsy showing ≥10% plasma cells.[10]

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 150,000 Americans are currently living with MM. [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.[11] 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.[12]

The last 15 years have seen a proliferation of new, approved therapies for MM, resulting in substantial improvements in survival.[2] 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 most 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. Patients whose disease does not respond to treatment, or initially respond but are no longer responding to line of treatment are considered refractory. These patients with relapsed or refractory multiple myeloma (RRMM) 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 or isatuximab; immunomodulatory drugs or IMiD's such as thalidomide, lenalidomide or pomalidomide; and proteasome inhibitors or PI's such as bortezomib, carfilzomib or ixazomib) are termed "triple class refractory" (TCR) MM.

Currently, there is no widely accepted preferred ordering of lines of therapy for TCRMM patients. General principles that guide treatment choice include previous treatments, how patient's disease responded to these previous treatments, comorbidities, and risk stratification. One major consideration is incorporating as many new agents as possible (medications to which the patient has not been previously exposed) into each new line of treatment.[13] This often results in regimens incorporating newer agents in one of the three major classes of anti-myeloma medications (such as pomalidomide or carfilzomib) as well as agents in other classes such elotuzumab or alkylator based treatments. Even with these treatments, TCRMM patients unfortunately have limited survival, with overall survival <1 year.[7] These TCRMM represent the population that may potentially benefit from the three medications in this review. For our review, we focused on agents commonly used in the TCR population; thus, some agents, such as Selinexor, were not included as a component of usual care (and comparator to new treatments) due to low rates of use in these patients.

Three new treatments, idecabtagene vicleucel ("ide-cel", Bristol Myers Squibb and bluebird bio), ciltacabtagene autoleucel ("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 appears 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.[14] Blenrep is an antibody-drug conjugate, with a monoclonal antibody specific for BCMA that is linked to a cytotoxic drug. Belantamab mafodotin is given as an intravenous infusion every 3 weeks. Belantamab mafodotin received FDA approval in August 2020 for adult patients with relapsed or refractory MM who have received 4 prior lines of therapy including an anti-CD38 monoclonal antibody, a PI and an IMiD.

Ide-cel and cilta-cel are chimeric antigen receptor T (CAR-T) cell therapies, requiring a patient's own T lymphocytes to be obtained via leukapheresis and transduced in the lab with a gene to encode an anti-BCMA antibody. Ide-cel uses a mouse-derived CAR with a single BCMA recognition domain. Cilta-cel uses a camelid CAR with 2 BCMA recognition domains, which theoretically may strengthen the interaction between the CAR and target cells. 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 was submitted December 21, 2020.

2. Patient and Caregiver Perspectives

ICER engaged with patients with MM (including those treated with anti-BCMA medications), representatives from advocacy organizations, and clinical experts to understand the patient perspective of living with MM. We also spoke with two patient advocacy groups who helped us identify patients who could speak to their experiences. We spoke with five patients over five calls. Finally, we also conducted a focus group with four patients, where we elicited patient perspectives of their lived experiences. Additional details, including the semi-structured interview guide and questions, are available in the Supplement.

Patients spoke about the importance of **quality of life** beyond survival. One patient noted, "I don't want to lie in my bed. I want to meet with friends, go places." In addition, patients mentioned the negative impact of being continually tethered to the health care system. Another patient mentioned, "it's a burden to wake up early, go to the hospital, wait (there's always a delay), then get infused, and not get back home [until after dark]." A second patient summarized, "Visiting the doctor every week or two gets old." Thus, patients reported wanting low side effect treatments that would not require frequent returns to the clinic or hospital.

One of the most frequent side effects that patients mentioned was **fatigue** and **weakness**. While some spoke of fatigue as a symptom of poorly controlled MM, for others, it was clearly a side effect of treatment. One patient mentioned, "The fatigue is bad—I find it more on POM [pomalidomide]. I have to take a break from cutting veggies." Others noted, "The weakness is the worst thing...it interferes with your ability to exercise and take care of yourself."

Patients also mentioned the impact their disease had on their loved ones and **caregivers**. One patient mentioned, "My wife was greatly impacted. I couldn't do the grocery shopping anymore and I had to sleep in an office chair because of the pain." One patient mentioned that the irritability caused by dexamethasone led to "a temporary estrangement with my spouse because of my short temper." Thus, MM and its treatments have profound effects on families and caregivers as well as the patients.

Several patients reported tremendous **financial strain** due to MM treatments. One patient stated, "My drugs were about $250,000 a year. That first year I went into debt and had to refinance my home. I was 3 years from paying off my house and I had to start over." Another patient noted, "on top of being filled with cancer, you have to deal with all of these bills." Clinicians noted, "We still see cases where patients decline to take their drugs because the out-of-pocket expenses are so high that they'd have to choose between meds and food/housing." 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.

Patients and clinicians mentioned that **African American** MM patients face additional barriers to effective treatment. One patient noted, "there's a mistrust of medical community [in the African American community] and is a real thing, and not as much awareness and understanding of MM. [African Americans] are wary in participating in trials and refuse stem cell transplant when its offered." A patient advocacy group mentioned, "navigating newer therapies can be like a maze...African Americans and patients with lower socioeconomic status are more like to get lost in that maze." These comments suggest that newer treatments must proactively engage with historically disadvantaged populations; otherwise, these treatments, because of their complexity, may worsen disparities.

We spoke with 2 patients who had **received CAR T-cell therapies** as part of a clinical trial. Both patients described the infusion and subsequent hospitalization as relatively easy ("a piece of cake") but long and monotonous. One patient described CAR-T therapies as "very liberating", since his doctors did not feel like he needed maintenance medications after CAR-T therapies. Thus, the frequency of doctors' visits and laboratory tests have decreased, and he noted, "if it wasn't for COVID [I could] travel to New York or Italy." A second CAR-T therapy patient had a different experience, since he required continued maintenance medications after CAR-T therapy.

We spoke with several patients who were **considering CAR T-cell therapies.** One patient stated, "I'm afraid of CAR-T." When asked what she was afraid of, she talked about how intensive it sounded and that it "only lasts for about a year." A second patient was more interested in CAR-T therapy, stating that he is currently responding to treatment, but that he would consider it for a future line of therapy. Even a patient who had undergone CAR-T therapy stated that he did so because he felt he had no other options. All patients spoke about the importance of having CAR-T therapy as an option saying, "At some point, we're all going to need this because all combinations eventually seem to stop working." The fact that CAR-T therapies could only be coordinated in larger cancer centers was a consideration for patients, since it would require more frequent, longer drives to doctors' appointments.

Our conversations with patients informed our review by reinforcing the importance of specific symptoms including fatigue and weakness. In addition, patient perspectives helped focus our review on the side effects of both current treatments as well as the side effects of the new interventions. Finally, all these issues reinforced the importance of considering health-related quality of life as a primary outcome for our review.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic review assessing the evidence on ide-cel, cilta-cel, and belantamab mafodotin for heavily pre-treated relapsed and refractory multiple myeloma are described in the Detailed Methods section of the Report Supplement.

Scope of Review

This review compares the clinical effectiveness of ide-cel and cilta-cel for the treatment of adults with TCRMM who have received at least three prior lines of therapy, as well as belantamab mafodotin for adults with TCRMM who have received at least four prior lines of therapy in comparison with usual care (i.e., commonly used regimens for those exposed to ≥3 and ≥4 prior lines of therapy respectively). The primary patient-important outcomes included OS, PFS, overall reORR, and health-related quality of life (HRQoL). The full scope of the review is detailed in the Data Sources and Searches section of the Report Supplement.

Evidence Base

The clinical evidence is summarized qualitatively for each intervention separately because the key trials were all single arm studies, so quantitative comparisons were not possible. Details of key studies are described below and summarized in Table 3.1.

Ide-cel

A total of 11 references relating to two single-arm (one Phase I, one Phase II), open label trials of ide-cel met our inclusion criteria. At the time of this report, only the results of the CRB-401 trial, a Phase I trial of bb2121 (ide-cel) had been published.[15,16] Data from both trials were obtained from conference abstracts, press releases, and information provided by the manufacturers (Table 3.1). In this report, we will report on the Phase II trial (KarMMa), but additional details of both trials are included in the Additional Clinical Evidence section of the Report Supplement.

KarMMa

The KarMMa trial is an ongoing Phase II multi-center, open-label, single-arm trial being conducted at 24 locations worldwide, including North America, Europe, and Japan.[5] The trial screened 158 adults who had previously been exposed to an immunomodulatory drug (IMiD), a proteasome inhibitor (PI), an anti-CD38 antibody, and were refractory to the last prior therapy and enrolled 149 patients.[17] 140 patients underwent leukapheresis and most(88%) received bridging therapy during the manufacturing process, before lymphodepletion with fludarabine and cyclophosphamide five

days prior to infusion (a total of 128 patients, or 86% of the enrolled population, were analyzed). The primary outcome was ORR. Secondary outcomes were complete response (CR), safety, duration of response (DoR), PFS, OS, pharmacokinetics, and HRQoL (Table 3.1).

Cilta-cel

A total of 10 references relating to two open-label, single arm trials (one Phase I and one Phase Ib/II) of cilta-cel met our inclusion criteria. At the time of this report, only results from selected sites from the Phase I trial (LEGEND-2) had been published.[18] Because at the time of this report, median PFS and OS had not yet been reached in the Pivotal phase Ib/II trial (CARTITUDE-1), we also include outcomes from the largest site in the Phase I trial (LEGEND-2). Since the population enrolled in LEGEND-2 was younger with fewer previous lines of therapy, it is unclear whether LEGEND-2 results are applicable to a more heavily pre-treated MM population. We identified data from conference abstracts, posters, presentations, and regulatory documents to inform the clinical effectiveness review (Table 3.1).

CARTITUDE-1

CARTITUDE-1 is an ongoing Phase Ib/II single-arm trial of cilta-cel being conducted in 21 sites in the United States and Japan.[19] The trial enrolled 126 adults with TCRMM who had progressive disease after at least three prior therapies (including a PI, an IMiD, and anti-CD38 antibody), who are double refractory to an IMiD and PI.[20] A total of 113 patients underwent leukapheresis (90% of the enrolled population), 101 underwent lymphodepletion with fludarabine and cyclophosphamide five days prior to infusion (80%), and 97 patients (77% of the enrolled population) were included in the analysis. The primary outcomes were adverse events (AEs) and ORR. Secondary outcomes were OS, PFS, and minimal residual disease (MRD) (Table 3.1).

LEGEND-2

LEGEND-2 is a Phase I single-arm trial of cilta-cel that was conducted at four sites in China.[18,21,22] The trial enrolled 74 adults with TCRMM who had progressive disease after at least 3 prior therapies (including a PI, an IMiD, and anti-CD38 antibody). The trial explored the differences between a single and three CAR-T cell infusion approach with varying doses ($0.2\text{-}2.0\times10^6$ CAR-T cells/kg) as well as cyclophosphamide alone versus in combination with fludarabine during conditioning. For this report, we will include data from the largest study site (Xi'an, N=57) because data was not aggregated across all four sites. The primary outcome was AEs; the secondary outcome was CR (Table 3.1).

Belantamab mafodotin

A total of eight references pertaining to one open-label Phase II clinical trial (DREAMM-2), one conference abstract relating to a pooled post-hoc analysis, and one conference abstract relating to an expanded access program met our inclusion criteria. At the time of this report, two published manuscripts were available for the DREAMM-2 trial,[8,23] which were supplemented with conference abstracts and information provided by the manufacturer. Additional details are available in the Supplement.

DREAMM-2

DREAMM-2 is an ongoing Phase II, open-label, global, multicenter trial comparing the efficacy and safety of two doses of belantamab mafodotin (2.5 mg/kg and 3.4 mg/kg) in adults with TCRMM.[8] In total, 196 patients (97 in the 2.5 mg/arm and 99 in the 3.4 mg/kg arm) who had been treated with at least three prior lines of treatment and who were refractory to an IMiD, a PI, and refractory to and/or were not able to tolerate an anti-CD38 monoclonal antibody were enrolled in the trial.[8] At the time of this report, information on the proportion of patients who are classified as penta-refractory was not publicly available (submitted as academic in confidence). In August 2020, the FDA granted accelerated approval to belantamab mafodotin for the treatment of RRMM patients with progressive disease after having been treated with four prior lines of therapy. For the purpose of this review, we only present data for the FDA approved dose of 2.5 mg/kg (N=97). The primary outcome assessed was ORR, and secondary outcomes assessed included DoR, time to response, PFS, OS, and safety. All patients who received at least one dose of belantamab mafodotin were included in the evaluation of efficacy outcomes (ITT population, N=97).

See Report Supplement for detailed inclusion and exclusion criteria, and definitions of measurable disease and outcomes reported.

Table 3.1 Overview of Key Studies of Ide-cel, Cilta-cel, and Belantamab mafodotin

Intervention & Trial	Inclusion/Exclusion Criteria	Outcomes	Baseline Characteristics‡
Ide-cel KarMMa[5,17] Phase II, open-label single-arm N=149†	Inclusion: – Received at least 2 cycles of ≥3 prior treatment regimens (incl. PI, IMiD, anti-CD38 antibody) and refractory to last regimen Exclusion: – Previous allogeneic SCT	Primary: ORR Secondary: CR, OS, PFS, AEs, HRQoL	– Age, median (range): 61 (33-78) – Prior lines of therapy, median (range): 6 (3-16) – Triple-refractory: 84% – Penta-refractory: 26% – EMD: 39% – High-risk cytogenetics: 35%
Cilta-cel CARTITUDE-1[6,20] Phase II, open-label single-arm N=126†	Inclusion: – Received ≥3 prior treatment regimens (incl. PI, IMiD, anti-CD38 antibody) or are double refractory to a PI and IMiD Exclusion: – Allogeneic SCT within 6 months or autologous SCT within 4 months	Primary: AEs, ORR Secondary: OS, PFS, MRD	– Age, median (range): 61 (43-78) – Prior lines of therapy, median (range): 6 (3-18) – Triple-refractory: 88% – Penta-refractory: 42% – EMD: 13% – High-risk cytogenetics: 23%
Cilta-cel LEGEND-2[22] (Xi'an site) Phase I, open single-arm N=57	Inclusion: – Received ≥3 prior treatment regimens (incl. PI, IMiD, anti-CD38 antibody) or are double refractory to a PI and IMiD Exclusion: Allogeneic SCT within 6 months or autologous SCT within 4 months	Primary: AEs Secondary: CR	– Age, median (range): 54 (27-72) – Prior lines of therapy, median (range): 3 (1-9) – Triple-refractory: NR – Penta-refractory: NR – EMD: 29.8% – High-risk cytogenetics: NR
Belantamab mafodotin DREAMM-2[8] Phase II, open-label, two-arm N=97*	Inclusion: – Received ≥3 previous lines of treatments – Refractory to IMiD and PI, and refractory/intolerant to an anti-CD38 therapy Exclusion: – Received allogeneic SCT – Current corneal epithelial disease	Primary: ORR Secondary: DoR, time to response, PFS, AEs	– Age, median (IQR): 65.0 (60.0-70.0) – Prior lines of therapy, median (range): 7 (3-21) – Triple-refractory: 100% – Penta-refractory: [redacted] – EMD: 23% – High-risk cytogenetics: 42%

AEs: Adverse events, CR: Complete response, DoR: Duration of response, EMD: Extramedullary disease, HRQoL: Health-related quality of life, IQR: interquartile range, MRD: Minimal residual disease, N: total number, ORR: Overall response rate, OS: Overall survival, PFS: Progression free survival, SCT: stem cell transplant.

*2.5 mg/kg arm only.

† Sample sizes are based on the intention-to-treat population

‡ Baseline characteristics from KarMMa and CARTITUDE-1 are based on the as-treated population

Usual Care

Our systematic literature review did not reveal any prospective studies evaluating the effectiveness of usual care (defined as commonly-used combination regimens described in our research protocol (https://osf.io/3dtr4/) in triple-class refractory patients. The most relevant evidence to support the clinical effectiveness of usual care for triple-class refractory patients to compare with CAR T-cell treatments, came from a retrospective observational study (Table 3.2).[7]

The MAMMOTH study was a multi-center US-based retrospective analysis of 275 multiple myeloma patients (data were collected between January 2017 and June 2018), of whom 218 were refractory to at least three lines of therapy (PI, IMiD, and anti-CD38 monoclonal antibody).[7] 70 (25%) were "penta-refractory" (refractory to two PIs, two IMiDs, and an anti-CD38 monoclonal antibody). Primary outcomes were OS, PFS, and ORR. Two additional retrospective studies were identified and are described in the Additional Clinical Evidence Section of the Report Supplement.

Table 3.2. Overview of MAMMOTH Study

Study	Inclusion/Exclusion Criteria	Outcomes	Patient Characteristics
MAMMOTH[7] Retrospective chart review N=275 (54% triple/ quad-refractory, 25% penta-refractory)	Inclusion: – Refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 Exclusion: NR	Primary: OS, PFS, ORR	– Age, median (range): 65 (27-90) – Prior lines of therapy, median (range): 4 (1-16) – Triple- and quad-refractory: 75% – Penta-refractory: 25% – High-risk cytogenetics: 29%

IMiD: Immunomodulatory drug, N: total number, NR: not reported, PI: Proteasome inhibitor, ORR: Overall response rate, OS: Overall survival, PFS: Progression free survival

Key Differences Across Studies

See the Report Supplement Table D3.2 for details on baseline characteristics of the key trials of the interventions. Key differences are summarized below.

Although the study participants in KarMMa and CARTITUDE-1 were of similar ages (median age 61 in both) and had received a similar amount of pre-treatment (median of 6 prior lines of therapy), patients in the CARTITUDE-1 trial were more likely to be penta-refractory than patients in the KarMMa trial (42% vs 26%), but less likely to have extramedullary disease (EMD, the presence of plasma cells outside the bone marrow, a marker of more aggressive disease) (13% vs 39%), and high-risk cytogenetics (23.7% vs 35.2%).[5,6] Patients in the LEGEND-2 (Xi'an site) were younger than patients in KarMMa (median age 54 vs 61), were less heavily pre-treated (median three prior lines of treatment vs. six), and less likely to have EMD (30% vs 39%).[22,24] In DREAMM-2, the patients undergoing treatment with belantamab mafodotin were typically older (median age 65), had undergone more pre-treatment (median of seven prior lines of therapy), and were more likely to

have high-risk cytogenetics (42.3%);[8] the percentage of penta-refractory patients was provided to us as academic in confidence ([redacted]).

A key difference between the pivotal CAR-T therapy trials and DREAMM-2 was the approach for inclusion in the outcomes analysis. KarMMa and CARTITUDE-1 both only included patients who were infused in the analysis (86% and 77% of enrolled and 91% and 86% of leukapheresed patients, respectively) in an as-treated approach, whereas DREAMM-2 reports the full intention-to-treat (ITT) population. In LEGEND-2, all patients who were leukapheresed were infused and thus, making the distinction between an as-treated versus ITT analysis moot.

The study populations in MAMMOTH were of similar age (median 60 years) to those in KarMMa and CARTITUDE-1 (median 61 years), but appeared to have received less pre-treatment overall (median of four prior lines of therapy versus six or seven).[7]For this reason, we report the outcomes for triple and quad-penta-refractory patients separately. Furthermore, the exclusion criteria for MAMMOTH were not reported, making it difficult to interpret differences in study populations relative to the key studies of the interventions. See the Report Supplement Table D3.19 for details on baseline characteristics of the studies of usual care.

3.2. Results

Clinical Benefits

The primary outcomes that are used in the economic model are PFS and OS as defined in the clinical trials. The key clinical benefits of ide-cel are described first, followed by cilta-cel, and belantamab mafodotin. Additional outcomes are described in the Report Supplement.

Ide-cel

In the KarMMa trial, as of the January 14th, 2020 study data cutoff, median follow-up time was 13.3 months.[5] The as-treated median PFS across all target CAR-T therapy doses was 8.8 months, and the as-treated median OS was 19.4 months. The as-treated median PFS varied by dose, with the highest dose ($450x10^6$ CAR-T cells) achieving the longest median PFS (11.3 months). The as-treated ORR was 73% (94 out of 128 infused patients) and the as-treated stringent complete or complete response rate (sCR or CR) was 33% (42 out of 128) across all doses. The reported outcomes from KarMMa likely represents an optimistic estimate of the results since they are based on patients who received infusion of CAR-T cells, excluding patients who did not receive the therapy due to death prior to infusion, disease progression, or AEs. When calculated on an ITT (that is, including all enrolled patients, including those who were enrolled, leukapheresed but not infused), however, ORR was 63% (94 out of 149 enrolled patients) and sCR or CR was 28% (42 out of 149) (Table 3.3).[20]

In the KarMMa trial, HRQoL was assessed using the EQ-5D, EORTC QLQ-C30, and MY20 scales (details on these cancer-specific instruments are available at https://qol.eortc.org/) prior to induction and at day one and nine months post-infusion with ide-cel. Physical functioning, fatigue, pain, and global health sub-scales all improved at nine months compared to baseline (Table 3.4); however data on only 59 of 111 (53%) patients assessed at day one were available at nine months.[25] More details on patient-reported outcomes for ide-cel are available in Table D3.10 of the Report Supplement.

Cilta-cel

At the time of this report, as-treated median PFS and OS were not reached with a median of 12.4 months of follow-up in the CARTITUDE-1 trial.[6] Using an as-treated approach, ORR was 97% (94 out of 97 infused patients) and sCR was 67% (65 out of 97 infused patients had an sCR). However, in an ITT analysis, using the overall enrolled population, ORR was 75% (94 out of 126 enrolled patients) and sCR was 52% (65 out of 126) (Table 3.3).[20] In the Phase I trial (LEGEND-2, Xi'an study site), with a median follow-up time of 25 months, median PFS was 19.9 months, median OS was 36 months, and ORR was 87.7%.[24,26] Because all patients in LEGEND-2 who were enrolled were leukapheresed and underwent infusion, an ITT analysis was not applicable, however comparisons based on data from LEGEND-2 should be interpreted with caution due to differences in the patient population. More details on outcomes data for cilta-cel are available in Table D3.4 of the Report Supplement.

In CARTITUDE-1 the EORTC QLQ-C30 was administered prior to induction and at various time points post-treatment. At the time of the report, only data on fatigue and pain sub-domains were available. At 184 days , both fatigue and pain scores improved relative to baseline (Table 3.4), however data were available for only 30 out of the 68 (44%) patients who were assessed at baseline.[27] More details on patient-reported outcomes for cilta-cel are available in Table D3.10 of the Report Supplement.

Belantamab mafodotin

At the 13-month follow-up (data cut-off date: January 14 2020), patients treated with 2.5 mg/kg belantamab mafodotin had a median PFS of 2.8 months and median OS of 13.7 months.[9] Please refer to the Report Supplement for OS rates at three, six, nine, and 12 months. PFS rates at three to 12 months were submitted as academic in confidence Thirty-one out of 97 participants (32%) achieved an overall response, with five and two patients achieving CR and sCR, respectively.

In DREAMM-2 HRQoL was assessed by means of the EORTC-QLQ-C30, EORTC-QLQ-MY20, and Ocular Surface Disease Index (OSDI) scales. At 25 weeks, patients reported experiencing a deterioration (worsening) in the fatigue, pain, and global health sub-domain scores of the EORTC-QLQ-C30. Scores for the physical functioning sub-domain of the EORTC-QLQ-C30 were found to be comparable to baseline values, as were scores of the disease symptoms sub-domain of the EORTC-

QLQ-MY20.[28] Additional data on HRQoL data for belantamab mafodotin can be found in Table D3.10 of the Report Supplement.

Table 3.3. Key Trial Results of Ide-cel, Cilta-cel, and Belantamab mafodotin

Intervention	Trial (N)	Median Follow-Up Duration	As-treated PFS, Median Months (95% CI)	As-treated OS, Median Months (95% CI)	ITT ORR, n (%); [95% CI]
Ide-cel	**KarMMa[5,17] (N=149)‡**	13.3 months§	8.8 (5.6, 11.6)§	19.4 (18.2, NE)§	94 (63); [NR]
Cilta-cel	**CARTITUDE-1[6,20] (N=126)‡**	12.4 months§	Not reached at 12.4 months§	Not reached at 12.4 months§	94 (75); [NR]
	LEGEND-2[24] (N=57)†	25 months	19.9 (9.6, 31.0)	36.1 (26.4, NE)	50 (87.7); [76.0, 95.0]
Belantamab mafodotin	**DREAMM-2[8] (N=97*)**	13 months	2.8 (1.6, 3.6) ‡	13.7 (9.9, not reached)‡	31 (32.0); [97.5%CI: 21.7, 43.6]

95%CI: 95% confidence interval, 97.5%CI: 97.5% confidence interval, NE: not estimable, NR: not reported, n: number, ORR: Overall response rate, OS: Overall survival, PFS: progression free survival

*2.5 mg/kg arm only.

† Xi'an site only.

‡ Intention-to-treat.

§ Median Follow-up duration, PFS and OS for KarMMa and CARTITUDE-1 are based on the as-treated population.

Table 3.4. Change from Baseline in Health-Related Quality of Life (Selected EORTC QLQ-C30* Sub-Domains)

Intervention (Trial)	Time from Baseline (N)	Physical Functioning, Mean (95% CI)	Fatigue, Mean (95% CI)†	Pain, Mean (95% CI)†	Global Health, Mean (95% CI)
Ide-cel‡ (KarMMa)[25]	9 months (N=59)	13.2 (7.9, 17.9)	-22.8 (-29.1, -17.1)	-23.8 (-30.2, -18.3)	15.4 (9.8, 20.9)
Cilta-cel‡ (CARTITUDE-1)[27]	6 months (N=30)	NR	-9.2 (-16.4, -2.0)	-8.9 (-17.6, -0.3)	NR
Belantamab mafodotin‡ (DREAMM-2)[28,29]	6 months (N=19)	-0.1 (-5.3, 5.3)	3.6 (-7.6, 14.6)	2.6 (-6.5, 11.4)	-4.7 (-12.1, 2.8)

95%CI: 95% confidence interval, N: total number, NR: not reported, ORR: Overall response rate.

*EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer Patients

†Negative changes indicate a reduction in pain or fatigue

‡Mean changes from baseline have been digitized and should be interpreted with caution

Usual Care

We identified three retrospective observational studies to inform our comparison of usual care to the interventions.[7,30,31] In this report, we present outcomes from the MAMMOTH study because outcomes are available across triple and quad/penta-refractory populations as well as overall[7]. The majority of patients in the MAMMOTH study were refractory to daratumumab (93%), lenalidomide (77%), bortezomib (68%), and pomalidomide (65%) and a minority were refractory to carfilzomib (47%), ixazomib (12%), and thalidomide (8%). Median PFS was 3.4 months in the overall population but was not separately reported in the triple-quad and penta-refractory populations. Median OS was 9.3 months in the overall population, 9.2 months in the triple-quad population, and 5.6 months in the penta-refractory population. Overall response was 29-31% (Table 3.5). Additional details on the outcomes from MAMMOTH and the additional retrospective studies are provided in Tables D3.15 and D3.16 in the Report Supplement.

Table 3.5. Key Results MAMMOTH Study

Study	Population (N)	PFS, Median Months, (95% CI)	OS, Median Months (95% CI)	ORR, n (%)
MAMMOTH[7]	Overall (N=275)	3.4† (2.8-4.0)	9.3† (8.1, 10.6)	85 (31.0)*
	Triple- and quad-refractory (N=148)	NR	9.2 (7.1, 11.2)	80 (29.0)*
	Penta-refractory (N=70)	NR	5.6 (3.5, 7.8)	83 (30.0)*

95%CI: 95% confidence interval, N: total number, n: number, ORR: Overall response rate, OS: overall survival, PFS: progression-free survival.

***** ORR calculated based on first line of therapy.

† PFS and OS on next line after T_0.

Harms

Harms of ide-cel, cilta-cel, and belantamab mafodotin are presented based on the number of study participants who were actually infused/treated ("safety population").

Ide-cel

In the KarMMa trial, cytokine release syndrome (CRS) was the most commonly-reported AE, reported by 84% of patients (48% Grade 1; 31% Grade 2) and lasting a median of 5 days.[5] Of 107 patients who had CRS, 9 (8.4%) required intensive care unit admission.[32] CRS was most likely to be managed with tocilizumab (52%), followed by corticosteroids (15%). Risk of CRS appeared to be dose-related, reported by 96% of patients in the $450x10^6$ dose compared to 76% in the $300x10^6$ dose. Patients in the $450x10^6$ dose were also more likely to require tocilizumab to manage their CRS than patients in the $300x10^6$ dose (67% vs 43%). Older patients were also more likely to experience CRS; all 20 patients ≥70 reported CRS across all doses. Other important AEs included neurotoxicity (18%), thrombocytopenia (63%), and neutropenia (91%) (Table 3.6). Five deaths (4%)

were reported within 8 weeks of infusion, 2 from progressive disease, and 3 from treatment-related AEs (CRS, pneumonia, gastrointestinal hemorrhage). An additional treatment-related death from pneumonia was reported within 6 months of infusion.[5] More information on harms of ide-cel are available in Table D3.11 of the Report Supplement.

Cilta-cel

In CARTITUDE-1, 95% of patients reported CRS, with most 95% experiencing low to moderate CRS (51% Grade 1 and 39% Grade 2). [6] Median time to onset of CRS was seven days (range 1-12) and lasted a median of four days (range 1-97). CRS was most likely to be managed with tocilizumab (69%), followed by corticosteroids (22%) and anakinra (19%). Other important AEs included neurotoxicity (21%), thrombocytopenia (79%), and neutropenia (96%) (Table 3.6). A total of 14 deaths (14.4%) were reported during the study, five due to progressive disease, three due to AEs unrelated to treatment (pneumonia and other cancers), and six due to AEs related to treatment (sepsis, CRS, lung abscess, respiratory failure, neurotoxicity).[6] In LEGEND-2 (Xi'an site), 89.5% of patients reported CRS.[24] Other important AEs included neurotoxicity (1.8%) and thrombocytopenia (49%). At 25 months of follow up, 17 deaths were reported (29.8%), 14 (24.6%) due to progressive disease, two (3.5%) due to AEs, and one (1.8%) other.[26] More information on harms of cilta-cel are available in Table D3.12 of the Report Supplement.

Belantamab mafodotin

In DREAMM-2, AEs were reported by 97.9% of patients treated with belantamab mafodotin 2.5 mg/g (N=95).[9] The vast majority of AEs were considered to be related to the study treatment (88.4%). Three patients (3.2%) died during the study due to AEs (myocardial infarction (n=2), sepsis (n=1)), with one death being treatment related (sepsis).[9] At 6.3 months of follow-up, over three-quarters of the enrolled participants had discontinued study treatment, mainly due to disease progression or death (60.8% and 32.6%, respectively).[8] Nine patients (10%) discontinued study treatment due to AEs (one due to keratopathy and one due to blurred vision).[9] AEs frequently led to dosing modifications, with over half (54%) experiencing dose delays and over a third (35%) requiring dose reductions. Keratopathy, defined as changes to the corneal epithelium, was reported by 72% of patients; however at 13 months follow-up, 77% had recovered from their first, and 48% from their last corneal event.[8,23] 30% of patients experienced a severe decline in vision, which resolved in most patients at the end of study follow-up. No patients reported permanent vision loss. More information on harms of belantamab mafodotin are available in Table D3.13 of the Report Supplement.

Table 3.6. Key Harms of Ide-cel, Cilta-cel, and Belantamab mafodotin

Intervention	Trial (N)	Treatment-related SAEs	Important AEs	D/C due to AEs	Mortality
Ide-cel	KarMMa[5] (N=128)	3.1%	- CRS: 84% - NT: 18% - Thrombocytopenia: 63%	NR	5%
Cilta-cel	CARTITUDE-1[6] (N=97)	NR	- CRS: 95% - NT: 21% - Thrombocytopenia: 79%	NR	14%
	LEGEND-2[21] (N=57)*	NR	- CRS: 90% - NT: 2% - Thrombocytopenia: 49%	NR	30%
Belantamab mafodotin	DREAMM-2[8,9] (N=95)†	11.6%	- CRS: 0% - NT: 0% - Thrombocytopenia: 38% - Ocular Toxicity: 72% - Severe decline in vision (BVCA scale): 30%	10%	33%

AE: adverse event, CRS: cytokine release syndrome, D/C: discontinuation, N: total number, NT: neurotoxicity, SAE: serious adverse event, BCVA: Best Corrected Visual Acuity

* Xi'an site only.

† safety population (2.5 mg/kg).

Usual Care

The retrospective observational studies we selected to represent the effectiveness of usual care did not provide sufficient or consistent information on the harms of the treatment regimens. Therefore, we selected representative prospective trials of commonly used treatments that make up the market basket of therapies in the economic model (Elo-Pom-Dex: elotuzumab-pomalidomide-dexamethasone, Car-Cy-Dex: carfilzomib-cyclophosphamide-dexamethasone, Ixa-Len-Dex: ixazomib-lenalidomide-dexamethasone).[33-35] Serious AEs were common, reported by roughly half of the participants. The most commonly reported grade 3 or 4 AEs included neutropenia, anemia, infection, and thrombocytopenia. Discontinuation rates due to AEs varied from 14 to 18% (Table 3.7). Differences in harms between these regimens and that of the interventions should be interpreted with caution, however, as the trials were generally conducted in less heavily pre-treated populations.

Table 3.7. Harms of Selected Commonly-Used Usual Care Regimens

Treatment	Trial (N)	Serious AEs	Important Grade 3/4 AEs	Deaths (all)	Discontinuation Due to AEs
Elo-Pom-Dex	**ELOQUENT-3[35] (N=60)**	53%	– Neutropenia: 13% – Anemia: 10% – Infection: 13%	22%	18%
Car-Cy-Dex	**Bringhen 2014[34] (N=56)**	NR	– Neutropenia: 20% – Anemia: 11% – Infection: 5%	13%	14%
Ixa-Len-Dex	**TOURMALINE-MM1[33] (N=361)**	46.5%	– Neutropenia: 22% – Anemia: 9% – Infection: <1%	4%	17%

AE: adverse events, Car: carfilzomib, Cy: cyclophosphamide, Dex: dexamethasone, Elo: elotuzumab, Ixa: Ixazomib, Len: lenalidomide, n: number, N: total number, Pom: pomalidomide.

Subgroup Analyses and Heterogeneity

Data on efficacy outcomes by subgroups of patients (such as by age, high risk cytogenetics, race/ethnicity, etc.) were not consistently reported. In the KarMMa trial, as-treated median PFS for ide-cel was 8.6 months for patients 65 years or older (n=45) and 10.2 months for 70 or older (n=20), compared to 8.8 months for the overall population.[36] As-treated median PFS for the 50 patients in the KarMMa trial who had EMD was 7.9 months, and for the 45 patients with high cytogenetic risk was 8.2 months.[37] At the time of this report, efficacy data by subgroups was not available for the CARTITUDE-1 trial. In LEGEND-2, as-treated median PFS for cilta-cel for patients with EMD was significantly lower (8.1 months) than for patients without EMD (25 months, p<0.001).[38]

In DREAMM-2, ITT median PFS for belantamab mafodotin was 2.9 months for patients who had previously been unsuccessfully treated with three to six therapies and 2.2 months for those who had received seven lines of treatment or more.[39] ITT median PFS for patients with high cytogenetic risk factors was 2.1 months.[40] For those with mild to moderate renal impairment, ITT median PFS was 2.2 and 3.7 months, respectively.[41] At 6.3 months of follow up, 43.6% of patients aged 65 to < 75 years achieved an overall response, while only one patient (7.7%) in the age group 75 and above achieved an overall response. 31.6% of White, and 37.5% of Black patients achieved an overall response at 6.3 months of follow-up. ORR at 13 months of follow-up was submitted to ICER as academic in confidence ([redacted]). Similar to other studies, substantially fewer Black patients were enrolled in this study compared to White patients (16 and 72 patients, respectively).[8]

Uncertainty and Controversies

Several important uncertainties remain in our evaluation of CAR T-cell therapies. First, 9% of the ide-cel patients who were leukapheresed did not receive treatment (14% for cilta-cel) and were not

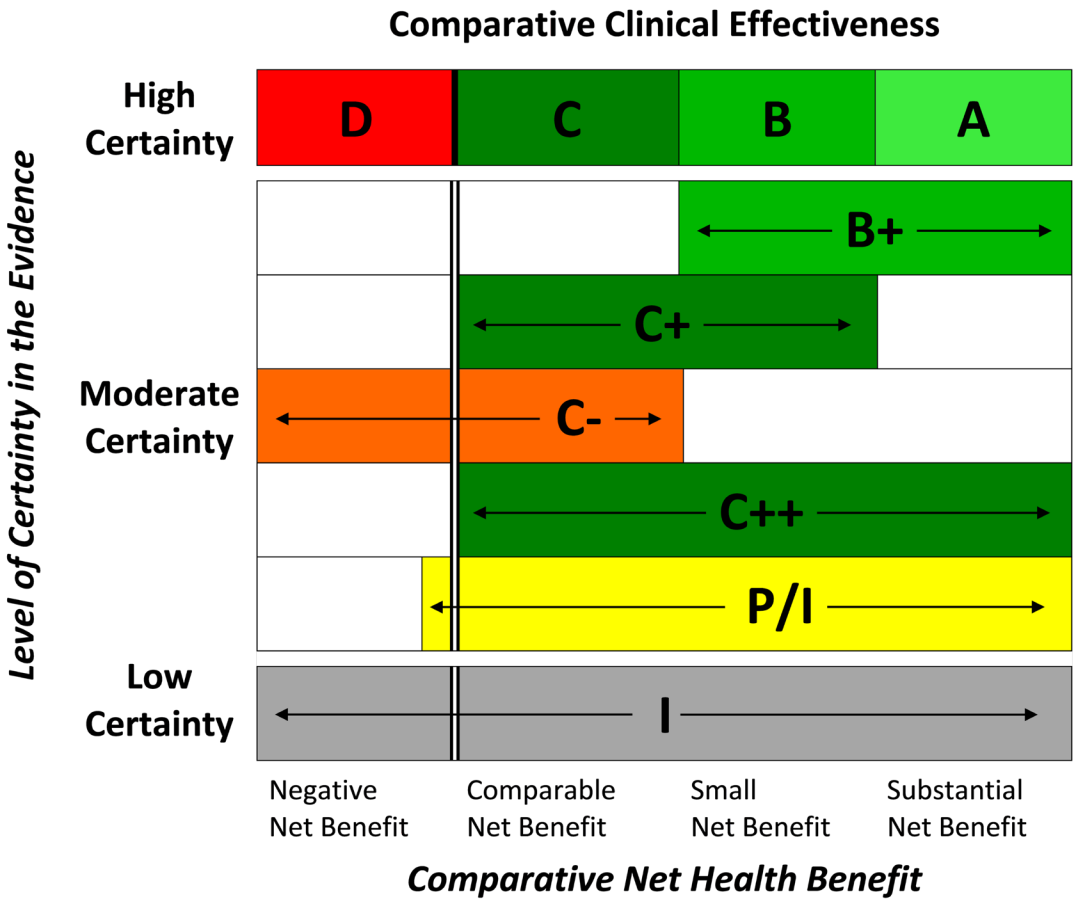
included in the published ORR and PFS estimates. Since manufacturing failures (i.e., inability to successfully encode the patients' T-cells) are now rare, most patients who were enrolled but not able to receive treatment likely had more severe or more aggressive disease. Thus, it is likely that accounting for these patients would diminish the benefits seen with ide-cel and cilta-cel; future studies should publish an ITT analysis incorporating these patients. Our calculated ITT analysis decreased the ORR from 73% to 63% for KarMMa and from 97% to 75% for CARTITUDE-1. Second, longer follow-up data are needed for ide-cel and cilta-cel to quantify the median PFS and OS. Longer-term data may also allow us to definitively determine whether a small minority of patients are able to achieve a long-term, durable response, and to understand whether re-treatment with CAR-T therapy might be necessary in others. Although longer-term data on cilta-cel is available from the Phase 1 LEGEND-2 trial, these results should be interpreted with caution since the LEGEND-2 population is substantially younger and less heavily pre-treated than the MAMMOTH and KarMMa populations. Third, additional information is needed regarding cilta-cel treatment related deaths (6% in CARTITUDE-1). Fourth, while there is interest in utilizing CAR T-cell therapies earlier in the MM disease course, studies are needed to determine whether these therapies are superior to current therapies for first or second relapse of MM.

Uncertainties also remain in our evaluation of belantamab mafodotin. First, additional studies should examine the median OS with belantamab. Across a wide range of MM studies, the ratio seen between PFS and OS is relatively consistent at between 2.5 to 3.0. However, in the pivotal DREAMM-2 study, the 2.5mg/kg arm had a median PFS of 2.8 months and a median OS of 13.7 months, for a 4.9 ratio. It is unlikely that belantamab would increase OS dramatically without increasing PFS; further studies are needed to explore PFS and OS with belantamab treatment. Second, while belantamab was approved as a single-agent treatment, other MM treatments are most effective as doublet or triplet therapies. We await the results of ongoing studies combining belantamab with other treatments to determine whether belantamab would be helpful as a component of novel combination therapies. Lastly, more research is needed to determine a treatment approach best suited for the management of keratopathy, and ultimately to reduce the burden of ocular toxicities on patients, improve patient outcomes and reduce the need for dose adjustments or treatment discontinuation.23 Longer-term data is also needed to allow for an assessment of the proportion of patients who eventually fully recover from ocular events.

3.3. Summary and Comment

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

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 likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Our systematic review of the evidence suggests that CAR T-cell therapies for patients with triple-class refractory MM likely provides small to substantial net health benefits over current usual care. Benefits included longer survival as well as improved quality of life. Counterbalancing these benefits were the harms, including CRS, which is temporary but often requires hospitalization and intensive care unit level care.

Our systematic review of cilta-cel and ide-cel suggests that the evidence is insufficient to determine whether one agent is superior to the other. There are no studies comparing these agents directly, nor sufficient data to perform quantitative indirect comparisons. We conclude that belantamab is promising but inconclusive compared to usual care for quad- and penta- refractory MM patients. The ORR and OS suggests a possible small net benefit. However, the frequency and severity of visual impairment and lack of improvement in HRQoL suggests that any net benefits are likely to be modest. The current evidence precludes a substantial benefit; additional data is required to preclude small overall net harm.

Table 3.8. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with triple-class refractory MM		
Ide-cel	Usual Care	B+
Cilta-cel	Usual Care	B+
Ide-cel	Cilta-cel	I
Adults with quad and penta-class refractory MM		
Belantamab mafodotin	Usual Care	P/I

MM: multiple myeloma

4. Long-Term Cost-Effectiveness

4.1. Methods Overview

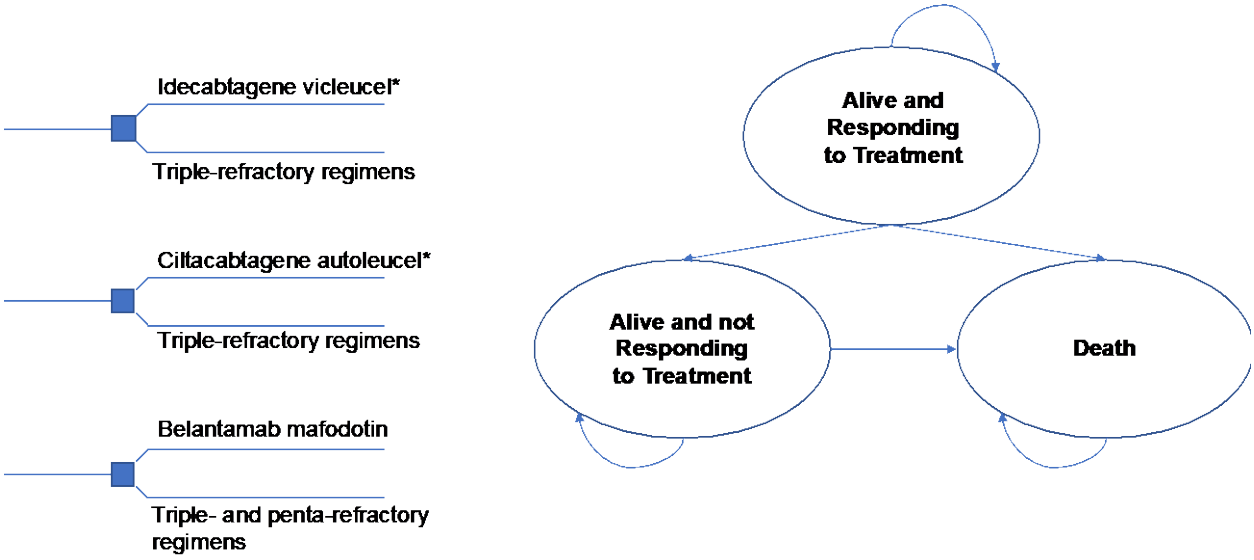
The primary aim of this section of the review was to assess the lifetime cost-effectiveness of ide-cel, cilta-cel, and belantamab mafodotin as compared to relevant comparator treatments. We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.[42]

Specific to CAR-T therapies, an upfront decision tree was used to calculate the costs and consequences from treatment initiation (i.e., leukapheresis) to T-cell infusion. (We note that this differs somewhat from our reporting of "intent to treat" results based on all enrolled trial patients, but better fits the purpose of the model, which is to reflect costs and outcomes following the initiation of the CAR-T therapy process.) The decision tree included patients who were eligible for CAR-T therapy and who had undergone leukapheresis. After initiating leukapheresis, patients could continue to receive the infusion of the engineered T-cells; discontinue (before infusion but after leukapheresis) because of disease progression, adverse events, or manufacturing failures; or die before receiving the infusion. Those who discontinued prior to T-cell infusion received the costs, benefits, and risks of the market basket of triple class refractory comparators.

The cohort of patients were assigned to three mutually exclusive and exhaustive health states in a partitioned survival model (Figure 4.1). Health states included 1) alive and progression free or responding to therapy, 2) alive and not responding to therapy/subsequent relapse, and 3) dead from multiple myeloma-related complications or other causes. We accounted for on/off therapy through application of differential health state utilities. At the end of each cycle, patients in the alive and progression free or responding to therapy health states did not transition treatments. Those in the alive and not responding to therapy/subsequent relapse health state transitioned to a progressed state that included a market basket of subsequent therapies. Patients remained in the model until they died. Health state occupancy was derived using partitioned survival techniques that included the direct extrapolation of progression-free survival (PFS) and overall survival (OS) Kaplan-Meier curves. A detailed description of curve digitization is available in Supplement Section E1.

Model outcomes included total life years (LYs) gained, quality-adjusted life years (QALYs) gained, equal-value life years gained (evLYG), time progression free/responding to treatment, and total costs for each intervention over a lifetime time horizon discounted at 3% per annum. Supplement Table E.3.1 presents undiscounted results.

Figure 4.1. Model Structure



*Includes up-front decision tree to account for patient disposition from leukapheresis and through CAR-T infusion.

Target Population

The model focused on an intention-to-treat analysis, with a hypothetical cohort of heavily pre-treated MM patients beginning at age 60. The CAR T trials enrollment criteria required patients to have been treated with 3 previous lines of therapy. However, enrolled patients had received a median of 6 previous lines of therapy and were 84 – 88% TCRMM, suggesting these characteristics define our target population for CAR T therapy. For belantamab mafodotin, 100% were triple refractory and enrolled patients had received a median of 7 previous lines to therapy, suggesting these characteristics define our target population for belantamab. Cohort characteristics for each treatment group are described in Supplemental Table E.1.2 and E.1.3.

Treatment Strategies

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Idecabtagene vicleucel (Bristol Myers Squibb, Bluebird bio, Inc.)
- Ciltacabtagene autoleucel (Janssen, Legend Biotech)
- Belantamab mafodotin-blmf (Blenrep®, GlaxoSmithKline)

Comparator Treatments

Given the numerous available therapies used by clinicians at various lines of therapy, a market basket approach was used to compare to each intervention based on level of pretreatment using the MAMMOTH study and a recent conference proceeding that estimated the distribution of therapies by line of therapy.[7,31] The market basket composition was approximated by both broad-therapy and specific-therapy estimations. PFS and OS curves were either directly informed by the MAMMOTH study or derived as described in the model structure section.[7] Supplement Tables E.2.3 and E.2.4 provide dosing, administration schedules, and unit costs for each market basket of comparators.

4.2. Key Model Assumptions and Inputs

Our model includes several key assumptions described in Table 4.1.

Table 4.1. Key Model Assumptions

Assumption	Rationale
For CAR-T therapies, patients receive a single full course of therapy. Retreatment with CAR-T therapy is not included in the model.	There is no evidence available related to retreatment with CAR-T therapies for MM patients after non-response/discontinuation.
Subsequent treatments received after progression are uniform within each population/line of therapy.	Patients progressing but still alive are assumed to receive subsequent therapy consistent with the line of therapy by population.
Parametric curve functions were fit separately for each population/treatment and used to extrapolate the data over a lifetime horizon.	Given different populations and lines of treatment, an indirect treatment comparison with the same baseline comparator across populations/treatments was not feasible.
Recent observational evidence on patients using a mix of therapies was used to estimate PFS and OS of relevant comparators.	There is wide variation in therapies used by line of therapy; we used a population with a mix of the most recently used therapies to reflect survival under conditions of current practice in RRMM.
In cases with immature survival data, calibration methods were used to adjust the relationship between PFS and OS based on prior evidence in multiple myeloma.	In some cases, OS data were immature and to calculate health outcomes, we used calibration methods to adjust relationships between PFS and OS.
Patients who discontinue CAR-T therapy due to an AE, or manufacturing failure before receiving the T-cell infusion received comparator treatment benefits, risks, and costs; those who died were accounted for prior to CAR-T infusion.	Patients with MM often receive some level of therapy or intervention until death and therefore patients that discontinued received a market basket of subsequent therapies consistent between each arm of the model.
The model will include only grade 3/4 adverse events and specific toxicities as well as all grades of cytokine release syndrome.	Less severe adverse events are not expected to significantly impact patient health outcomes or costs, although there is evidence to suggest an impact of cytokine release syndrome and keratopathy on outcomes and cost across all grades.

95%CI: 95% confidence interval, CAR-T: chimeric antigen receptor T-cell, MM: multiple myeloma, OS: overall survival, PFS: progression-free survival

Model inputs were estimated from the clinical review, published literature, and information from expert stakeholders. model inputs included PFS, OS, occurrence of adverse events, quality-of-life utility values, and health care costs. We note that data are on PFS are extremely limited for cilta-cel; we used reported data for PFS from CARTITUDE-1 and used prior estimates of relationship between PFS and OS to estimate median OS. Probabilities, costs, and other inputs differed between treatments to reflect varying effectiveness between interventions. Health state utility values were consistent across interventions within the same disease, although different utilities were applied for patients in the progression-free state depending on whether they were on or off therapy. Key model inputs are described in Tables 4.2 and 4.3 for interventions in the populations exposed to three or more lines of therapy and the population exposed to four or more lines of therapy, respectively.

Table 4.2. Key Model Inputs for Population Exposed to Three or More Lines of Therapy

Parameter	Ide-Cel	Cilta-Cel	CAR-T Comparator Market Basket
Progression-Free Survival, Median	8.9 Months	15 Months	3.4 Months
Overall Survival, Median	19.4 Months	NR	9.9 Months
Progression-Free on Therapy and Responding Utility	0.78		
Progression-Free Off Therapy and Responding Utility	0.82	0.82	N/A
Progressed Disease/Not Responding to Therapy Utility	0.71		
Price per 28-Day Cycle	Price estimated through threshold analysis	Price estimated through threshold analysis	$23,965
Administration, Monitoring, and Adverse Event Management (except CRS) Costs Applied Cycles 1-2 (Pre-Infusion Costs for CAR-T Therapies)	$11,094	$11,086	$2,961
CRS-Related Treatment) *	$18,500 (grade 1) - $121,500 (grade 4)	$18,500 (grade 1) - $121,500 (grade 4)	N/A
Other Management-Related Costs per Cycle	$540		
Key Sources (see inputs section and supplement for all sources)	Munshi et al, 2020[5];Shah et al, 2020[25];Hari et al, 2020[32];Delforge et al, 2020[43]	Madduri et al, 2020[19];Legend Biotech, 2020[24];Hari et al, 2020[32];Delforge et al, 2020[43]	Gandhi et al, 2019[7];Mehra et al, 2020[31];Delforge et al, 2020[43]

CAR-T: chimeric antigen receptor T-cells, N/A: not applicable, NR: not reported.

* Applied to only those experiencing CRSs; for ide-cel approximately 80% had a grade 1-4 CRS event, whereas for cilta-cel approximately 95% had a grade 1-4 CRS event

Table 4.3. Key Model Inputs for Population Exposed to Four or More Lines of Therapy

Parameter	Belantamab mafodotin	Belantamab Comparator Market Basket
Progression-Free Survival, Median	2.8 Months	2.3 Months
Overall Survival, Median	13.7 Months	6.9 Months
Progression-Free on Therapy and Responding Utility	0.78	
Progressed Disease/Not Responding to Therapy Utility	0.71	
WAC Price per 28-Day Cycle*	$24,831	$19,260
Administration and Monitoring Costs per Cycle	$355	$1,250
Adverse Event Management Costs for First Two Cycles	$4,152	$2,813
Other Management-Related Costs per Cycle	$540	
Key Sources (see inputs section and supplement for all sources)	Delforge et al,2020[43];Lonial et al,2020[44]	Gandhi et al, 2019[7];Mehra et al, 2020[31];Delforge et al, 2020[43]

*Comparator market basket price assumes 15% discount for oral therapies based on Federal Supply Schedule pricing

Clinical Inputs

Base-case survival was derived from parametric fits to each intervention's available PFS and OS Kaplan-Meier curves.[19,44,45] Tables E.2.5 and E.2.6 delineate the evidence that was used to calculate transition probabilities. The model included any grade 3/4 adverse events that occur in 5% of patients for any of the treatments and comparators. Given the potentially significant impact of cytokine release syndrome on health care resource utilization and quality of life, we included all grades 1-4 for these adverse events and adjusted costs and quality of life estimates accordingly. The costs and disutility of adverse events were applied to the first two cycles for each intervention and comparator. After cycle 2 of the model, we applied a dose adjustment factor, assuming adverse events would be resolved with lower dosing of each therapy. Supplement Table E.2.8 lists the adverse events considered. Health state utilities were applied for each model health state to adjust for quality-of-life changes over time. Utilities were derived from publicly available sources.[43] Tables 4.2 and 4.3 show health utility values by line of therapy. Supplement Table E.2.9 describes the adverse event disutilities.

Economic Inputs

All costs used in the model were updated to 2020 US dollars using methods following the ICER reference case. The unit cost for each treatment is reported in Supplement Table E.2.10. The regimens used for each comparator treatment can be found in Supplement Table E.2.3 and E.2.4. We calculated threshold prices at $50,000 per QALY, $100,000 per QALY, $150,000 per QALY, and $200,000 per QALY for each CAR-T therapy given these therapies are investigational and initial price projections are not available. For each CAR-T therapy, the price to achieve a threshold of $100,000 per QALY was used in all subsequent sensitivity and scenario analyses. The wholesale acquisition

cost for belantamab mafodotin was used.[46] Comparator therapy pricing was based on WAC pricing with 15% discounts on oral therapies based on the Federal Supply Schedule. Costs associated with additional health care utilization that occurred from administration and monitoring, and post-treatment were included in the model. Supplement Table E.2.12 details the health care utilization unit costs used in the model and the evidence sources. AE costs were derived from reasonable treatment assumptions used in previous analyses mentioned as evidence sources in Supplement Table E.2.14.

4.3. Results

Base-Case Results

The total discounted costs, life years (LYs), quality-adjusted life years (QALYs), and equal value of life year gained (evLYG) over the lifetime time horizon are detailed in Tables 4.4 and 4.5. In the case of CAR-T therapies, given there is no price established, we do not present cost-effectiveness estimates but instead provide prices that meet various thresholds in tables 4.10 and 4.11. In the cohort of patients treated with three or more lines of therapy, ide-cel had discounted LYs, QALYs, and evLYG gained of 1.65, 1.25, and 1.34, respectively. Cilta-cel had discounted LYs, QALYs, and evLYGs gained of 4.48, 3.36, and 3.77, respectively. The CAR-T therapy comparator market basket cohort had discounted LYs, QALYs, and evLYGs gained of 0.68, 0.94, and 0.68, respectively. In the cohort of patients treated with four or more lines of therapy, the belantamab arm had a total discounted cost of approximately $243,000 with discounted LYs, QALYs, and evLYGs gained of 1.39, 1.00, 1.06, respectively. The belantamab comparator market basket had a total discounted cost of $202,000 with discounted LYs, QALYs, and evLYGs gained of 0.77, 0.56, and 0.56, respectively. We note that cost differences between belantamab and its comparator were mitigated by dose reduction and/or discontinuation due to adverse events for belantamab.

Table 4.4. Results for the Base-Case for Ide-cel Compared to Population Exposed to Three or More Lines of Therapy

Treatment	Time Spent in PFS State (months)	QALYs	Life Years	evLYGs
Ide-Cel	10.15	1.25	1.65	1.34
CAR-T Comparator Market Basket	5.38	0.68	0.94	0.68

CAR-T: chimeric antigen receptor T-cells, evLYG: equal-value of life years gained, QALYs: quality-adjusted life years gained, OS: overall survival, PFS: progression-free survival, TBD: to be determined.

Table 4.5. Results for the Base-Case for Cilta-cel Compared to Population Exposed to Three or More Lines of Therapy

Treatment	Time spent in PFS State (months)	QALYs	Life Years	evLYGs
Cilta-Cel	25.82	3.36	4.48	3.77
CAR-T Comparator Market Basket	5.38	0.68	0.94	0.68

CAR-T: chimeric antigen receptor T-cells, evLYG: equal-value of life years gained, QALYs: quality-adjusted life years gained, OS: overall survival, PFS: progression-free survival.

Table 4.6. Results for the Base-Case for Belantamab Compared to Population Exposed to Four or More Lines of Therapy

Treatment	Intervention Cost	Other non-intervention costs*	Total Cost	Time Spent in PFS State (months)	QALYs	Life Years	evLYGs
Belantamab	$145,000	$99,000	$243,000	[redacted]	1.00	1.39	1.06
Belantamab Comparator Market Basket	$109,000	$94,000	$202,000		0.56	0.77	0.56

evLYG: equal-value of life years gained, QALYs: quality-adjusted life years gained, OS: overall survival, PFS: progression-free survival.

*Other non-intervention costs include costs for monitoring, progressed treatment costs, physician visits, adverse event management (first two cycles only) and monthly laboratory costs for complete blood count and liver testing

Table 4.7 presents the incremental results from the base-case analysis, which include incremental cost-effectiveness ratios for incremental cost per LY gained, incremental cost per QALY gained, and incremental cost per evLYG gained. Only incremental results related to the cohort treated with four or more lines of therapy are included given the lack of pricing data available for the CAR-T therapies. In the cohort treated with four or more lines of therapy, total costs for the belantamab arm were approximately $40,000 greater than total costs for the comparator arm; gains in LYs, QALYs, and evLYGs were more than 0.62, 0.44, and 0.50 than that of the comparator arm. This resulted in an incremental cost-effectiveness ratio of approximately $93,000 per QALY gained, $67,000 per LY gained, $82,000 per evLYG gained, and $19,000 per additional PFS month gained for belantamab versus the comparator arm.

Table 4.7. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG gained	Cost per additional PFS month gained
Belantamab mafodotin	Belantamab Comparator Market Basket	$93,000 per QALY	$67,000 per LY	$82,000	$19,000

evLYG: equal-value of life years gained, QALY: quality-adjusted life year, LY: life years, TBD: to be determined.

Threshold Analyses

Tables 4.8 and 4.9 present the unit price needed for each therapy to reach commonly cited cost-effectiveness thresholds. The price needed to achieve these thresholds would be inclusive of both the manufacturer price and any potential hospital mark-up that may be applied. As above, we note that threshold prices differ substantially between the CAR-T therapies in part because of a paucity of available data on PFS and OS for cilta-cel.

Table 4.8. QALY-Based Threshold Analysis Results

	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY
Ide-Cel	N/A	N/A	$136,000	$167,000	$198,000	$230,000
Cilta-cel	N/A	N/A	$266,000	$422,000	$578,000	$734,000
Belantamab mafodotin	$8,277	[redacted]	$7,100	$8,400	$9,732	$11,000

N/A: not available, evLYG: equal-value life years gained, QALY: quality-adjusted life years gained, WAC: wholesale acquisition cost.

Table 4.9. evLYG-Based Threshold Analysis Results

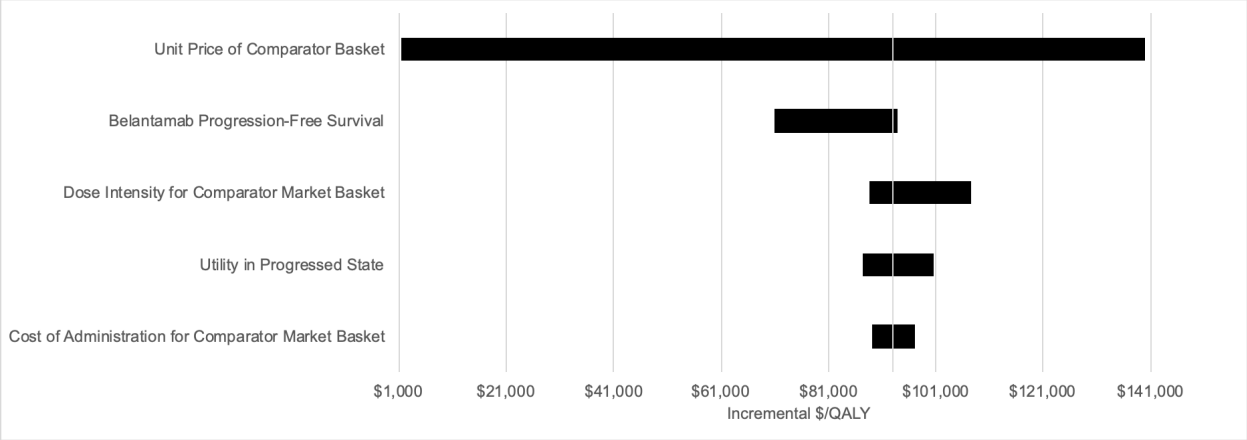
	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per evLYG	Unit Price to Achieve $100,000 per evLYG	Unit Price to Achieve $150,000 per evLYG	Unit Price to Achieve $200,000 per evLYG
Ide-Cel	N/A	N/A	$140,000	$177,000	$213,000	$249,000
Cilta-cel	N/A	N/A	$290,000	$470,000	$650,000	$829,000
Belantamab mafodotin	$8,277	[redacted]	$7,300	$8,800	$10,200	$11,700

N/A: not available, evLYG: equal-value life years gained, QALY: quality-adjusted life years gained, WAC: wholesale acquisition cost.

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 plausible parameter ranges). Figure 4.2 presents an example tornado diagram resulting from the one-way sensitivity analysis for belantamab versus triple-class comparators. When varying PFS, we assumed the same proportional relationship in terms of gains in OS. Key Drivers of model findings include the unit price of the comparator market basket of therapies, progression-free survival for the active interventions, and dose intensity for comparator market basket. This comparison was made after fixing the price of ide-cel to meet a threshold of $100,000 per QALY. Please see Supplement Section E4 for additional results from the one-way sensitivity analyses, including tornado diagrams for the two CAR-T therapies assuming the price to reach $100,000 per QALY.

Figure 4.2. Tornado Diagram for Belantamab



With noted uncertainty outside of that modeled, a probabilistic sensitivity analysis was conducted to assess variation across all model inputs with quantified uncertainty simultaneously and to vary the results over 5,000 iterations. Tables 4.10 and 4.11 present the probability of reaching certain willingness-to-pay thresholds for belantamab. A total of 74% of the iterations for belantamab versus the comparator were beneath a threshold of $150,000 per QALY gained. A total of 82% of the iterations for belantamab versus the comparator were beneath a threshold of $150,000 per evLYG gained. Sensitivity analyses for each CAR-T therapy are available in Supplement Section E4.

Table 4.10. Probabilistic Sensitivity Analysis Cost Per QALY Gained Results: Population Exposed to Four or More Lines of Therapy

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Belantamab	27%	48%	74%	95%

QALY: quality-adjusted life years gained

Table 4.11. Probabilistic Sensitivity Analysis Cost Per evLYG Gained Results: Population Exposed to Four or More Lines of Therapy

	Cost Effective at $50,000 per evLYG	Cost Effective at $100,000 per evLYG	Cost Effective at $150,000 per evLYG	Cost Effective at $200,000 per evLYG
Belantamab	28%	55%	82%	99%

evLYG: equal-value life years gained

Scenario Analyses

We ran two main scenario analyses: 1) a modified societal perspective (see section E5) and 2) a scenario analysis that adjusts the proportional relationship between PFS and OS for belantamab to be within a similar range as suggested by a recent synthesis of the evidence. Recent evidence synthesis in multiple myeloma suggest a proportional relationship between PFS and OS consistent with a three month gain in OS for every one month gain in PFS.[47] While both CAR-T therapies were within the range of these proportional relationships, evidence from the DREAMM-2 trial suggests a nearly five month gain for every one month gain in PFS. We ran a scenario analysis that adjusted the relationship between PFS and OS for belantamab to be consistent with prior published data. In this scenario, belantamab adjusted OS estimates were set at an approximate median of 9 months (vs. 13.7 months from the trial). As expected, this scenario increased the cost per QALY base-case estimate, in this case to over $200,000 per QALY (Table 4.12). Please see Supplement Section E5 for both scenario analyses.

Table 4.12. Incremental Cost-Effectiveness Ratios for Scenario Analysis 2

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG	Cost per Month of PFS Gained
Belantamab mafodotin	Belantamab Comparator Market Basket	$209,000	$150,000	$192,000	$18,000

evLYG: equal-value of life years gained, QALY: quality-adjusted life year, LY: life years, PFS: progression-free survival

Model Validation

We used several approaches to validate the model. First, we attempted multiple survival extrapolation techniques and compared estimates to findings from each intervention's most recent published paper or abstract to ensure outcomes were consistent with clinical evidence. Second, we presented preliminary results to manufacturers and clinical experts, and based on feedback from those groups, we refined data inputs or extrapolations as needed. Third, we varied model input parameters to evaluate face validity of changes in results. Finally, we compared model results to other cost-effectiveness findings in this therapy area.

Uncertainty and Controversies

There were important uncertainties and controversies relevant to generating model outcomes. Given that evidence was abstracted from single-arm studies, there were challenges when selecting the most appropriate comparator. In order to calculate incremental costs, risks, and benefits, we compared each therapy to a contemporaneous population of RRMM patients within the MAMMOTH observational study, i.e., a triple-class refractory cohort treated with three or more prior lines of therapy as a comparator to CAR-T therapies and a weighted average cohort treated with three and four or more lines of therapy as a comparator to belantamab. While we were unable to perform an indirect treatment comparison given absence of a common comparator and/or access to patient-level data, we estimated differences in outcomes such as median PFS and OS from recently published or presented indirect-treatment comparison evidence.[45] Advantages of using the MAMMOTH population as a comparator include a generalizable population in metropolitan areas, with academic medical centers treating patients with currently-recommended regimens. This allowed us to include not only survival evidence but also the mix of therapies used to estimate a monthly cost for each comparator. However, given that the treatment landscape changes dramatically over short time periods in RRMM, and the lack of an indirect treatment comparison against each therapy, caution should be used when interpreting cost-effectiveness estimates. A further complication in identifying a relevant comparator to belantamab was the mix of patients exposed to three or more lines of therapy and four or more lines of therapy. To address this limitation, we assumed a population mix from MAMMOTH to estimate weighted average outcomes and costs. Moreover, comparison across therapies were not estimated given differences in populations from each single-arm study. Other differences across populations indicate that any naïve comparison across interventions should not be made.

We acknowledge the challenge of interpreting incremental cost-effectiveness ratios for recently approved or pre-approval therapies when they are compared to existing high-cost comparators. Model outcomes were sensitive to the price of comparators as well as future health care costs for survivors. In sensitivity analyses, we varied the price of the market basket by the minimum and maximum estimated combination regimen in the market basket (which varied from approximately $17,000 to $37,000 per cycle of therapy). Therefore, interpretation of the cost-effectiveness of each therapy should include review of the one-way sensitivity analyses. In general, we found lower comparator prices led to less favorable cost-effectiveness estimates for the interventions.

The relationship between PFS and OS for each therapy was fairly consistent with prior meta-analysis evidence that suggests for every one month in PFS, patients gain approximately two to three months of OS. However, one exception to these estimates was the population in the key belantamab trial. The single arm study suggested that relationship was closer to a five month gain in OS for every one month gain in PFS. To address this limitation and the uncertainty around these estimates, we adjusted the relationship between PFS and OS for the belantamab arm to be

consistent with recent meta-analysis evidence.[47] When adjusting the PFS and OS relationship to a three month gain in OS for every one month gain in PFS, the cost per QALY estimates exceeded $200,000 per QALY. This suggests that as new evidence emerges, cost-effectiveness findings should be updated.

Specific to cilta-cel, interpretation of the cost-effectiveness findings should be noted as a very optimistic scenario. The evidence used in the model relies on limited clinical study evidence with a PFS estimate that has yet to reach its median and no reported estimate for OS. The only study with longer follow-up data was the Phase 1 LEGEND-2 study, which focused on a younger population who had received fewer previous lines of treatment. Therefore, extrapolations of survival are likely overestimates of the benefit of cilta-cel. We found through sensitivity analyses that at lower PFS and OS levels, the incremental cost-effectiveness ratios become less favorable.

Survival curve fitting relies on assumptions that may differ substantially between parametric models. There are further limitations to piecewise modeling approaches such as seemingly arbitrary cut-point intervals and modeled "jumps" in the hazard that may appear clinically unjustifiable.[48] We ensured our assumptions did not lead to invalid and unrealistic survival estimates, for example the tail of the extrapolated PFS curve crossing the tail of the OS curve. We relied on reported estimates of percentage alive and in PFS and OS states to further calibrate model estimates. Survival estimates were sensitive to base-case findings as shown in the one-way sensitivity analyses.

Finally, the model did not account for durability of response. Given we have very little data or extended follow-up on all three therapies, we were unable to assess whether re-treatment would improve outcomes beyond what was observed in trial evidence. For example, if CAR-T therapies require retreatment than these cost-effectiveness estimates would likely be altered.

4.4 Summary and Comment

The base-case findings from our analysis suggest that CAR-T therapies provide clinical benefit in terms of gains in QALYs and LYs over current treatment options for patients exposed to three or more lines of therapy. However, the benefits of ide-cel and cilta-cel should be reviewed separately given that evidence is still emerging. Threshold pricing suggests ide-cel would meet the $100,000 per QALY threshold at a price of around $170,000. Cilta-cel would meet this threshold at a price of around $420,000, but as noted above this is likely an optimistic estimate given the limited evidence currently available. Base-case findings for belantamab suggest current pricing is in line with commonly cited cost-effectiveness thresholds. However, given that belantamab' s reported relationship between PFS and OS appears to be higher than seen for other MM therapies, updated data should be generated and incorporated into future modeling analyses. Model findings across all interventions were sensitive to the cost of comparators, PFS and OS estimates, and overall health care costs for multiple myeloma patients.

5. 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 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. Categories of Contextual Considerations

Contextual Considerations	Relevant Information
Acuity of need for treatment of individual patients based on the severity of the condition being treated	The acuity of need for treatment is high. These heavily pre-treated MM patients have relatively short life expectancy without treatment, and their treatment options are currently limited.
Magnitude of the lifetime impact on individual patients of the condition being treated	MM has a moderate lifetime impact on individual patients. Many patients present with pre-symptomatic disease. While the disease becomes the primary focus of medical care for the heavily pre-treated subpopulation that is the focus of this review, this represents a relatively short proportion of the patient's lifespan.
New mechanism of action may provide benefits for patients who are unresponsive to current therapies	Anti-BCMA activity of both CAR-T therapies and belantamab suggests that these treatments may be efficacious for patients who are unresponsive to other treatments.

Table 5.2. Categories of Potential Other Benefits

Patients' ability to achieve major life goals related to education, work, or family life	For CAR-T therapy, suppressing the symptoms of MM appears to support patients' ability to achieve life goals. For belantamab, substantial side effects of treatment balance the decrease in disease effects, making it less clear whether belantamab supports patients' ability to achieve life goals.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	For CAR-T therapy, suppressing the symptoms of MM appears to support caregivers' ability to achieve life goals. For belantamab, substantial side effects of treatment balance the decrease in disease effects, making it less clear whether belantamab supports caregivers' ability to achieve life goals.
Patients' ability to manage and sustain treatment given the complexity of regimen	For CAR-T therapy, patient burden may be substantially less since much of the monitoring is done immediately after infusion and many patients appear to need no maintenance therapy. For belantamab, patient burden may be less since the studies focused on monotherapy. However, studies are underway focusing on combining belantamab with other treatments, which may negate patient burden advantages with belantamab.
Health inequities	Anti-BCMA therapies have the potential to worsen existing disparities. Therapies with high cost or high side effect burden (such as the current anti-BCMA therapies), as well as those requiring treatment at specialized centers, are often utilized at lower rates among historically disadvantaged populations.

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Using results from the cost-effectiveness model, we estimated the potential budgetary impact of each B-cell maturation antigen CAR-T cell and antibody drug conjugate therapy for refractory multiple myeloma. We used the price from the base-case analysis (if available) and three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for each intervention. Potential budget impact is defined as the total differential cost of using each new therapy rather than the relevant existing therapy for the treated population, calculated as differential health care costs (including intervention costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon.

The analysis included the estimated number of individuals in the US who would be eligible for each treatment. To estimate the size of the potential candidate populations for each intervention, we used the total number of adults 18 years and older with at a minimum triple-class refractory multiple myeloma. It is estimated that 140,000 Americans are living with MM.[1] Patients with MM are treated with CD38-targeting antibodies which are generally well tolerated and result in a response in approximately 30% of MM patients. Thus, we assumed that 70% of MM patients are refractory to CD38-targeted antibodies. Further, among MM patient's refractory to CD38-targeting antibodies, 54% are triple-refractory and 25% are penta-refractory.[7] Applying these sources results in estimates of 98,000 MM patient's refractory to CD38-targeting antibodies, with approximately 52,900 classified as triple-refractory and 24,500 classified as penta-refractory in the US. We assumed that 20% of these patients would initiate treatment in each of the five years, or approximately 10,580 triple-refractory patients per year (eligible for CAR-T therapy) and 4,900 penta-refractory patients per year (eligible for belantamab mafodotin). Because the two CAR-T therapies will be launched (if approved) within a short period of each other, the eligible population of approximately 10,580 triple-refractory patients per year was split in half between the two interventions (approximately 5,290 triple-refractory patients per year per CAR-T therapy).

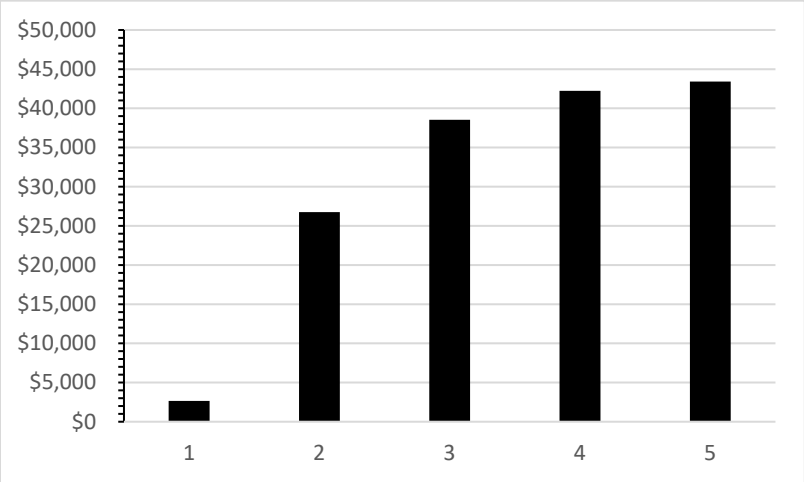
The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at select prices within 5 years without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For reports begun in 2019-2020, the five-year annualized ICER potential budget impact threshold that should trigger policy actions to manage access and affordability is approximately $819 million per year for new drugs. More detail on these methods can be found in the Section G of the Report Supplement.

7.2. Results

Belantamab mafodotin

Figure 7.1 depicts the cumulative per-patient potential budget impact calculations for belantamab mafodotin as compared to the market basket comparator, based on the wholesale acquisition cost. The average potential budgetary impact for belantamab mafodotin was approximately $2,700 per patient in year one, with cumulative net cost increasing in years two and three and beginning to plateau at year four, reaching approximately $44,400 per patient in year five.

Figure 7.1. Cumulative Net Cost per Patient Treated with Belantamab Mafodotin at Wholesale Acquisition Cost

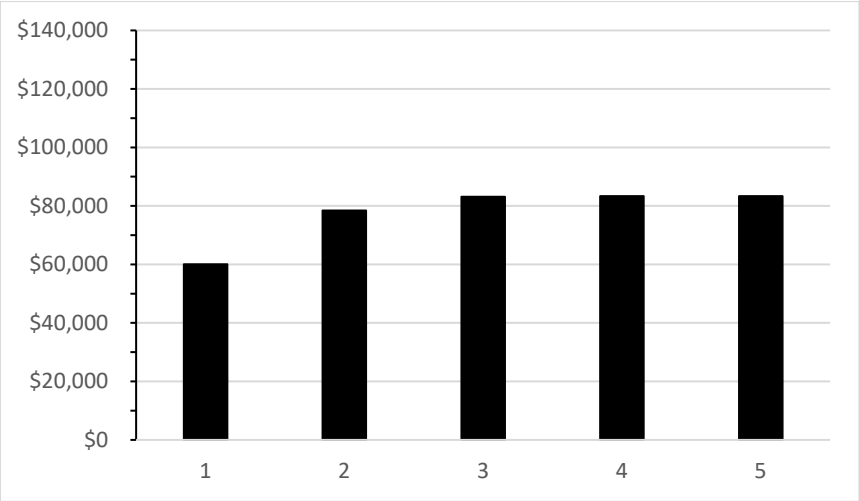


Assuming the wholesale acquisition cost (unit price of approximately $8,280), all eligible patients could be treated within five years (assuming 20% uptake each year), reaching 18% of the ICER budget impact threshold of $819 million per year over five years. Similarly using the prices to reach $150,000, $100,000, and $50,000 per QALY (unit prices of $7,730, $8,450, and $7,160, respectively), all eligible patients could be treated within five years (assuming 20% uptake each year) without crossing the ICER budget impact threshold.

Idecabtagene vicleucel

Figure 7.2 depicts the cumulative per-patient potential budget impact calculations for ide-cel as compared to the market basket comparator, assuming the threshold price to achieve $100,000 per QALY gained ($167,400). The average potential budgetary impact was approximately $60,000 per patient in year one, with an increase to approximately $80,000 per patient in years two through five.

Figure 7.2. Cumulative Net Cost per Patient Treated with Ide-cel at Price to Achieve $100,000 per QALY

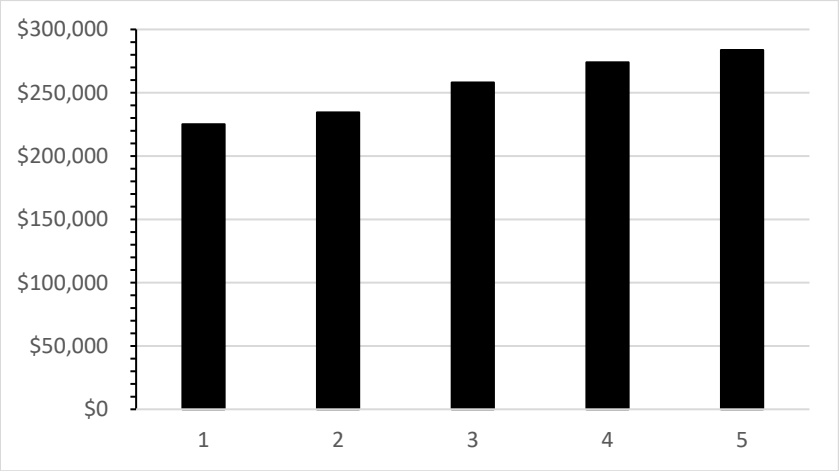


Assuming the price to achieve a threshold of $100,000 per QALY ($167,400), all eligible patients could be treated within five years (assuming 20% uptake each year), reaching 50% of the ICER budget impact threshold of $819 million per year over five years. Similarly using the prices to reach $150,000 and $50,000 per QALY (prices of approximately $198,800 and $136,100, respectively), all eligible patients could be treated within five years (assuming 20% uptake each year) without crossing the ICER budget impact threshold. At the price to achieve a threshold of $150,000 per QALY gained, 69% of the ICER budget impact threshold would be reached over five years.

Ciltacabtagene autoleucel

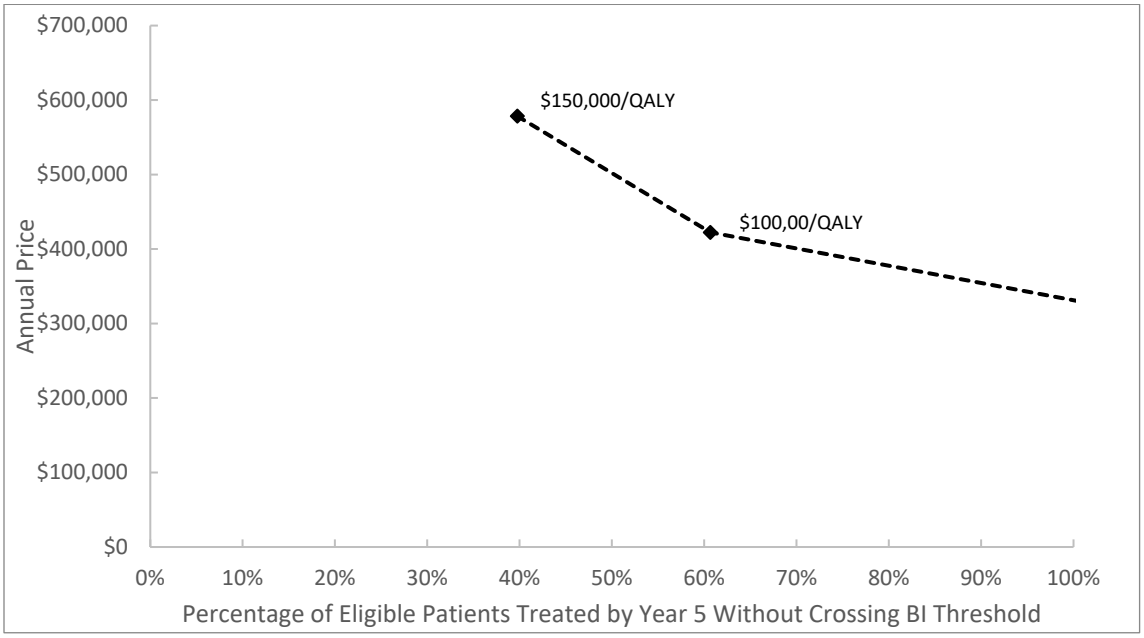
Figure 7.3 depicts the cumulative per-patient potential budget impact calculations for cilta-cel as compared to the market basket comparator, assuming the threshold price to achieve $100,000 per QALY gained ($422,400). The average potential budgetary impact was approximately $225,000 per patient in year one, with a steady increase each year to approximately $285,000 per patient in year five.

Figure 7.3. Cumulative Net Cost per Patient Treated with Cilta-cel at Price to Achieve $100,000 per QALY



Assuming the price to achieve a threshold of $100,000 per QALY ($422,400), 61% of the eligible patients could be treated within five years (assuming 20% uptake each year) before reaching the ICER budget impact threshold of $819 million per year over five years. At the price to achieve a threshold of $50,000 per QALY gained, all eligible patients could be treated within five years before reaching the ICER budget impact threshold.

Figure 7.4. Potential Budgetary Impact of Cilta-Cel in Triple Refractory Multiple Myeloma



Additional net costs per year are presented along with cumulative net costs in section G of the supplement for each of the three treatments.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Disease Definitions:

Triple-Class Refractory Multiple Myeloma: Multiple myeloma that has become refractory to the three common classes of myeloma medications: immunomodulators (I.e., lenalidomide), proteasome inhibitors (I.e., bortezomib) and a monoclonal antibody (I.e., daratumumab).

Quad Refractory Multiple Myeloma: Multiple myeloma that has become refractory to 4 commonly used myeloma medications. Most commonly, quad-refractory disease is refractory to: 1 anti-CD38 monoclonal antibody (most often daratumumab), 1 or 2 immunomodulators (most often lenalidomide +/- pomalidomide) and 1 or 2 proteasome inhibitors (most often bortezomib +/- carfilzomib).

Penta Refractory Multiple Myeloma: Multiple myeloma that has become refractory to 5 commonly used myeloma medications. Most commonly, penta-refractory disease is refractory to 2 immunomodulators (most often lenalidomide and pomalidomide), 2 proteasome inhibitors (most often bortezomib and carfilzomib) and an anti CD38 monoclonal antibody (most often daratumumab).

Extramedullary disease: Multiple myeloma in which plasma cells form tumors outside of the bone marrow. Extramedullary disease is a sign of more aggressive myeloma and portends a worse prognosis.

High-risk Cytogenetics: A chromosomal abnormality which has been shown to increase the risk of more aggressive disease.

Intervention Definitions:

CAR T-cell therapy: Chimeric antigen receptors (CAR's)_are artificial fusion proteins constructed to recognize specific antigens. CAR T-cells are T-cell lymphocytes that have been genetically modified to express these CAR's, so that these T-cells can identify and to marshal an immune response against cancer cells that produce these antigens. The focus of this review, ide-cel and cilta-cel utilize CAR T-cells that recognize the B-cell Maturation Antigen which appears to be expressed on most malignant plasma cells. CAR T-cell therapy starts with 1) harvesting of the patient's lymphocytes with leukapheresis. 2) Lymphocytes are then modified in the laboratory to express the CAR protein. 3) These modified lymphocytes are expanded to sufficient numbers and 4) the modified, expanded lymphocytes are reinfused back into the patient.

Ide-cel: Idecabtagene vicleucel is a chimeric antigen receptor (CAR) T-cell therapy based on the first anti-BCMA CAR developed at the National Cancer Institute (11D5-3-CD828Z), using a mouse origin anti-BCMA moiety. CARs are artificial fusion proteins that combine a BCMA-recognition domain with a costimulatory domain[49]. When reinfused into the patient, the genetically modified lymphocytes with the CAR proteins triggers a multi-pronged immune response, resulting in the destruction of cancer cells.

Cilta-cel: Ciltacabtagene autoleucel is a chimeric antigen receptor (CAR) T-cell therapy based on the camelid heavy chain only anti-BCMA CAR. The camelid heavy chain (LCAR-B38M) incorporates 2 BCMA recognition domains, which theoretically should increase the specificity for BCMA. Otherwise, cilta-cel has a similar mechanism of action and treatment logistics to ide-cel.[49]

Belantamab mafodotin: a first-in-class, antibody-drug immunoconjugate consisting of an anti-BCMA monoclonal antibody and an anti-cancer drug. Belantamab mafodotin binds to BCMA-antigens and kills multiple myeloma cells via a multimodal mechanism. Belantamab mafodotin induces cell apoptosis in addition to antibody-dependent cellular cytotoxicity (ADCC).[50,51]

Outcome definitions: Studies rely on the International Myeloma Working Group (IMWG) Uniform Response Criteria definitions for outcomes.[52]

Complete Response (CR): Negative immunofixation on serum and urine AND disappearance of any soft tissue plasmacytomas AND <5% plasma cells in the bone marrow.

Stringent Complete Response (sCR): Meets CR criteria AND normal free light chain ratio AND absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

Partial Response (PR):

> ≥ 50% reduction of serum M-protein AND reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 h
>
> If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria.
>
> If serum and urine M-protein are not measurable and serum free light chain assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%.
>
> In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.

Very Good Partial Response (vgPR): Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h

Overall Response Rate (ORR): Proportion of patients treated who had a partial response to treatment or better (PR + vgPR + CR + sCR)

Minimal Residual Disease (MRD): Small number of cancer cells that can remain after treatment. MRD status predicts relapse. In MM, MRD is assessed in patients with CR, via sensitive techniques such as next-generation flow cytometry or next-generation sequencing.[53]

B. Patient Perspectives: Supplemental Information

B1. Methods

ICER conducted a wide-ranging effort to engage patients and advocacy groups to develop an understanding of MM patient perspectives. We drew on experience from the prior ICER review of MM therapies in 2016, reaching out to patient advocacy groups and individual patients engaged in the previous review. Specifically, we had a series of conversations with the Cancer Support Community, who were able to provide us with invaluable insights into the experience of MM patients within their community. They also helped us engage with specific patients who were able and willing to speak with us. We also engaged with Patients for Affordable Drugs, who also helped us identify patients we could speak to about their experience. We purposefully tried to engage African American patients to elicit their experiences, since they are overrepresented in the MM population and may face disparities in diagnosis and access to care. We contacted the International Myeloma Foundation and the Black Women's Health Imperative for further guidance on reaching out to specific myeloma patients and advice on any relevant data resources to assess racial disparities in myeloma care. We connected with the Association of Community Cancer Centers and spoke with an expert who commented on the differences in access to new myeloma treatments between large academic medical centers and community cancer centers.

We had a series of conversations with individual MM patients, as well as one focus group discussion. Conversations were informed by a semi-structured interview guide which focused the conversation on several themes, including:

1. What is your experience with different treatments that you have tried?
    - What has worked, what has not?
    - Side-effects
    - Impact on daily life, family, work
2. What are the financial aspects of the treatments you have tried?
    - Any issues with insurance, paying for the treatment
3. Where have you received care (in what type of hospital), what doctors have you seen?
4. What are you hoping to get from any new treatments that become available?

5. What do you think are some key issues about patients' experience with multiple myeloma that are not being captured in major clinical studies or trials, including:

    - Symptoms and complications of disease
    - Impact of disease on function and quality of life
    - Side effects of treatment
    - Effects on caregivers and family members
    - Any other issues

6. For patients who have experience with CAR-T therapies:

    - How well did it work for you?
    - What were the side effects?
    - What was the impact like on daily life, family, work?
    - How was it like finding these treatments, how available or accessible do you think these are for patients?
    - Compared to other treatments you have received for multiple myeloma, what was your experience like? Specifically, how did it feel to be "off" treatment after you received the CAR-T infusion?
    - Have you required any follow-up after CAR-T infusion? If so, is this routine follow-up or for complications of treatment?

We had an iterative process, where emerging themes were incorporated into subsequent conversations to determine whether these themes were universally felt by all (or most) patients or were idiosyncratic to a single (or few) patient(s). Furthermore, patients submitted individual feedback and shared their experiences via the Patient Input Questionnaire on ICER's website.

After each of these conversations, patient comments were transcribed, collated, organized, and summarized. We drew upon the themes that emerged from our conversations and our summaries for the patient perspective sections of this report.

C. Clinical Guidelines

Due to the number of treatments that have recently become available, we focus on guidelines that have been published in the last 2 years.

National Comprehensive Cancer Network (NCCN) Multiple Myeloma, V4, May 2020[54]

The NCCN convened a panel of nationally recognized expert clinicians in the care of MM to develop a consensus statement on currently accepted approaches to treatment. While there are not specific recommendations for the triple/quad/penta refractory population that is the focus of our current review, they do provide recommendations on relapsed or refractory MM.

Recommendation 1 (MYEL-7): For relapsed patients, consider a) treatments for previously treated myeloma, b) clinical trial and c) allogeneic stem cell transplant.

Recommendation 2 (MYEL-7): For patients with refractory disease and lack of treatment options, refer to palliative care.

Recommendation 3 (MYEL-F, 3 of 3): The NCCN listed a wide range of therapeutic options for patients with relapsed, previously treated MM, representing the lack of clear evidence on the preferred ordering of treatments. Specifically, they listed 8 preferred regimens, 24 other recommended regimens and 6 regimens listed as "useful in certain circumstances". Most were triplet regimens and nearly all regimens included dexamethasone. In addition, bortezomib, pomalidomide, carfilzomib, daratumumab, ixazomib and elotuzumab were common components of listed regimens.

American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) Joint Clinical Practice Guideline for Multiple Myeloma, Apr 2019[55]

The American Society of Clinical Oncology and Cancer Care Ontario convened an expert panel of medical oncologists, surgeons, radiation oncologists, and patient advocates to conduct a review of the literature to develop evidence-based guidelines. While they did not address triple-class refractory patients, they did produce recommendations for myeloma patients with a first relapse.

Recommendation 7.3: Triplet therapy (3 agents including a steroid, and 2 of the following 3 classes: proteasome inhibitor, immunomodulator and monoclonal antibody) is preferred. While toxicity appears to be increased with triplet vs doublet therapy, triplet therapy leads to improved PFS, ORR and OS, even in older adults.

Recommendation 7.5: Prior therapies should be taken into consideration when selecting the treatment in patient with relapsed multiple myeloma. Patients who have been off of a particular medication for >1 year are likely to respond to a repeat course of that medication. However, patients who relapse <1 year after exposure to a medication are less likely to respond; thus, novel medications are recommended in these situations.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

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). The indication for belantamab mafodotin involves a population subset with somewhat more advanced disease (at least four prior lines of treatment) than those in the current Ide-cel and Cilta-cel trials (at least three prior lines). We therefore did not make any explicit comparisons between belantamab mafodotin and Idecabtagene vicleucel and Ciltacabtagene autoleucel, and we summarized evidence on relevant comparator therapies to match these population differences (see below). Data permitting, we included 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 (Ide-cel)
- Ciltacabtagene Autoleucel (Cilta-cel)
- Belantamab mafodotin

Comparators

We used 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 belantamab mafodotin study focused on a more refractory population, the comparator cohort for belantamab mafodotin differs from the comparator cohort for Ide-cel and Cilta-cel.

We compared the selected interventions to commonly used regimens in triple-class refractory populations as well as to palliative care (no active anti-cancer therapy). The comparator regimens include:

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

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 was derived from studies of any duration.

Settings

Evidence from all relevant settings were considered.

Table D1.1 PRISMA 2009 Checklist

		Checklist Items
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for relapsed and refractory multiple myeloma followed established best research methods.[56,57] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[58] The PRISMA guidelines include a checklist of 27 items, which are described further in Supplemental Table D1.1.

We searched MEDLINE and EMBASE. 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 https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/) Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/)

Table D1.2. Search Strategies for 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*

#	Search Term
1	Exp Multiple Myeloma/
2	("Multiple Myeloma" or "Multiple Myelomas" or "Myeloma, Multiple" or "Myeloma, Plasma cell" or "Plasma cell myeloma" or "Plasma cell myelomas" or "Myelomatosis" or "Kahler Disease" or "Myeloma" or "Myelomas").ti,ab OR (("relapsed" or "refractory" or "pretreated" or "high risk") and ("multiple myeloma")).ti,ab
3	1 or 2
4	("CAR T" or "CAR-T" or "chimeric antigen receptor" or "CAR-T cell" OR "Anti BCMA" or "anti-BCMA" or "CMA CAR-T" or "b-cell maturation antigen" OR "anti b-cell maturation antigen" OR "CD269").ti,ab
5	("blenrep" or "belantamab" or "belantamab mafodotin" OR "belantamab mafodotin-blmf" or "GSK2857916" or "GSK 2857916" OR "GSK-2857916" OR "gsk916" OR "gsk 916" or "gsk-916").ti,ab.
6	("bb2121" or "bb-2121" OR "bb 2121" or "idecabtagene vicleucel" or "ide-cel" OR "ide cel").ti,ab.
7	("JNJ-68284528" OR "JNJ68284528" OR "JNJ 68284528" OR "JNJ4528" OR "JNJ 4528" OR "LCAR-B38M" OR "cilta-cel" OR "cilta cel" OR "ciltacabtagene autoleucel").ti,ab.
	((("pomalidomide" or "pomalyst") and ("Cyclophosphamide" or "Cytoxan") and ("dexamethasone" or "decadron" or "Dexamethasone Intensol" or "Dexpak Taperpak" or "prednisone")) or (("Carfilzomib" or "Kyprolis") and ("pomalidomide" or "pomalyst") and ("dexamethasone" or "decadron" or "Dexamethasone Intensol" or "Dexpak Taperpak" or "prednisone")) OR (("Elotuzumab" OR "Empliciti") AND ("pomalidomide" OR "pomalyst") AND ("dexamethasone" OR "decadron" OR "Dexamethasone Intensol" OR "Dexpak Taperpak" or "prednisone")) OR (("Carfilzomib" OR "Kyprolis") AND ("Cyclophosphamide" OR "Cytoxan") AND ("dexamethasone" OR "decadron" OR "Dexamethasone Intensol" OR "Dexpak Taperpak" or "prednisone"))).ti,ab.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	animals not (humans and animals).sh.
12	10 not 11
13	limit 12 to English language
14	13 and ("chapter" OR "comment" OR "editorial" OR "letter" OR "note" OR "short survey" OR "review" OR "opinion").pt
15	13 not 14

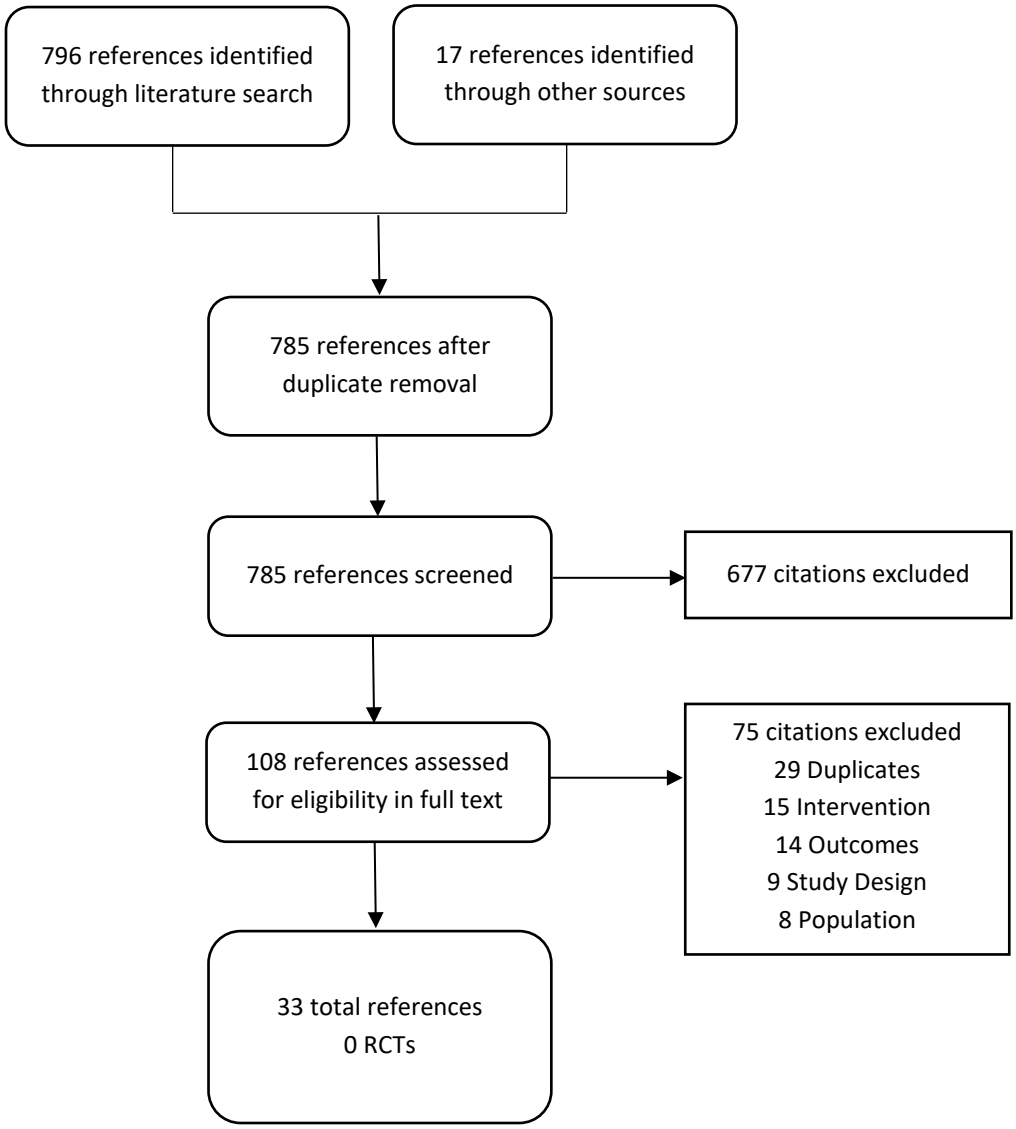
* Search ran on October 28, 2020.

Table D1.3. Search Strategy for EMBASE*

#	Search Term
#1	'multiple myeloma'/exp
#2	('multiple myeloma' OR 'refractory multiple myeloma' OR 'relapsed multiple myeloma' OR 'Kahler disease' OR 'morbus Kahler' OR 'myeloma multiplex' OR 'Myelomatosis' OR 'Myeloma' OR 'Myelomas' OR 'plasma cell myeloma' OR (('relapsed' OR 'refractory' OR 'pretreated' OR 'high risk') and 'multiple myeloma')):ti,ab
#3	#1 or #2
#4	('car t' OR 'CAR-T' OR 'chimeric antigen receptor' OR 'anti-BCMA' OR 'anti bcma' OR 'b cell maturation antigen' OR 'anti b-cell maturation antigen' OR 'CD269'):ti,ab
#5	'belantamab mafodotin'/exp OR 'belantamab'/exp
#6	('gsk2857916' OR 'gsk 2857916' or 'gsk-2857916' or 'gsk916' or 'gsk 916' OR 'gsk-916' OR 'belantamab' or 'belantamab mafodotin' or 'belantamab mafodotin-blmf' or 'blenrep'):ti,ab
#7	#5 OR #6
#8	'idecabtagene vicleucel'/exp
#9	('bb2121' OR 'bb 2121' OR 'bb-2121' OR 'ide-cel' OR 'idecabtagene vicleucel' OR 'ide cel'):ti,ab
#10	#8 OR #9
#11	'jnj 68284528'/exp or 'ciltacabtagene autoleucel'/exp
#12	('jnj 4528' OR 'jnj68284528' OR 'lcar-b38m' or 'cilta-cel' or 'cilta cel' or 'ciltacabtagene autoleucel'):ti,ab
#13	#11 OR #12
#14	((('pomalidomide') AND ('cyclophosphamide') AND ('dexamethasone' OR 'prednisone')) OR ('carfilzomib' AND 'pomalidomide' AND ('dexamethasone' OR 'prednisone')) OR ('elotuzumab' AND ' pomalidomide' AND ('dexamethasone' or 'prednisone')) OR ('carfilzomib' AND 'cyclophosphamide' AND ('dexamethasone' OR 'prednisone'))):ti,ab
#15	#3 AND (#4 OR #7 OR #10 OR #13 OR #14)
#16	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp OR 'animal model'/exp) NOT 'human'/exp
#17	#15 NOT #16
#18	#17 AND [English]/lim
#19	#18 AND ('chapter'/it or 'comment'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'review'/it OR 'opinion'/it)
#20	#18 NOT #19

* Search ran on October 28, 2020.

Figure D1. PRISMA flow Chart Showing Results of Literature Search for Idecabtagene vicleucel, Ciltacabtagene autoleucel, and Belantamab mafodotin



Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. 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. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to belantamab. 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 and Quality Assessment

Because we did not identify any comparative trials of the interventions, we did not assess the quality of the individual trials.

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 Figure 3.1 of the main report).[66,67]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for Ide-cel, Cilta-cel and belantamab mafodotin using the clinicaltrials.gov. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias. The primary concern is the lack of peer-reviewed, published data for the KarMMa and CARTITUDE-1 trials as well as the lack of head-to-head trials of the interventions compared to usual care.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (See Supplement D3) and synthesized qualitatively in the body of the review. Due to differences in study populations and limitations of study design (single-arm trials), outcomes are described for each trial separately.

D2. Additional Clinical Evidence

Evidence Base

Ide-cel

In addition to the pivotal phase II KarMMa trial described in the main report, we also identified a phase I trial of bb2121 (ide-cel), CRB-401.[15,16] CRB-401 was a phase 1 open-label single-arm dose-escalation and dose-expansion, multi-center US-based trial. The trial enrolled 62 adults (21 in the dose-escalation and 41 in the dose-expansion phase) who had previously received three lines of therapy (including an IMiD and a PI), or were refractory to both classes. The dose-expansion phase also required exposure to daratumumab and that patients be refractory to the last line of therapy. Patients underwent leukapheresis, bridging therapy during manufacturing, and lymphodepletion with fludarabine and cyclophosphamide prior to infusion with 50, 150, 450, or $800x10^6$ CAR-T cells in the dose-escalation phase and 150 to $450x10^6$ CAR-T cells in the expansion phase. 33 patients were analyzed in the original publication and 62 patients were analyzed in the updated analysis as of January 2020. [15,16] The primary outcome was safety. Secondary outcomes were overall response rate (ORR) and duration of response.

More details on both KarMMa and CRB-401 are provided in Table D3.1.

Cilta-cel

Both the pivotal phase Ib/II CARTITUDE-1 trial and phase I LEGEND-2 trial are described in the main report. More details on both trials are provided in Table D3.1**.**

Belantamab mafodotin

In addition to the pivotal phase II, open-label, two-arm, multicenter trial of belantamab (DREAMM-2), we identified a pooled post-hoc analysis of DREAMM-1 and DREAMM-2 and one expanded access study. Neither of the two additional studies had been published at the time of this report, and data was only available in form of conference abstracts/posters.

DREAMM-2: DREAMM-2, the pivotal trial of belantamab mafodotin in adults with triple-class refractory multiple myeloma, is an ongoing global, open-label, phase II randomized multicenter trial comparing the efficacy and safety of two doses of belantamab mafodotin (2.5 mg/kg and 3.4 mg/kg).[8] Patients were treated with intravenous belantamab mafodotin every three weeks until disease progression, or unacceptable toxicity occurred. Dosing delays or reductions were permitted for the management of adverse events. Efficacy and safety outcomes were assessed every three weeks after the first course of treatment had been administered.[8] Due to the risk for ocular toxicity of belantamab mafodotin, ophthalmic testing was required prior to each round of treatment.[8] To

further mitigate corneal events, patients were administered prophylactic corticosteroid eye drops as well as artificial tears.

Pooled post-hoc analysis: Trudel 2020 presented pooled tolerability and safety data from the DREAMM-1 and DREAMM-2 trials.[61] DREAMM-1 was an open-label phase I trial and included adult patients with RRMM, who had previously failed 3 or more lines of treatment, and were refractory to an alkylator, PI, and IMiD. DREAMM-2 has been described previously in this report. A total of 264 patients were randomized to either 2.5 mg/kg (N=103) or 3.4 mg/kg (N=161) every three weeks.[61] For the purpose of this review, we will only discuss the arm that received the FDA approved dose of 2.5 mg/kg.

The median age of patients was 65 years and 50% of the randomized patients were male. The study population also included a subset of RRMM patients at higher risk of more aggressive disease, including 40% with ISS stage III, 20% who exhibited extramedullary disease (EMD), and 27% with high-risk cytogenetic features. The median number of prior lines of therapy was 7 (range 3 to 21).

Expanded Access Program: This multicenter, observational study included 32 patients with RRMM who were treated under the expanded access compassionate care program at 6 Israeli multiple myeloma centers.[62] The primary outcome assessed was progression-free survival. Secondary outcomes included overall response rate, overall survival, as well as safety and tolerability.

Between July 2019 and February 2020, 32 patients were treated with at least one dose of belantamab mafodotin (median 3; range 1-11) and identified for inclusion in this study. Median follow-up duration was 5.7 months (range 0.5 – 13.8 months) and data were obtained from medical charts. A total of 13 patients received the 2.5 mg/kg dose, and 17 patients received the 3.4 mg/kg dose, respectively. Of note, this study did not present stratified results of the two separate doses, and therefore, the results presented contain both doses. Thus, these results should be synthesized cautiously with other studies which focused solely on patients receiving the FDA approved 2.5 mg/kg dose.

Patients included had a median age of 70 years, over half were male (59%), and roughly 20% were considered to have high-risk cytogenetics. The heavily pre-treated patients had received a median of 6 prior lines of treatments (range 3-11), with a majority having been previously exposed to bortezomib (94%), carfilzomib (74%), lenalidomide (91%), pomalidomide (87%), or daratumumab (97%). The overwhelming majority of included participants (97%) had also received an autologous stem-cell transplant.

Usual Care

The main report discusses the primary source of outcomes data to inform our comparison of the interventions to usual care, the MAMMOTH study[7]. Two additional retrospective studies were identified with sufficient numbers of triple-class refractory patients (Mehra 2020 and Goldsmith

2020). In Mehra 2020, patient data were abstracted from a US-based electronic health record system from January 2011 to October 2019.[31] A total of 251 patients with at least triple-class refractory multiple myeloma were included in the analysis. Of those, 73 (29%) were "penta-refractory". Primary outcomes were overall survival (OS), progression free survival (PFS), and time to next treatment (TTNT). In Goldsmith 2019, data from 58 patients were abstracted from health records at a single US-based academic center from January 2013 and August 2018.[30] Patients were either quad or penta-refractory and treated with at least one cycle of bendustamine/prednisone (BP) or dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP). Primary outcomes were PFS and OS. Additional information on the study design of the usual care studies are available in Table D3.18 and baseline characteristics are available in Table D3.19.

Efficacy

Ide-cel

Outcomes from the pivotal phase II trial of ide-cel (KarMMa) are described in the main report. In the phase 1 dose-escalation/expansion trial, CRB-401 (n=62), as of January 2020, median follow-up was 14.7 months, as-treated median PFS was 8.8 months (95% CI: 5.9-11.9 months), and as-treated median OS was 34.2 months (95% CI: 19.2-not estimable). As-treated ORR was 75.8% and as-treated stringent or complete response (sCR or CR) was 38.7%. As with KarMMa, ORR appeared to be dose-related in CRB-401. As-treated ORR in the higher dose ($450x10^6$) was 90% compared to 50% in the lower dose ($150x10^6$). As-treated median duration of response was 10.3 months overall (95% CI: 7.7-13.7 months).[16] More detailed outcomes from both the KarMMa and CRB-401 trial are provided in Table D3.3. Details on HRQoL outcomes from KarMMa are provided in Table D3.10.

Cilta-cel

The main report provides outcomes from both the pivotal phase Ib/II trial (CARTITUDE-1) and phase I trial (LEGEND-2 Xi'an study site). Detailed outcomes from both trials are provided in Table D3.4. Details on HRQoL outcomes from CARTITUDE-1 are provided in Table D3.10.

Belantamab mafodotin

DREAMM-2: The DREAMM-2 study reported ITT results; thus, the following results are all calculated on an ITT basis. At 13-month follow-up (data cut-off date: January 2020), 13 and 11 patients treated with 2.5 mg/kg belantamab mafodotin achieved PR and vgPR, respectively. The median duration of response was 11 months (95% CI: 4.2 to not reached). Time to initial response and time to CR was not reported.[9] Out of 97 participants, 59 had progressive disease at 6.3 months of follow-up.[8] More detailed outcomes from DREAMM-2 are provided in Table D3.5 and for additional data on HRQoL please refer to Table D3.10.

Expanded Access Program: Overall, the median duration of PFS achieved by DREAMM-2 trial participants was 2.6 months. Twelve out of 29 patients who were evaluable, achieved an ORR (with 3 participants achieving PR, 8 achieving VGPR, and one participant achieving CR). OS at 6 months was 68%. Statistical analyses were not reported. A subgroup analysis showed that ORR and PFS were comparable between patient who had been previously treated with ≤ 5 prior lines of treatments, and those who had previously received more than 5.[62] More detailed outcomes from the Expanded Access Program can be found in Table D3.17.

Usual Care

Outcomes from the retrospective MAMMOTH study are discussed in the main report[7]. We also identified two additional retrospective studies (Goldsmith 2020 and Mehra 2020) to inform our comparison of usual care to the interventions. In these trials, median PFS varied from 1.4 months to 4.8 months, median OS varied from 6.2 months to 11.0 months, and ORR was around 31%[30,31]. The patient populations of these studies varied, particularly in the percentage of patients with penta-refractory disease (29% in Mehra and 78% in Goldsmith). Additional outcomes data for the MAMMOTH study is available in Table D3.20 and for the two additional retrospective studies is available in Table D3.21.

Harms

Ide-cel

AEs from the pivotal phase II trial of ide-cel (KarMMa) are described in the main report. In the phase 1 dose-escalation/expansion trial, CRB-401 (n=62), the most frequent grade three or higher AEs were neutropenia (92%), leukopenia (61%), anemia (57%), and thrombocytopenia (57%). CRS was also common, occurring in 76% of patients and requiring tocilizumab in 21%. Sixty-nine percent had low to moderate (Grade 1 or 2) CRS, 7% had severe (Grade 3) CRS, and none had a grade 4 CRS. As in the KarMMa trial, risk of CRS in CRB-401 was dose-related. 92% of patients in the higher dose group ($450x10^6$) reported any grade CRS compared to 11% in the lower dose group ($150x10^6$). 82% of patients ≥65 experienced any grade CRS. As of the January 2020 cutoff date, 49 (79%) had discontinued due to progressive disease (58%), withdrawal by patient (10%), or death (10%).[63] More detailed safety data from both the KarMMa and CRB-401 trials are provided in Table D3.11.

Cilta-cel

The main report provides adverse events from the pivotal phase Ib/II trial of cilta-cel (CARTITUDE-1). In the phase I trial (LEGEND-2, Xi'an site) of cilta-cel, CRS was common (89.5%) and with 25 months of follow-up, 17 deaths (29.8%) were reported, 14 (24.6%) due to progressive disease and 2

(3.5%) due to AEs. Other important AEs included thrombocytopenia (49.1%) and neurotoxicity (1.8%).[24,26] Detailed safety data from both trials are provided in Table D3.12.

Belantamab mafodotin

DREAMM-2: Most dose delays, as well as dose reductions were due to keratopathy (45/51 and 24/33 patients, respectively).[9] Adverse events grade 3 or above were reported by 84% of patients treated with belantamab mafodotin, and the most commonly reported events were keratopathy (46%), thrombocytopenia (22%), and anemia (21%).

Median time to onset of the first corneal event was 37 days and lasted for a median duration of 86.5 days.[23] The occurrence of ocular toxicities increased with increasing number of doses; 25% of patients reported ocular toxicities after the first dose, 69% reported their first corneal event after by the fourth dose. Only two patients developed a corneal event subsequent to having received 4 doses. Overall, 24 patients reported experiencing blurred vision and 14 patients experienced dry eyes. CRS or neurotoxicity was not reported by any patient in the DREAMM-2 trial. Please refer to Table D3.13 for a more detailed description of safety data.

Pooled Analysis: Patients received a median of 3 courses of treatment with 2.5 mg/kg belantamab mafodotin (range 1 – 15). Most patients (98%) experienced at least one AE, of which 90% were considered treatment related. Serious adverse events (SAEs) were reported by 42 participants, with 13 reporting SAEs related to the study treatment. One participant died due a treatment-related SAE (sepsis). Keratopathy, which was only assessed in the DREAMM-2 trial, was the most commonly reported AE of any grade (66%), followed by anemia (26%) and thrombocytopenia (23%). Blurred vision and dry eye were reported by 20 and 12 patients, respectively. Grade 3/4 adverse events most frequently experienced by patients were keratopathy (27%), anemia (18%) and thrombocytopenia (17%). Four patients experienced grade 3/4 blurred vision, and no patients reported experiencing grade 3/4 dry eye. Generally, adverse events were managed by means of dose reductions (32%) and/or delays in treatment administration (51%). Keratopathy was the most frequently cited reason for delays or reduction in dosing by 45% and 24% of patients, respectively, as well as for treatment discontinuation (2%).

Expanded Access Program: Seventeen study participants (53%) were still receiving treatment at the time of data cut-off, while the remaining 15 had discontinued treatment. The most commonly cited reason for treatment discontinuation was progression or death (13 patients). Twenty out of 31 evaluable patients experienced ocular toxicity (keratopathy) of any grade, and eight reported grade ≥3 keratopathy. 62.5% of patients who experienced grade ≥3 ocular toxicity reported an improvement to grade ≤2 ocular toxicity, and one person discontinued treatment. Other adverse events commonly reported by ≥ 20% of study participants were thrombocytopenia (30%), neutropenia (22%), and infections (22%). Thrombocytopenia, neutropenia, and infections grade 3 or higher were reported by three, four, and three patients, respectively. Adverse events were

managed by means of dosing delays (13 patients) and dosing reductions (11 patients). Ocular toxicity was most commonly cited as requiring dosing delays or reductions (9 patients).

Please refer to Table D3.17 for a more detailed description of safety data for the Pooled Analysis and Expanded Access Program.

Subgroup Analyses

Ide-cel

Subgroup data from the pivotal phase II trial of ide-cel (KarMMa) are described in the main report. In the phase 1 dose-escalation/expansion trial, CRB-401, subgroup efficacy data was only available from the original publication (n=33).[15] At a median of 11.3 months of follow-up, as-treated ORR was 85% (28 patients had a response out of 33 infused). Response appeared to be dose-related, with the highest dose (>150x10^6 CAR-T cells) achieving the highest as-treated ORR (96%). Those with high cytogenetic risk (n=15) had a lower as-treated ORR (73%).[15]

More detailed subgroup data from both the KarMMa and CRB-401 trial are provided in Tables D3.6 and D3.7.

Cilta-cel

At the time of the report, subgroup data from the pivotal phase Ib/II trial (CARTITUDE-1) of cilta-cel was not available. In the phase I trial (LEGEND-2, Xi'an site) median PFS for the 17 patients with EMD was 8.1 months, compared with 19.9 months in the overall population.[26] Additional subgroup data is presented in Table D3.8.

Belantamab mafodotin

In DREAMM-2 the probability of PFS reaching a duration of 6 months or more was 35% for patients who had received 3 to 6 prior lines of treatment, and 30% for both those who had received 7 prior lines of therapy or more, and for patients with high-risk cytogenetics. Median OS, which was only reported for the subgroup considered to have high-risk cytogenetics, was 9.4 months. The probability of OS at 12 months was 45%.

At 12.4 months of median follow up time, 34% of the patients who had received three to six prior treatments achieved an overall response compared to 30% of patients who had received seven prior lines of treatments or more. Very good partial response was achieved by 17% of those who had received three to six prior lines of therapies and by 20% of those who had received seven or more.

ORR at nine months was achieved by 27% who had a high-risk cytogenetic risk profile, with 22% achieving a vgPR. Of the patients who had mild to moderate renal impairment, ORR was achieved

by 31.3% and 33.3%, respectively. The median duration of response achieved by patients who had been treated with three to six prior lines of therapy was 11 months versus 13.1 months for those who had received seven or more. The probability of a response lasting six months or longer was 63% and 73%, respectively. At nine months of follow-up, the median duration of response for the high-risk cytogenetics and renal impairment subgroups had not yet been reached. The probability of a response lasting for six months or more was 52% for the high-risk cytogenetics subgroup. For the renal impairment subgroups (mild to moderate), the probability of a duration of response of six months or more was not reported.

More patients with moderate renal impairment experienced serious adverse events (50%) compared to those with mild renal impairment (33.3%). Of those with high-risk cytogenetics, 46.3% reported experiencing SAEs. For more information regarding subgroup safety outcomes refer to Table D3.13.

Usual Care

As discussed in the main report, the retrospective studies we selected to represent the effectiveness of usual care did not provide sufficient information on the harms of the treatment regimens. See Table D3.22 for what safety data was available in two of the retrospective studies.[7,30] Therefore we selected representative prospective trials of commonly used treatments that make up components of the market basket of therapies in the economic model (Elo-Pom-Dex: elotuzumab-pomalidomide-dexamethasone, Car-Cy-Dex: carfilzomib-cyclophosphamide-dexamethasone, Ixa-Len-Dex: ixazomib-lenalidomide-dexamethasone).[33-35] In these prospective trials, treatment-related AEs were reported by 7-8% of patients. Discontinuation rates varied from 14 to 18%. Grade 3 or 4 AEs were common (57-74%). The most common grade 3 or 4 AEs were neutropenia (13-22%), anemia (9-11%), and thrombocytopenia (4-19%). Mortality ranged from 4.2% to 21.7%, however follow-up time varied (median 9 to 23 months). Deaths were most likely due to progressive disease (3.6-13.3%) followed by AEs (7.1-8.3%). Differences in harms between these regimes and that of the interventions should be interpreted with caution, however, as the trials were generally conducted in less heavily pre-treated populations (median of 2-3 prior therapies). See Table D3.23 for more details on harms of the usual care treatment regimens.

D3. Evidence Tables

Interventions

Table D3.1. Study Design: Interventions

Trial (NCT)	Study Design & Location	Treatment	Inclusion Criteria	Exclusion Criteria
Ide-cel				
KarMMa[5,17] (NCT03361748)	Phase II, open label, two-part, single-arm, multicenter trial N (enrolled) = 149 N (leukapheresed) = 140 N (treated) = 128 Location: Global	– 150 x 10^6 CAR+ T cells/kg – 300 x 10^6 CAR+ T cells/kg – 450 x 10^6 CAR+ T cells/kg *Single infusion*	– ≥ 18 years of age – Documented diagnosis of multiple myeloma – Received ≥ 3 prior treatment regimens, including a PI, IMiD, and an anti-CD38 antibody – Must have undergone ≥2 consecutive treatment cycles for each regimen – Must be refractory to last treatment regimen – ECOG status of 0-1 – Subjects must have measurable disease	– History of clinically relevant central nervous system pathology – Active or history of plasma cell leukemia – Solitary plasmacytomas or non-secretory myeloma without other evidence of measurable disease – Inadequate organ function – Ongoing treatment with chronic immunosuppressants – Previous allogeneic hematopoietic SCT; or treatment with any gene therapy-based therapy for cancer or investigational cellular therapy for cancer or BCMA targeted therapy – HIV, hepatitis B, hepatitis C – History of class III or IV, CHF or severe non-ischemic cardiomyopathy, history of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia within the previous 6 months – Secondary malignancies in addition to myeloma
CRB-401[15,63,64] (NCT02658929)	Phase I, open-label, single-group, multicenter trial N = 62 Location: United States	Dose-escalation phase (N=21): – 150 x 10^6 CAR+ T cells/kg – 450 x 10^6 CAR+ T cells/kg **50 x 10^6 and 800 x 10^6 CAR+ T cells/kg arms*	– 18 years of age and older – ≥3 lines of therapy (including a PI and IMiD) – ECOG status of 0-1 – Measurable disease or more than 30% bone	– Known CNS disease – Inadequate hepatic, renal, bone marrow function – Presence of active infection within 72 hours – Malignancies in addition to myeloma if the second malignancy has required therapy in the last 3 years or is not in complete remission – History of class III or IV CHF or non-ischemic cardiomyopathy,

Trial (NCT)	Study Design & Location	Treatment	Inclusion Criteria	Exclusion Criteria
		were not abstracted Expansion phase (N=41): – 150 x 10^6 CAR+ T cells/kg – 450 x 10^6 CAR+ T cells/kg	marrow plasma cells	unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the previous 6 months – HIV – Plasma cell leukemia or clinically significant amyloidosis
Cilta-cel				
CARTITUDE-1[6,20] (NCT03548207)	Phase Ib/II, single-group, open-label, multi-center study N (enrolled) = 126 N (apheresed) = 113 N (treated) = 97 Location: Japan, United States	Target dose: – 0.75 × 10^6 CAR+ T cells/kg (Range: 0.5–1.0 × 10^6) Median Dose: – 0.71 x 10^6 CAR+ T cells/kg (Range: 0.51-0.95 x 10^6) *Single infusion*	– ≥ 18 years of age – Documented MM diagnosis per IMWG criteria – ECOG status ≤1 – Measurable disease – Previously received ≥ 3 therapies (including PI, IMiD, anti-CD38 antibody therapy) or are double refractory to an IMiD and PI – Documented evidence of progressive disease per IMWG criteria or within 12 months of most recent therapy	– Prior CAR-T treatment directed at any target – Prior therapy that is targeted to B-cell maturation antigen (BCMA) – NYHA stage III or IV CHF; myocardial infarction or CABG within 6 months; history of clinically significant ventricular arrhythmia or unexplained syncope; history of severe non-ischemic cardiomyopathy; impaired cardiac function – Received a cumulative dose of corticosteroids equivalent to >= 70 mg of prednisone within 7 days prior to apheresis – Received an allogenic SCT within 6 months or an autologous SCT within 12 weeks – History of CNS involvement or clinical signs of meningeal involvement of multiple myeloma
LEGEND-2[22,65] (NCT03090659)	Phase I, open-label, single-group, multicenter trial N = 74 Location: China	(Xi'an site) Median dose: – 0.5 × 10^6 CAR+ T cells/kg (Range: 0.07 - 2.1 × 10^6) (Changzheng, Jiangsu, Ruijin	– 18-75 years of age – Documented initial diagnosis of multiple myeloma according to IMWG diagnostic criteria	– NYHA Stage III-IV CHF, myocardial infarction, or CABG ≤6 months prior – History of ventricular arrythmia or unexplained syncope – Impaired cardiac function (LVEF <45%) – Systemic corticosteroid therapy of greater than 5 mg/day of prednisone (or equivalent dose

Trial (NCT)	Study Design & Location	Treatment	Inclusion Criteria	Exclusion Criteria
		sites) Mean dose: –0.7 x 10^6 CAR+ T cells/kg *3 separate infusions within 7 days (One clinical site administered the treatment in one single-dose)*	– Measurable disease at screening – Received at least 3 prior lines of treatment for multiple myeloma (incl. PI and/or IMiD) – Documented disease progression during/within 12 months of most recent anti-myeloma therapy – ECOG status of 0 -2	of another corticosteroid) within 2 weeks – Received autologous SCT within 12 weeks – Received allogeneic SCT
Belantamab mafodotin				
DREAMM-2[8,66] (NCT03525678)	Phase II, open-label, multicenter study N (total) = 196 N (2.5mg/kg dose) = 97 Location: Global	2.5 mg/kg every three weeks *The studied 3.4 mg/kg dose was not approved by the FDA and will not be presented here*	– ≥ 18 years of age – Confirmed relapsed or refractory multiple myeloma according to IMWG – ECOG status of 0-2 – Received ≥3 previous lines of anti-myeloma treatments – Refractory to an PI and IMiD, refractory and or intolerant to an anti-CD38 monoclonal antibody – Autologous SCT ineligible or transplantation >100 days – Adequate organ system function	– Previous BCMA therapies, systemic high-dose corticosteroids, or investigational drug – Received allogeneic SCT – Current corneal epithelial disease (except mild punctate keratopathy) – Active renal condition; active mucosal or internal bleeding – POEMS syndrome

BCMA: B-cell maturation antigen, CABG: coronary artery bypass graft, CAR+: chimeric antigen receptor positive, CHF: congestive heart failure, CNS: central nervous system, ECOG: Eastern Cooperative Oncology Group, IMWG:

International Myeloma Working Group, IMiD: immunomodulatory drug, kg: kilogram, LVEF: left ventricular ejection fraction, mg: milligram, N: total number, NYHA: New York Heart Association, PI: proteasome inhibitor, POEMS: polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes, SCT: stem cell transplant

Table D3.2. Baseline Characteristics: Ide-cel, Cilta-cel, and Belantamab mafodotin

Intervention		Ide-cel		Cilta-cel			Belantamab
Trial		KarMMa[5]	CRB-401[15,63]	CARTITUDE-1[6]	LEGEND-2[22] Xi'an	LEGEND-2[22] Changzheng, Ruijin, Jiangsu	DREAMM-2[8]
Arms		Overall	Overall	0.71x10^6 CAR+ T cells/kg	0.5 × 10^6 CAR+ T cells/kg	0.71x10^6 CAR+ T cells/kg	Belantamab mafodotin (2.5 mg/kg)
N		128	62**	97	57	17	97
Age, Median Years (Range)		61.0 (33.0-78.0)	61 (NR)	61.0 (43.0-78.0)	54.0 (27.0-72.0)	55.1 (35.0-73.0)	65.0 (IQR: 60-70)
Male, n (%)		76 (59.4)	21/33 (63.6)	57 (58.8)	34 (59.6)	11 (64.7)	51 (52.6)
Race, n (%)	White	NR	NR	NR	NR	NR	72 (74.2)
	Black						16 (16.5)
Time since Diagnosis, Median Years (Range)		6 (1–18)	5 (1–36); N=33	5.9 (1.6-18.2)	4.0 (1.0-9.0)	NR	5.5 (IQR: 4.0-7.0)
Age at Diagnosis, Mean Years (SD)		NR	NR	NR	NR	NR	NR
Tumor BCMA Expression*, n (%)		109 (85.0)	23/33 (69.7)	57 (91.9)	NR	16 (94.1)	NR
High Risk Population, n (%)	Extramedullary Disease	50 (39.1)	9/33 (27.2)	13 (13.4)	17 (29.8)	NR	22 (22.7)
	Received Bridging Therapy Prior to Lymphodepletion	112 (87.5)	14/33 (42.4)¤	73 (75.2)	NR		NR
	High Cytogenetic Risk	45 (35.2)	15/33 (45.5)§	23 (23.7)	NR		41 (42.3)
	High Tumor Burden	65 (50.8)	16/33 (48.5)	NR	NR		NR
	ISS Disease Stage III	21 (16.4)	8/33 (24.2)	NR	21 (36.8)		42 (43.3)
	>1 Treatment Regimen per Year	60 (46.9)	NR	NR	NR		NR
Number of Prior Regimens, Median (Range)		6 (3-16)	7 (3–23); N=33	6 (3-18)	3 (1-9)	4 (3-11)	7 (3-21)
Triple-exposed, n (%)		128 (100)	62/62 (100)	97 (100)	NR	17 (100)	97 (100)

Intervention		Ide-cel		Cilta-cel			Belantamab
Trial		KarMMa[5]	CRB-401[15,63]	CARTITUDE-1[6]	LEGEND-2[22] Xi'an	LEGEND-2[22] Changzheng, Ruijin, Jiangsu	DREAMM-2[8]
Arms		Overall	Overall	0.71x10^6 CAR+ T cells/kg	0.5 × 10^6 CAR+ T cells/kg	0.71x10^6 CAR+ T cells/kg	Belantamab mafodotin (2.5 mg/kg)
Triple-refractory, n (%)		108 (84.0)	NR	85 (87.6)	NR	NR	97 (100)
Penta-exposed, n (%)		NR	26/33 (78.8)	81 (83.5)	NR	7 (41.2)	[redacted]
Penta-refractory, n (%)		33 (26.0)	6/33 (18.2)	41 (42.3)	NR	NR	
Anti-CD38 Ab-refractory, n (%)		120 (94.0)	NR	96 (99.0)	NR	NR	97 (100)
Prior Therapies Received, n (%)	Bortezomib	NR	33/33 (100)	NR	39 (68.4)	14 (82.4)	95 (97.9)
	Carfilzomib		30/33 (90.9)		1 (1.8)	2 (11.8)	74 (76.3)
	Lenalidomide		33/33 (100)		25 (43.9)	10 (58.8)	97 (100)
	Pomalidomide		31/33 (93.9)		2 (3.6)	1 (5.9)	89 (91.8)
	Daratumumab		56/62 (90.0)		NR	NR	97 (100)
	Isatuximab		NR		NR	1 (5.9)	3 (3.1)
Refractory to Prior Therapies, n (%)	Bortezomib	NR	20/33 (60.6)	NR	NR	NR	74 (76.3)
	Carfilzomib		19/33 (57.6)	63 (64.9)			63 (64.9)
	Lenalidomide		24/33 (72.7)	NR			87 (89.7)
	Pomalidomide		26/33 (78.8)	81 (83.5)			84 (86.6)
	Daratumumab		48/62 (77.0)	NR			97 (100)
	Isatuximab		NR	NR			3 (3.1)
D/C Last Line of Therapy due to Refractoriness, n (%)		128 (100)[#]	21/33 (63.6)[‡]	96 (99.0)	NR	NR	NR
Received Autologous SCT, n (%)	1	120 (94.0)	32/33 (97.0)	87 (89.7)	10 (17.5)	8 (47.1)	[redacted]
	≥1	44 (34.0)					
EORTC QLQ-C30, Mean Score (SD)	Fatigue	39.3 (24.4[†])	NR	NR	NR	NR	NR
	Pain	39.9 (28.1[†])					
	Physical Functioning	69.4 (25.1[†])					

Intervention		Ide-cel		Cilta-cel			Belantamab
Trial		KarMMa[5]	CRB-401[15,63]	CARTITUDE-1[6]	LEGEND-2[22] Xi'an	LEGEND-2[22] Changzheng, Ruijin, Jiangsu	DREAMM-2[8]
Arms		Overall	Overall	0.71x10^6 CAR+ T cells/kg	0.5 × 10^6 CAR+ T cells/kg	0.71x10^6 CAR+ T cells/kg	Belantamab mafodotin (2.5 mg/kg)
	Global Health/QoL	60.7 (20.6†)					
EORTC QLQ-MY20	Disease Symptoms	32.4 (24.1)†	NR	NR	NR	NR	NR
	Side Effects	82.0 (15.3)†					
ECOG PS, n (%)	0	58 (45.0)	10/33 (30.3)	0 (0)#	21 (36.8)	17 (100)#	97 (100)#
	1	68 (53.0)	21/33 (63.6)	97 (100)#	27 (47.4)		
	2	3 (2.0)	2/33 (6.1)		9 (15.8)		
Data not reported for the following baseline characteristics: Height, weight, D/C last line of therapy due to side effects							

BCMA: B-cell maturation antigen, CAR+: chimeric antigen receptor positive, ECOG PS: Eastern Cooperative Oncology Group performance status, EORTC: European Organization for Research and Treatment of Cancer, D/C: discontinued, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, SCT: stem cell transplant, SD: standard deviation, QLQ: Quality of Life questionnaire

* Defined as ≥50% BCMA+.

† Data are digitized and should be interpreted with caution.

‡ Progressive disease during most recent line of therapy.

§ Defined by the presence of the following abnormalities: del(17p), t(4;14), or t(14;16).

Assumption made based on study protocol.

¤ Administered after leukapheresis and before lymphodepletion.

** N of 62 represents the entire treated CRB-401 population, N of 33 represents the first 33 patients to received Ide-cel treatment within the population.

Table D3.3. Efficacy Outcomes: Ide-cel

Trial		KarMMa[5]				CRB-401[63]		
Arms		150x10^6 CAR+ T cells/kg	300 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall	150 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall
N (as-treated)		4	70	54	128	18	38	62[#]
Median Follow-Up		13.3 Months				14.7 Months		
Response	Median Time to Initial Response, Months (Range)	NR	NR	NR	1 (0.5-8.8)	NR	NR	1 (0.5-3.0); N=33
	Median Time to CR, Months (range)	NR	NR	NR	2.8 (1.0-11.8)	NR	NR	NR
	Median Duration, Months (95%CI)	NR (2.8, NE)[*]	9.9 (5.4, 1.1.0)	11.3 (10.3, 11.4)	10.7 (9.0, 11.3)	13.7 (2.9, 39.6)	10.0 (6.3, 14.8)	10.3 (7.7, 13.7)
	ORR, n (%); [95%CI]	2 (50.0)	48 (69.0)	44 (82.0)	94 (73.4); [65.8, 81.1]	9 (50.0); NR	34 (89.5)	47 (75.8); NR
	sCR/CR, n (%)	1 (25.0)	20 (29)	21 (39.0)	42 (33.0)	7 (38.9)	14 (36.8)	24 (38.7)
	vgPR, n (%)	1 (25.0)	10 (14.0)	14 (26.0)	25 (19.5)	7 (38.9)	30 (78.9)	40 (64.5)
	PR, n (%)	0 (0)	18 (26.0)	9 (17.0)	27 (21.0)	NR	NR	NR
Overall Survival	Median Duration, Months (95%CI)	NR	NR	NR	19.4 (18.2, NE)	NE (10.8, NE)	34.2 (23.2, NE)	34.2 (19.2, NE)
	OS at 3 Months, n (%)				NR (95)[†]	NR	NR	NR
	OS at 6 Months, n (%)				NR (89)[†]	NR	NR	NR
	OS at 9 Months, n (%)				NR (84)[†]	NR	NR	NR
	OS at 12 Months, n (%)				NR (80)[†]	NR	NR	NR
Progression -Free Survival	Median Duration, Months (95%CI)	2.8 (1.0, NE)	5.8 (4.2, 8.9)	11.3 (8.8, 12.4)	8.8 (5.6, 11.6)	4.5 (2.0, 12.0)	9 (7.2, 12.2)	8.8 (5.9, 11.9)
	PFS at 3 Months, n (%)	NR (55.0)[†]	NR (82.0)[†]	NR (86.0)[†]	NR (80.0)[†]	NR	NR	NR
	PFS at 6 Months, n (%)	NR (34.0)[†]	NR (55.0)[†]	NR (72.0)[†]	NR (56.0)[†]	NR	NR	NR
	PFS at 9 Months, n (%)	NR (34.0)[†]	NR (47.0)[†]	NR (69.0)[†]	NR (48.0)[†]	NR	NR	NR
	PFS at 12 Months, n (%)	NR (34.0)[†]	NR (39.0)[†]	NR (58.0)[†]	NR (38.0)[†]	NR	NR	NR
MRD-negativity, n (%); [95%CI]		1 (25.0)[§]; [0.6, 80.6]	17 (24.0)[§]; [14.8, 36.0]	15 (28.0)[§]; [16.5, 41.6]	33 (26.0)[§]; [18.5, 34.3]	NR	NR	30/37 (81.0)[‡]

Trial		KarMMa[5]				CRB-401[63]		
Arms		150x10^6 CAR+ T cells/kg	300 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall	150 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall
Median peak CAR-T cell Expansion, Days (SE)		14 (NR)	11 (NR)	11 (NR)	11 (NR)	NR	NR	NR
CAR-T cells detectable	At 6 Months, n (%)	NR	NR	NR	29/49 (59.2)	NR	NR	13/23 (57.0)
	At 12 Months, n (%)				4/11 (36.4)			2/10 (20.0)
Disease Progression, n (%)		NR	NR	NR		NR	NR	36/62 (58.0)

95% CI: 95% confidence interval, CAR: chimeric antigen receptor, CAR+: chimeric antigen receptor positive, CR: complete response, kg: kilogram, MRD: minimal residual disease, n: number, N: total number, NE: not estimable, NR: not reported, ORR: overall response rate, PFS: progression-free survival, PR: partial response, sCR: stringent complete response, SE: standard error, vgPR: very good partial response.

* Due to small N.

† Data are digitized and should be interpreted with caution.

‡ Evaluable patients.

§ Patients with complete response or better.

N of 62 represents the entire treated CRB-401 population, N of 33 represents the first 33 patients to received Ide-cel treatment within the population.

Table D3.4. Efficacy Outcomes: Cilta-cel

Trial		CARTITUDE-1[6,19]	LEGEND-2[24,26] Xi'an	LEGEND-2[24,67] Changzheng, Ruijin, Jiangsu
Arms		**Overall**	**0.5x10^6 CAR+ T cells/kg**	**0.7x10^6 CAR+ T cells/kg**
N (as-treated)		97	57	17
Median Follow Up		12.4 Months	25 Months	26 Months
Response	**Median Time to Initial Response, Months (Range)**	1 (0.9-8.5)	1.0 (0.4-3.5)	1.0 (NR)
	Median Duration, Months (95%CI)	Not reached‡	27 (NR)	NR
	ORR, n (%); [95%CI]	94 (96.9)	50 (87.7); [76.0, 95.0]	15 (88.2); [64.0, 99.0]
	sCR, n (%)	65 (67.0)	NR	NR
	CR, n (%)	0 (0)	42 (73.7)	14 (82.4)
	vgPR, n (%)	90 (92.8)	2 (3.5)	1 (5.9)
	PR, n (%)	4 (4.1)	6 (10.5)	NR
Overall Survival	**Median Duration, Months (95%CI)**	Not reached‡	36.1 (26.4, NE)	Not reached¤
	At 3 months, n (%)	NR	NR (97.8)†	NR (89.1)†
	At 6 months, n (%)	NR (93.8)‡	NR (92.4)†	NR (89.1)†
	At 9 months, n (%)	NR	NR (81.5)†	NR (89.1)†
	At 12 months, n (%)	NR (88.5)	NR (78.3)†	NR (82.3)
Progression-Free Survival	**Median Duration, Months (95%CI)**	Not reached	19.9 (9.6, 31.0)	18.0 (NR)
	At 3 months, n (%)	NR (98.0)†	NR (86.4)†	NR (95.0)†
	At 6 months, n (%)	NR (87.5)†	NR (81.2)†	NR (83.4)†
	At 9 months, n (%)	NR (80.3)†	NR (65.3)†	NR (75.6)†
	At 12 months, n (%)	n (76.6)	NR (60.1)†	5/9 (57.0)
MRD-negativity, n (%)		53/57 (93.0)#	39/42§ (92.9)¤	NR
Median Peak CAR-T Cell Expansion, Days (Range)		13 (9-55)	NR	NR
Disease Progression, n (%)		NR	18/50†† (36.0)¤	11 (64.7)

Trial	CARTITUDE-1[6,19]	LEGEND-2[24,26] Xi'an	LEGEND-2[24,67] Changzheng, Ruijin, Jiangsu
Arms	**Overall**	**0.5x10^6 CAR+ T cells/kg**	**0.7x10^6 CAR+ T cells/kg**
Data not reported for the following efficacy outcomes: Median time to complete response, CAR-T cells detectable at 6 and 12 months			

95% CI: 95% confidence interval, CAR: chimeric antigen receptor, CAR+: chimeric antigen receptor positive, CR: complete response, kg: kilogram, MRD: minimal residual disease, n: number, N: total number, N/A: not available, NE: not estimable, NR: not reported, ORR: overall response rate, PFS: progression-free survival, PR: partial response, sCR: stringent complete response, SE: standard error, vgPR: very good partial response.

* 95.7% confidence interval.

† Data are digitized and should be interpreted with caution.

‡ 8.8-month follow up time.

§ Patients with complete response.

Evaluable patients.

¤ 12-month follow up time.

†† Patients with partial response or better.

Table D3.5. Efficacy Outcomes: Belantamab mafodotin

Trial		DREAMM-2[9]
Arms		**2.5 mg/kg**
N (ITT)		97
Median Follow Up		13 Months
Response	**Median Duration, Months (95%CI)**	11.0 (4.2, not reached)
	ORR, n (%); [95%CI]	31 (32.0); [21.7, 43.6]*
	sCR, n (%)	2 (2.1)
	CR, n (%)	5 (5.2)
	vgPR, n (%)	11 (11.3)
	PR, n (%)	13 (13.4)
Overall Survival	**Median Duration, Months (95%CI)**	13.7 (9.9, not reached)
	At 3 Months, n (%)	63/77 (82.2)†
	At 6 Months, n (%)	48/66 (72.6)†
	At 9 Months, n (%)	37/66 (63.0)†
	At 12 Months, n (%)	28/49 (56.9)†
Progression-Free Survival	**Median Duration, Months (95%CI)**	2.8 (1.6, 3.6)
	At 3 Months, n (%)	[redacted]
	At 6 Months, n (%)	[redacted]
	At 9 Months, n (%)	[redacted]
	At 12 Months, n (%)	[redacted]
Disease Progression, n (%)		59 (60.8)‡
Data not reported for the following efficacy outcomes: Median time to complete response, CAR-T cells detectable at 6 and 12 months, median time to initial response, MRD-negativity		

95% CI: 95% confidence interval, ITT: Intention to treat, CR: complete response, kg: kilogram, mg: milligram, MRD: minimal residual disease, n: number, N: total number, N/A: not available, NE: not estimable, NR: not reported, ORR: overall response rate, PFS: progression-free survival, PR: partial response, sCR: stringent complete response, SE: standard error, vgPR: very good partial response

* 95.7% confidence interval.

† Data are digitized and should be interpreted with caution.

‡ 6.3-month follow-up time.

Table D3.6. Subgroup Efficacy Data: Ide-cel

Trial	KarMMa[36,37]							
Subgroups	High Risk						Elderly Patients	
	Extramedullary Disease	Received Bridging Therapy	High Cytogenetic Risk	High Tumor Burden	ISS Disease Stage III	>1 Treatment Regimen per Year	≥ 65 years	≥ 70 years
Median Follow-Up	11.3 Months							
N (as-treated)	50	112	45	65	21	60	45	20
ORR, n (%), [95%CI]	35 (70.0); [55.4, 82.1]*	80 (71.0); [62.1, 79.6]	31 (69.0); [55.4, 82.4]	46 (71.0); [58.2, 81.4]*	10 (48.0); [25.7, 70.2]	39 (65.0); [51.6, 76.9]	38 (84.4); [70.5, 93.5]	18 (90.0); [76.9, 100]
CR, n (%); [95%CI]	12 (24.0); [13.1, 38.2]	38 (34.0); [25.3, 43.5]	14 (31.0); [17.6, 44.6]	19 (29.0); [18.6, 41.8]	2 (10.0); [1.2, 30.4]	18 (30.0); [18.8, 43.2]	14 (31.1); [18.2, 46.6]	7 (35.0); [14.1, 55.9]
Median DOR, Months [95%CI]	9.2 [5.4, 11.3]	10.9 [9.0, 11.4]	10.7 [6.5, NE]	10.4 [6.1, 11.3]	6.9 [1.9, 10.3]	10.5 [9.0, 11.3]	10.9 [4.5, 11.4]	11.0 [3.9, 11.4]
Median PFS, Months [95%CI]	7.9 [5.1, 10.9]	8.8 [5.5, 11.6]	8.2 [4.8, 11.9]	7.5 [4.9, 11.3]	4.9 [1.8, 8.2]	8.9 [3.1, 11.1]	8.6 [4.9, 12.2]	10.2 [3.1, 12.3]
Subgroup data not reported for the following: probability of DOR ≥6 months, probability of PFS at 6 months, median OS, OS at 12 months; vgPR, PR								

95% CI: 95% confidence interval, CR: complete response, DOR: duration of response, n: number, N: total number, ORR: overall response rate, OS: overall response, PFS: progression-free survival, PR: partial response, vgPR: very good partial response.

* Did not significantly differ between patients with versus patients without risk factors.

Table D3.7. Subgroup Efficacy Data: Ide-cel II

Trial	CRB-401[15]			
	Extramedullary Disease	**Received Bridging Therapy**	**High Cytogenetic Risk**	**High Tumor Burden**
Median Follow-Up	11.3 Months			
N (as-treated)	9	14	15	16
ORR, n (%); [95% CI]	8 (88.9); [51.8, 99.7]	14 (100); [76.8, 100]	11 (73.3); [44.9, 92.2)	12 (75.0); [47.6, 92.7]
CR, n (%)	1 (11.1)	2 (14.3)	1 (6.7)	0 (0)
vgPR, n (%)	2 (22.2)	4 (28.6)	3 (20.0)	4 (25.0)
PR, n (%)	2 (22.2)	1 (7.1)	1 (6.7)	1 (6.3)
Subgroup data not reported for the following outcomes: Probability of DOR ≥6, probability of PFS at 6 months, median DOR, median PFS, median OS, OS at 12 months				

95% CI: 95% confidence interval, BCMA: B-cell maturation antigen, CR: complete response, DOR: duration of response, EMD: extramedullary disease, n: number, N: total number, NE: not estimable, NR: not reported, ORR: overall response rate, OS: overall response, PFS: progression-free survival, PR: partial response, vgPR: very good partial response

Table D3.8. Subgroup Efficacy Data: Cilta-cel

Trial	LEGEND-2[24,38] Xi'an			
Subgroups	**BCMA Expression**	**High Risk**	**Complete Response**	
	≥40%	**EMD**	**Achieved**	**Not Achieved**
Median Follow-Up	8 months	25 months		
N (as-treated)	27/53	17	42	15
ORR, n (%); [95% CI]	22 (81.5); [NR]	14 (82.4); [NR]	NR	NR
CR, n (%)	17 (63.0)	10 (60.0)*	NR	NR
vgPR, n (%)	1 (3.7)	2 (11.6)*	NR	NR
PR, n (%)	4 (14.8)	2 (11.6)*	NR	NR
Median DOR, Months [95%CI]	NR	NR	29.1 [NR]	NR
Median PFS, Months [95%CI]	11 [6-NE]	8.1 [NR]	28.2 [19.9, NE]	3.2 [1.7, 6.4]
Median OS, Months [95%CI]	Not reached	13.9 [NR]	Not reached [35.0, NE]	7.5 [3.8, 13.1]
OS at 12 Months, n (%)	NR	NR	NR (92.9)	NR
Subgroup data not reported for the following outcomes: Probability of DOR ≥6, probability of PFS at 6 months, subgroup data for CARTITUDE-1 or LEGEND-2 (Changzheng, Ruijin, Jiangsu sites)				

95% CI: 95% confidence interval, BCMA: B-cell maturation antigen, CR: complete response, DOR: duration of response, EMD: extramedullary disease, n: number, N: total number, NE: not estimable, NR: not reported, ORR: overall response rate, OS: overall response, PFS: progression-free survival, PR: partial response, VGPR: very good partial response

* Data are digitized and should be interpreted with caution.

Table D3.9. Subgroup Efficacy Data: Belantamab mafodotin

Trial	DREAMM-2[8,39-41]								
Subgroups	Prior Therapies		High Risk	Renal Impairment†		Age		Race / Ethnicity	
	3-6 Therapies	≥ 7 Therapies	High Risk Cytogenetics	Mild	Moderate	65 to < 75 years	≥75 years	White	Black
Median Follow-Up	12.4 Months		9 Months	9 Months		6.3 Months		6.3 Months	
N (ITT)	47	50	41	48	24	39	13	76	16
ORR, n (%); [95%CI]	16 (34.0); [19.3, 51.4]*	15 (30.0); [16.5, 46.6]*	11 (27.0); [14.2, 42.9]*	15 (31.3); [18.7, 46.3]	8 (33.3); [15.6, 55.3]	17 (43.6); [27.8, 60.4]	1 (7.7); [0.2, 36.0]	24 (31.6); [21.4, 43.3]‡	6 (37.5); [15.2, 64.6]§
vgPR, n (%)	8 (17.0)	10 (20.0)	9 (22.0)	NR	NR	NR		NR	
Median DOR, Months [95%CI]	11.0 [4.2, Not reached]	13.1 [4.0, Not reached]	Not reached [1.4, Not reached]	Not reached	Not reached				
Probability DOR ≥6 Months, % [95%CI]	63 [31, 83]	73 [44, 89]	52 [20, 77]	NR	NR				
Median PFS, Months [95%CI]	2.9 [1.5, 5.7]	2.2 [1.2, 3.6]	2.1 [0.8, 3.7]	2.2 [2.1, 3.6]	3.7 [1.0, Not reached]				
Probability of 6-Month PFS, % [95%CI]	35 [20, 50]	30 [17, 43]	30 [16, 45]	NR	NR				
Median OS, Months [95%CI]	NR	NR	9.4 [4.3, 13.1]	NR	NR				
Probability of 12-Month OS, % [95% CI]	NR	NR	45 [27, 61]	NR	NR				
Subgroup data not reported for the following outcomes: CR, PR									

95% CI: 95% confidence interval, ITT: Intention to treat, CR: complete response, DOR: duration of response, GFR: glomerular filtration rate, m^2: meters squared, min: minute, mL: milliliter, n: number, N: total number, NR: not reported, ORR: overall response rate, OS: overall response, PFS: progression-free survival, PR: partial response, VGPR: very good partial response

* 97.5% confidence interval.

† Mild renal impairment defined as GFR ≥60-<90 mL/min/1.73 m^2, moderate renal impairment defined as GFR ≥30-<60 mL/min/1.73 m^2.

‡ ORR at 13 months of follow-up was received as academic in confidence ([redacted]).

§ ORR at 13 months of follow-up was received as academic in confidence ([redacted]).

Table D3.10. Patient Reported Outcomes: Ide-cel, Cilta-cel, Belantamab mafodotin

Intervention			Ide-cel (as-treated)		Cilta-cel (as-treated)		Belantamab (ITT)			
Trial			KarMMa[25]		CARTITUDE-1[27]		DREAMM-2[28,29]			
Arms (N)			Overall (N=128)		Overall (N=68)		2.5 mg/kg (N=97)			
Follow-Up			Day 1	Month 9	Day 100	Day 184	Week 7	Week 13	Week 19	Week 25
EQ-5D-5L Index	N		111	59	NR		NR			
	Improvement		33 (29.7)	32 (54.2)						
	No Change		57 (51.4)	22 (37.3)						
	Deterioration		49 (44.1)	5 (8.5)						
EQ VAS	N		111	59	NR		NR			
	Improvement		46 (41.4)	48 (81.3)						
	No Change		16 (14.4)	1 (1.8)						
	Deterioration		49 (44.1)	10 (16.9)						
EORTC QLQ-C30	N		110	59	47	30	46	29	19	19
	Physical Functioning	Change from BL, Mean Score (95%CI)	-1.2 (-4.3, 2.0)†	13.2 (7.9, 17.9)†	NR	NR	5.1 (0.5, 9.9)†	3.0 (-2.8, 8.7)†	0.3 (-6.3, 6.9)†	-0.1 (-5.3, 5.3)†
		Improvement‡	40 (36.4)	35 (59.3)	34 (72.1)	NR	13 (28.3)	8 (27.6)	3 (15.8)	4 (21.1)
		No Change	31 (28.2)	19 (32.2)	NR	NR	NR	NR	NR	NR
		Deterioration	39 (35.5)	5 (8.5)	NR	NR	NR	NR	NR	NR
	Cognitive Functioning	Change from BL, Mean Score (95%CI)	0.8 (-3.1, 3.4)†	6.6 (2.7, 11.2)†	NR		NR			
		Improvement‡	22 (20.0)	42 (71.2)						
		No Change	38 (34.5)	10 (16.9)						
		Deterioration	50 (45.5)	7 (11.9)						
	Role Functioning	Change from BL, Mean Score (95%CI)	NR	NR	NR		1.9 (-8.1, 11.9)†	7.3 (-5.7, 20.4)†	-4.4 (-19.3, 10.7)†	8.0 (-4.9, 20.7)†
		Improvement‡	23 (20.9)	34 (57.6)			NR	NR	NR	NR
		No Change	49 (44.5)	19 (32.2)			NR	NR	NR	NR
		Deterioration	38 (34.5)	6 (10.2)			NR	NR	NR	NR

Intervention			Ide-cel (as-treated)		Cilta-cel (as-treated)		Belantamab (ITT)			
Trial			KarMMa[25]		CARTITUDE-1[27]		DREAMM-2[28,29]			
Arms (N)			Overall (N=128)		Overall (N=68)		2.5 mg/kg (N=97)			
Follow-Up			Day 1	Month 9	Day 100	Day 184	Week 7	Week 13	Week 19	Week 25
	Emotional Functioning	Improvement‡	32 (29.1)	30 (50.8)	NR		NR			
		No Change	34 (30.9)	17 (28.8)						
		Deterioration	44 (40.0)	12 (20.3)						
	Social Functioning	Improvement‡	25 (22.7)	36 (61.0)	NR		NR			
		No Change	42 (38.2)	16 (27.1)						
		Deterioration	43 (39.1)	7 (11.9)						
	Fatigue	Change from BL#, mean score (95%CI)	7.7 (3.7, 11.4)†	-22.8 (-29.1, -17.1)†	-1.5 (-9.1, 5.1)†	-9.2 (-16.4, -2.0)†	-3.9 (-11.1, 2.5)†	-7.3 (-16.6, 1.8)†	-0.8 (-11.2, 10.6)†	3.6 (-7.6, 14.6)†
		Improvement‡	28 (25.5)	39 (66.1)	NR (62.2)	NR	21 (45.7)	12 (41.4)	6 (31.6)	6 (31.6)
		No Change	32 (28.8)	17 (28.8)	NR	NR	NR	NR	NR	NR
		Deterioration	51 (46.4)	3 (5.1)	NR	NR	NR	NR	NR	NR
	Pain	Change from BL#, mean score (95%CI)	-8.7 (-13.0, 5.6)†	-23.8 (-30.2, -18.3)†	-8.9 (-16.6, NR)†	-8.9, (-17.6, -0.3)†	-4.7 (-13.0, 3.5)†	-4.4 (-14.4, 6.0)†	4.9 (-4.9, 14.2)†	2.6 (-6.5, 11.4)†
		Improvement‡	38 (34.5)	36 (61.0)	33 (71.1)	NR	14 (30.4)	9 (31.0)	4 (21.1)	3 (15.8)
		No Change	48 (43.6)	17 (28.8)	NR	NR	NR	NR	NR	NR
		Deterioration	24 (21.8)	6 (10.2)	NR	NR	NR	NR	NR	NR
	Nausea/ Vomiting	Improvement‡	7 (6.4)	15 (25.4)	NR		NR			
		No Change	41 (37.3)	38 (64.4)						
		Deterioration	62 (56.4)	6 (10.2)						
	Constipation	Improvement‡	9 (8.2)	11 (18.6)	NR		NR			
		No Change	60 (54.5)	45 (76.3)						
		Deterioration	41 (37.3)	3 (5.1)						
	Diarrhea	Improvement‡	17 (15.5)	13 (22.0)	NR		NR			
		No Change	76 (69.1)	44 (74.6)						
		Deterioration	17 (15.5)	2 (3.4)						
	Insomnia	Improvement‡	20 (18.2)	24 (40.7)	NR		NR			

Intervention			Ide-cel (as-treated)		Cilta-cel (as-treated)		Belantamab (ITT)			
Trial			KarMMa[25]		CARTITUDE-1[27]		DREAMM-2[28,29]			
Arms (N)			Overall (N=128)		Overall (N=68)		2.5 mg/kg (N=97)			
Follow-Up			Day 1	Month 9	Day 100	Day 184	Week 7	Week 13	Week 19	Week 25
		No Change	73 (66.4)	29 (49.2)						
		Deterioration	17 (15.5)	6 (10.2)						
	Dyspnea	Improvement‡	24 (21.8)	17 (28.8)	NR		NR			
		No Change	77 (70.0)	37 (62.7)						
		Deterioration	9 (8.2)	5 (8.5)						
	Appetite Loss	Improvement‡	7 (6.4)	18 (30.5)	NR		NR			
		No Change	47 (42.7)	35 (59.3)						
		Deterioration	56 (50.9)	6 (10.2)						
	Financial Difficulties	Improvement‡	11 (10.0)	10 (16.9)	NR		NR			
		No Change	79 (71.8)	40 (67.8)						
		Deterioration	20 (18.2)	9 (15.3)						
	Global Health / QoL	Change from BL, Mean Score (95%CI)	-5.1 (-2.5, -7.7)†	15.4 (9.8, 20.9)†	NR	NR	0.4 (-5.7, 6.4)†	-3.2 (-10.0, 3.8)†	-2.3 (-8.9, 4.5)†	-4.7 (-12.1, 2.8)†
		Improvement‡	23 (20.9)	24 (40.7)	24 (51.1)	NR	NR	NR	NR	NR
		No Change	64 (58.2)	29 (49.2)	NR	NR	NR	NR	NR	NR
		Deterioration	23 (20.9)	6 (10.2)	NR	NR	NR	NR	NR	NR
EORTC QLQ-MY20	N		109	57	47	NR	45	28	18	18
	Disease Symptoms	Change from BL, Mean Score (95%CI)	-1.14 (-3.4, 1.7)†	-20.00 (-14.3, -9.7)†	NR	NR	-2.5 (-8.1, 3.8)†	-0.8 (-7.2, 5.5)†	1.1. (NR, 8.5)†	0.0 (-7.5, 7.5)†
		Improvement‡	15 (13.8)	25 (43.9)	NR	NR	17 (37.8)	8 (28.6)	5 (27.8)	6 (33.3)
		No Change	72 (66.1)	28 (49.1)	NR	NR	NR	NR	NR	NR
		Deterioration	22 (20.2)	4 (7.0)	NR	NR	NR	NR	NR	NR
	Future Perspectives	Improvement‡	32 (29.4)	34 (59.6*)	NR		0 (0)	0 (0)	0 (0)	0 (0)
		No Change	41 (37.6)	14 (24.6)			NR	NR	NR	NR
		Deterioration	36 (33.0)	9 (15.8)			NR	NR	NR	NR
	Body Image	Improvement‡	13 (11.9)	17 (29.8)	NR		NR			

Intervention			Ide-cel (as-treated)		Cilta-cel (as-treated)		Belantamab (ITT)			
Trial			KarMMa[25]		CARTITUDE-1[27]		DREAMM-2[28,29]			
Arms (N)			Overall (N=128)		Overall (N=68)		2.5 mg/kg (N=97)			
Follow-Up			Day 1	Month 9	Day 100	Day 184	Week 7	Week 13	Week 19	Week 25
		No Change	79 (72.5)	36 (63.2)						
		Deterioration	17 (15.6)	4 (7.0)						
	Side Effects	Change from BL, Mean Score (95%CI)	-0.57 (-5.14, -2.86)†	6.29 (3.43, 9.14)†	NR		NR			
		Improvement‡	35 (32.1)	3 (5.3)						
		No Change	62 (56.9)	37 (64.9)						
		Deterioration	12 (11.0)	17 (29.8)						
OSDI	N		NR		NR		92	NR		
	Vision-related Functioning Domain	Change from BL, Mean Score (95%CI)	NR		NR		NR	NR		
		Deterioration from Baseline					46 (49.5)§			
		Improvement from Worst Severity post-BL					33 (72.0)			
		No Change					NR			
Patient reported outcomes not reported for the following trails: CRB-401, LEGEND-2										

95% CI: 95% confidence interval, ITT: Intention to treat, EORTC: European Organization for Research and Treatment of Cancer, EQ-5D-5L: EuroQol 5 dimensions 5 levels, kg: kilogram, mg: milligram, MY20: Myeloma Module questionnaire, n: number, N: total number, NR: not reported, OSDI: Ocular Surface Disease Index, QoL: quality of life, QLQ-C30: Quality of Life C30 questionnaire, VAS: visual analog scale.

* Statistically significant improvement, $p<0.05$.

† Data are digitized and should be interpreted with caution.

‡ Change of ≥10 points.

§ Change of ≥12.5-points.

Negative changes indicate a reduction in pain or fatigue.

Table D3.11. Safety Outcomes: Ide-cel

Trial		KarMMa[5]				CRB-401[63]		
Arms		150x10^6 CAR+ T cells/kg	300 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall	150 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall
N (as-treated)		4	70	54	128	18	38	62†
Any AE, n (%)		NR			NR	NR		33/33 (100)
Any SAEs, n (%)					NR			32/33 (96.7)
Treatment-related SAEs, n (%)					4 (3.1)			NR
Mortality, n (%)	Overall	NR			6 (4.7)	NR		6 (10.0)
	Disease Progression				2 (1.6)			NR
	AEs				4 (3.1)			NR
Hospitalizations, n (%)	n (%)	NR			9 (8.4)			
	Mean Length of Stay, Months (SD)				NR			
	ICU, n (%)				NR			
Study Discontinuation prior to Treatment, n (%)	Overall	NR			NR	NR		3/36 (8.3)
	Disease Progression				NR			3/36 (8.3)
Discontinuation, n (%)	Overall	NR			55 (43.0)	NR		49 (79.0)
	Disease Progression				NR			36 (58.0)
	Death				NR			6 (10.0)
CRS, n (%)	Median Onset, Days (Range)	7 (2-12)	2 (1-12)	1 (1-10)	1.0 (1-12)	NR	NR	2 (1-25); N=33
	Median Duration, Days (Range)	5 (3-7)	4 (2-28)	7 (1-63)	5 (1-63)	NR	NR	5 (1-32); N=33
	Overall	2 (50.0)	53 (75.7)	52 (96.3)	107 (83.6)	7 (11.3)	35 (92.1)	47 (76.0)
	Grade 1	1 (25.0)	33 (47.1)	27 (50.0)	61 (47.7)	NR	NR	43 (69.3)
	Grade 2	1 (25.0)	16 (22.9)	22 (40.7)	39 (30.5)	NR	NR	
	Grade 3	0 (0)	2 (2.9)	3 (4.3)	5 (3.9)	0 (0)	3 (7.9)	4 (6.5)
	Grade 4	0 (0)	1 (1.4)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)
	Grade 5	0 (0)	1 (1.4)	0 (0)	1 (0.8)	0 (0)	0 (0)	0 (0)

Trial		KarMMa[5]				CRB-401[63]		
Arms		150x10^6 CAR+ T cells/kg	300 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall	150 x10^6 CAR+ T cells/kg	450 x10^6 CAR+ T cells/kg	Overall
	Progression from Grade 1 to ≥2	NR	NR	NR	30 (65.2)*	NR	NR	NR
Required tocilizumab for CRS, n (%)	Overall	1 (25.0)	30 (42.8)	36 (66.7)	67 (52.3)	NR	NR	7/33(21.2)
	1 Dose	NR	NR	NR	44 (34.3)	NR	NR	NR
	≥1 Dose	NR	NR	NR	23(18.0)	NR	NR	NR
Neurotoxicity, n (%)	Median Onset, Days (Range)	N/A	3 (1-10)	2 (1−5)	2 (1−10)	NR	NR	NR
	Median Duration, Days (Range)	N/A	3 (2−26)	5 (1−22)	3 (1−26)	NR	NR	NR
	Overall	0 (0)	12 (17.1)	11 (20.4)	23 (18.0)	5 (27.8)	20 (52.6)	27 (43.5)
	Grade 1	0 (0)	7 (10.0)	5 (9.3)	12 (9.4)	NR	NR	25 (39.1)
	Grade 2	0 (0)	4 (5.7)	3 (5.6)	7 (5.5)	NR	NR	
	Grade 3	0 (0)	1 (1.4)	3 (5.6)	4 (3.1)	0 (0)	2 (5.3)	1 (1.6)
	Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	NR	NR	1 (1.6)
	Grade 5	0 (0)	0 (0)	0(0)	0 (0)	0 (0)	0 (0)	0 (0)
Cytopenia, n (%)		NR			124 (97.0)	NR		NR
Infections, n (%)					88 (69.0)			14/33 (42.4)
Anemia, n (%)	Overall				89 (69.5)			47 (76.0)
	≥Grade 3				77(60.2)			35 (57.0)
Thrombocytopenia, n (%)	Overall				81(63.3)			46 (74.0)
	≥ Grade 3				67 (52.3)			35 (57.0)
Data not reported for the following safety outcomes: Treatment-related AEs, study discontinuation prior to treatment due to death or patient withdrawal, discontinuation due to AE and lack of efficacy, bone disease, hypercalcemia, hyper viscosity, renal failure, thrombosis, corneal events								

AE: adverse event, CAR+: chimeric antigen receptor positive, CRS: cytokine release syndrome, ICU: intensive care unit, kg: kilogram, mg: milligram, n: number, N: total number, N/A: not applicable, NR: not reported, SAE: serious adverse events

* Patients categorized as having Grade ≥2 CR.

† N of 62 represents the entire treated CRB-401 population, N of 33 represents the first 33 patients to received Ide-cel treatment within the population.

Table D3.12. Safety Outcomes: Cilta-cel

Trial		CARTITUDE-1[6]	LEGEND-2[21,24,26] Xi'an	LEGEND-2[18,24,67] Changzheng, Ruijin, Jiangsu
Arms		**0.71x10^6 CAR+ T cells/kg**	**0.5x10^6 CAR+ T cells/kg**	**0.7x10^6 CAR+ T cells/kg**
N (as-treated)		97	57	17
Any AE, n (%)		97 (100)	57 (100)	NR
Treatment-related AE, n (%)		NR	NR	
Any SAEs, n (%)		NR	37 (64.9)*	
Treatment-related SAEs, n (%)		NR	NR	
Mortality, n (%)	**Overall**	14 (14.4)	17 (29.8)	NR
	Disease Progression	5 (5.2)	14 (24.6)	
	AEs	9 (9.3)	2 (3.5)	
	Other	NR	1 (1.8)	
Study Discontinuation Prior to Treatment, n (%)	**Overall**	16/113 (14.2)	NR	NR
	Death	9/113 (8.0)		
	Disease Progression	2/113 (1.8)		
	Patient Withdrawal	5/113 (4.4)		
Discontinuation, n (%)	**Overall**	14 (14.4)	NR	NR
	AEs	NR	NR	
	Lack of Efficacy	NR	NR	
	Disease Progression	NR	NR	
	Death	14 (14.4)	17 (29.8)	
CRS, n (%)	**Median Onset, Days (Range)**	7 (1-12)	9 (1-19)	NR
	Median Duration, Days (Range)	4 (1-97)	9 (3-57)	NR
	Overall	92 (94.8)	51 (89.5)	17 (100)
	Grade 1	49 (50.5)	27 (47.4)	10 (58.8)
	Grade 2	38 (39.2)	20 (35.1)	
	Grade 3	3 (3.1)	4 (7.0)	6 (35.3)
	Grade 4	1 (1.0)	0 (0)	0 (0)

Trial		CARTITUDE-1[6]	LEGEND-2[21,24,26] Xi'an	LEGEND-2[18,24,67] Changzheng, Ruijin, Jiangsu
Arms		**0.71x10^6 CAR+ T cells/kg**	**0.5x10^6 CAR+ T cells/kg**	**0.7x10^6 CAR+ T cells/kg**
	Grade 5	1 (1.0)	0 (0)	1 (5.9)
	Progression from Grade 1 to ≥ 2	NR	NR	NR
	Required tocilizumab, n (%)	67 (69.1)	26 (45.6)†	9 (52.9)
Neurotoxicity, n (%)	**Overall**	20 (20.6)	1 (1.8)	0 (0)
	Grade 1	10 (10.3)	1 (1.8)	
	Grade 2			
	Grade 3	9 (9.3)	0 (0)	
	Grade 4			
	Grade 5	1 (1.0)		
Cytopenia, n (%)		NR	NR	14 (82.0)
Anemia, n (%)	**Overall**	79 (81.4)	17 (29.8)	NR
	≥Grade 3	66 (68.0)	10 (17.5)	
Thrombocytopenia, n (%)	**Overall**	77 (79.4)	28 (49.1)	NR
	≥ Grade 3	58 (59.8)	13 (22.8)	
Data not reported for the following safety outcomes: Hospitalizations, bone disease, thrombosis, infections, renal failure, hyper viscosity, hypercalcemia				

AE: adverse event, CAR+: chimeric antigen receptor positive, CRS: cytokine release syndrome, kg: kilogram, n: number, N: total number, N/A: not available, NR: not reported, SAE: serious adverse events, SE: standard error

* Grade ≥3 AEs.

† Median 8-month follow up time.

Table D3.13. Safety Outcomes: Belantamab mafodotin

Trial		DREAMM-2[8,9,23]
Arms		Belantamab mafodotin 2.5 mg/kg
N (Safety Population)		95
Any AE, n (%)		93 (97.9)
Treatment-related AEs, n (%)		84 (88.4)
Any SAEs, n (%)		40 (42.1)
Treatment-related SAEs, n (%)		11 (11.6)
Mortality, n (%)	Overall	31 (32.6)†
	Disease Progression	25 (26.3)†
	AEs	3 (3.2)
	Other	3 (3.2)†
Discontinuation, n (%)	Overall	73 (76.8)†
	AEs	9 (9.5)
	Corneal Events	3 (3.2)
	Lack of Efficacy	1 (1.1)†
	Disease Progression	59 (60.8)†
	Death	31 (32.6)†
CRS, n (%)		0 (0)
Neurotoxicity, n (%)		0 (0)
Infections, n (%)		1 (1.1)*†
Renal Failure, n (%)		1 (1.1)†
Hyper viscosity, n (%)		0.0†
Hypercalcemia, n (%)	Overall	13 (13.7)†
	≥Grade 3	7 (7.4)
Anemia, n (%)	Overall	23 (24.2)†
	≥Grade 3	20 (21.1)
Thrombocytopenia, n (%)	Overall	36 (37.9)
	≥ Grade 3	21 (22.1)
Keratopathy (MECs), n (%)	Overall	68 (71.6)
	Grade 1	8 (8.4)

Trial		DREAMM-2[8,9,23]
Arms		**Belantamab mafodotin 2.5 mg/kg**
	Grade 2	16 (16.8)
	Grade 3	43 (45.3)
	Grade 4	1 (1.1)
Keratopathy (MECs) Grade ≥2, n (%)	**Median Time to Onset, Days (Range)**	37.0 (19.0-143.0)
	Median Duration, Days (Range)	86.5 (8.0-358.0)
	Recovered‡ from First Occurrence, n (%)	46/60 (76.7)§
Blurred Vision, n (%)		24 (25.3)
Dry Eye, n (%)		14 (14.7)
Permanent Vision Loss, n (%)		0 (0)
Changes in BCVA	**Overall, n (%)**	51 (53.7)
	Grade 1	7 (7.4)
	Grade 2	15 (15.8)
	Grade 3	28 (29.5)
	Grade 4	1 (1.1)
	Median Time to Onset, Days (Range)	64.0 (20–213)
	Median Duration, Days (Range)	33.0 (8–127)
	Recovered from First Occurrence, n (%)§	34/44 (77)
Clinically Meaningful Changes in BCVA (BCVA of 20/50 or worse in the better-seeing eye)	**n (%)**	17 (17.9)
	Median Time to Onset, Days (Range)	66.0 (20-442)
	Median Time to Resolution¤, Days (Range)	21.5 (7–64); N=14
	Not recovered as of last follow-up, n (%)	3/17 (17.6)
Clinically Meaningful Changes in BCVA (BCVA of 20/200 or worse in the better-seeing eye)	**n (%)**	1 (1.1)
	Median Time to Onset, Days (Range)	21.0 (21–21)
	Median Time to Resolution¤, Days (Range)	22.0 (22–22); N=1
	Not Recovered as of Last Follow-up, n (%)	0 (0)
Data not reported for the following safety outcomes: Hospitalizations, bone disease, thrombosis, cytopenia		

AE: adverse event, BCVA: best corrected visual acuity, CAR+: chimeric antigen receptor positive, CRS: cytokine release syndrome, kg: kilogram, MECs: Microcyst-like epithelial changes, mg: milligram, n: number, N: total number, N/A: not available, NR: not reported, SAE: serious adverse events, SE: standard error

* Viral infection

† 6.3-month follow up time.

‡ Any Grade 1 eye exam findings/no exam findings.

§ Data for Grade ≥2 events per the keratopathy and visual acuity (KVA) scale.

¤ in patients who recovered as of last follow-up.

Table D3.14. Subgroup Safety Data: Ide-cel

Trial		KarMMa[36]		CRB-401[15]		
Subgroups		Elderly Patients		Elderly Patients	High Risk	
		≥ 65 years	≥ 70 years	≥ 65 years	Bridging Therapy	High Tumor Burden
Median Follow-Up		11.3 Months		11.3 Months		
N		45	20	11	14	16
CRS, n (%)	Overall	40 (88.9)	20 (100)	9 (82.0)	11 (79.0)	12 (75.0)
	Grade ≥3	2 (4.4)	2 (10.0)	NR	NR	NR
Neurotoxicity, n (%)	Overall	11 (24.4)	6 (30.0)	NR	NR	NR
	Grade ≥3	4 (8.9)	1 (5.0)	NR	NR	NR
Subgroup data not reported for the following outcomes: Any adverse events, any serious adverse events, keratopathy, dry eye, blurred vision, thrombocytopenia, anemia; Subgroup safety data not available for the following: KarMMa high risk subgroups, CARTITUDE-1, LEGEND-2						

CRS: cytokine release syndrome, n: number, N: total number, NR: not reported, SAE: serious adverse event.

Table D3.15. Subgroup Safety Data: Belantamab mafodotin

Trial		DREAMM-2[39-41]				
Subgroups		Prior Therapies		High Risk	Renal Impairment*	
		3-6 Therapies	≥ 7 Therapies	High Risk Cytogenetics	Mild	Moderate
N		47	50	41	48	24
Median Follow-Up		12.4 Months		9 Months	9 Months	
Any SAEs, n (%)		NR		19 (46.3)	16 (33.3)	12 (50.0)
Keratopathy	Overall	NR	NR	24 (58.5)	33 (68.8)	15 (62.5)

Trial		DREAMM-2[39-41]				
Subgroups		Prior Therapies		High Risk	Renal Impairment*	
		3-6 Therapies	≥ 7 Therapies	High Risk Cytogenetics	Mild	Moderate
	Grade ≥3	16 (33.0)	14 (27.0)	NR	12 (25.0)	8 (33.3)
Dry eye	Overall	NR	NR	5 (12.2)	9 (18.8)	1 (4.2)
Blurred Vision	Overall	NR	NR	8 (19.5)	10 (20.8)	4 (1.7)
Thrombocytopenia	Overall	NR	NR	17 (41.5)	11 (22.9)	6 (25.0)
	Grade ≥3	8 (17.0)	10 (20.0)	NR	9 (18.8)	6 (25.0)
Anemia	Overall	NR	NR	10 (24.4)	13 (27.1)	7 (29.2)
	Grade ≥3	5 (11.0)	16 (31.0)	NR	9 (18.8)	6 (25.0)
Subgroup data not reported for the following: Any adverse events, cytokine release syndrome, neurotoxicity, grade ≥3 dry eye, grade ≥3 blurred vision						

GFR: glomerular filtration rate, m^2: meters squared, min: minute, mL: milliliter, n: number, N: total number, NR: not reported, NT: neurotoxicity, SAEs: serious adverse events

* Mild renal impairment defined as GFR ≥60-<90 mL/min/1.73 m^2, moderate renal impairment defined as GFR ≥30-<60 mL/min/1.73 m^2.

Table D3.16. Secondary Analyses: Ide-cel

Source			Rodriguez-Otero EHA 2020[68]		Jagannath ASCO 2020[69]		Shah ASH 2020[45]	
Trials			KarMMa vs. DREAMM-2		KarMMa vs. KarMMa Real World*		KarMMa vs. MAMMOTH	
Arms			KarMMa (N=128)	DREAMM-2 2.5 mg/kg (N=97)	KarMMa (N=128)	RW EC (N=190)	Ide-cel (ESS=67)	Ide-cel 450x10^6 CAR+ T cells/kg (ESS=33)
Median Follow Up, Months			13.3	Study level	11.3	10.2	13.3	
Baseline	Age, Median Years		61 (33-78)	65	61	64	NR	
	Male, n (%)		76 (59.4)	51 (52.6)	76 (59.4)	NR		
	Extramedullary Disease, n (%)		50 (39.1)	22 (22.7)	50 (39.1)	NR		
	ISS stage 3, n (%)		21 (16.4)	42 (43.3)	21 (16.4)	8 (4)		
	Median Prior Regimens Received (Range)		6 (3-16)	7 (3-21)	6 (3-16)	5 (NR)		
	High-risk Cytogenetics, n (%)		45 (35.2)	41 (42.3)	45 (35.2)	57 (30.0)		
	Prior Therapies Received, n (%)	Bortezomib	NR	95 (97.9)	NR		NR	
		Carfilzomib	NR	74 (76.3)				
		Lenalidomide	NR	97 (100)				
		Pomalidomide	NR	89 (91.8)				
		Daratumumab	NR	97 (100)				
		Isatuximab	NR	3 (3.1)				
	Triple-refractory, n (%)		108 (84.0)	97 (100)	108 (84.0)	82 (43.0)	NR	
Efficacy Outcomes	ORR, OR (95%CI)		5.12 (2.35, 11.13)		RR: 2.4 (1.7, 3.3), p<0.0001		5.11 (2.92, 8.94), p<0.001	6.96 (2.94, 16.49)
	vgPR, RR (95%CI)		NR		4.2 (2.4, 7.2), p<0.0001		NR	NR
	PFS, HR (95%CI)		0.45 (0.27,0.76)		0.48 (0.33, 0.69), p<0.0001		0.55 (0.42, 0.73), p<0.001	0.37 (0.23, 0.57)
	OS, HR (95%CI)		0.36 (0.15, 0.86)		NR		0.36 (0.24, 0.54), p<0.001	0.35 (0.18, 0.67), p=0.002
Data not reported for safety outcomes								

95% CI: 95% confidence interval, AE: adverse event, CAR+: chimeric antigen receptor positive, ESS: effective sample size, HR: hazard ratio, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, OR: odds ratio, ORR: overall response rate, PFS: progression-free survival, RR: risk ratio, SAE: serious adverse events, vgPR: very good partial response.
* Real world patients meeting KarMMa eligibility criteria (noninterventional, retrospective study (KarMMa-RW), patient-level data from clinical sites).

Table D3.17. Secondary Analyses: Belantamab mafodotin

Source			Trudel EHA 2020[61]	Shragai EHA 2020[62]
Trials			Pooled DREAMM-1 and DREAMM-2	Real World
Arms			Belantamab 2.5mg/kg (N=103)	Belantamab 2.5 and 3.4 mg/kg (N=32)
Median Follow Up, Months			NR	5.7 (0.5-13.8)
Baseline	Age, median years		65.0 (39.0-85.0)	69.6 (49-88)
	Male, n (%)		52 (50.5)	19 (59.4)
	Extramedullary Disease, n (%)		21 (20.4)	NR
	ISS Stage 3, n (%)		41 (39.8)	NR
	Median Prior Regimens (Range)		7 (3-21)	6 (3-11)
	High-risk Cytogenetics, n (%)		28 (27.2)	7 (21.9)
	Prior Therapies Received, n (%)	Bortezomib	NR	30 (93.8)
		Carfilzomib		25 (78.1)
		Lenalidomide		29 (90.6)
		Pomalidomide		28 (87.5)
		Daratumumab		31 (96.9)
		Isatuximab		6 (18.8)
	Triple refractory, n (%)		NR	NR
Efficacy Outcomes	ORR, OR (95%CI)		NR	n/N (%): 12/29 (41.4)
	vgPR, RR (95%CI)			n/N (%): 8/29 (27.6)
	Median PFS, months (95%CI)			2.6 (NR)
	OS at 6 months, n (%)			22 (68.0)
Safety Outcomes, n (%)	Any AEs		101 (98.1)	NR
	Treatment related AEs		91 (88.3)	
	Any SAEs		42 (40.8)	

Source			Trudel EHA 2020[61]	Shragai EHA 2020[62]
Trials			Pooled DREAMM-1 and DREAMM-2	Real World
Arms			Belantamab 2.5mg/kg (N=103)	Belantamab 2.5 and 3.4 mg/kg (N=32)
	Treatment-related SAEs		13 (12.6)	
	Fatal Treatment-related SAEs		1 (0.9)	
	Anemia	Overall	27 (26.2)	NR
		Grade ≥3	19 (18.4)	
	Thrombo-cytopenia	Overall	24 (23.3)	7/23 (30.4)
		≥ Grade 3	18 (17.5)	3/23 (13.0)
	Keratopathy	Overall	68 (66.0)	20/31 (64.5)
		≥ Grade 3	28 (27.2)	8/31 (25.8)
	Blurred Vision	Overall	20 (19.4)	NR
		≥ Grade 3	4 (3.9)	
	Dry Eye	Overall	12 (11.7)	NR
		≥ Grade 3	0 (0)	

AE: adverse event, CAR+: chimeric antigen receptor positive, ESS: effective sample size, HR: hazard ratio, kg: kilogram, mg: milligram, n: number, N: total number, NR: not reported, OR: odds ratio, ORR: overall response rate, PFS: progression-free survival, RR: risk ratio, SAE: serious adverse events, VGPR: very good partial response

Usual Care Regimens

Table D3.18. Study Design: Usual Care Regimens

Trial/Study	Design	Patient Characteristics
MAMMOTH[7]	Retrospective cohort study N = 275	– Diagnosis of active MM – Refractory to daratumumab or isatuximab (administered alone or in combination) – Treatment for at least 4 weeks with a CD38 MoAB-containing treatment regimen and with evidence of progressive disease
Mehra 2020[31]	Real-world treatment patterns; Flatiron Health electronic health records N =251	– MM diagnosis – Received at least 3 lines of therapy (including at least one PI, one IMiD, and an anti-CD38 MoAB)
Goldsmith 2020[30]	Single-center, retrospective cohort study N = 58	– Quad/Penta-refractory MM – Received at least one cycle of bendamustine/prednisone (BP) and/or dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP)

IMiD: immunomodulatory drug, MM: multiple myeloma, MoAB: monoclonal antibody, N: total number, PI: protease inhibitor

Table D3.19. Baseline Characteristics: Usual Care Regimens

Trial/Study		MAMMOTH[7]			Mehra 2020[31]	Goldsmith 2020[30]	
Arms		Overall	Triple/Quad-refractory	Penta-refractory	Triple-refractory	BP	DCEP
N		275	148	70	251	27	31
Median Follow-Up, Months (Range)		10.6 (1.9-42.3)			6.0 (IQR: 2.7-10.8)	NR	
Age, Median Years (Range)		65.0 (27.0–90.0)	60.0 (23.0–85.0)	58.5 (35.0–76.0)	67.9 (IQR: 61.3-75.7)	61 (38-85)	60 (38-73)
Male, n (%)		152 (55.3)	85 (57.4)	39 (55.7)	136 (54.2)	12 (44.4)	15 (48.4)
Race/Ethnicity, n (%)	White	202 (73.5)	116 (78.4)	47 (67.1)	173 (68.9)	23 (85.2)	27 (87.1)
	Black	45 (16.4)	19 (12.8)	13 (18.6)	38 (15.1)	4 (14.8)	3 (9.7)
	Hispanic	6 (2.2)	1 (0.7)	2 (2.9)	30 (12.0)	0 (0)	1 (3.2)
	Other	22 (8.0)	12 (8.1)	8 (11.4)			
Median Time since Diagnosis, Years (Range)		4.5 (0.4–19.4)	4.4 (0.4–19.4)	5.7 (0.6–14.4)	44.8 (IQR: 28.0, 62.4)	4.7 (1.1-23.1)	4.5 (1.1-2.32)
High Risk Cytogenetics, n (%)		80 (29.1)	42 (28.4)	25 (35.7)	62 (24.7)	NR	NR
Renal Function†, n (%)		22 (8.0)	11 (7.4)	5 (7.1)	NR	NR	NR
ISS Disease Stage, n (%)	Stage 1	69 (25.1)	40 (27.0)	17 (24.3)	49 (19.5)	4 (14.8)	9 (29.0)
	Stage 2	84 (30.5)	40 (27.0)	24 (34.3)	59 (23.5)	9 (33.3)	12 (38.7)
	Stage 3	80 (29.1)	47 (31.8)	13 (18.6)	62 (24.7)	7 (25.9)	5 (16.1)
ECOG Performance Status	Grade 0	NR			134 (53.4)	NR	
	Grade 1						
	Grade 2				N/A		
Received autologous SCT, n (%)		198 (72.0)	104 (70.3)	47 (67.1)	141 (56.2)*	22 (81.5)	28 (90.3)
Median Prior Regimens, n (Range)		4 (1–16)	4 (1–11)	5 (2–16)	4 (IQR: 3, 6)	6 (4-15)	8 (4-15)
Penta-exposed, n (%)		157 (57.1)	70 (47.3)	70 (100)	117 (46.6)	NR	NR
Quad-refractory, n (%)		NR	NR	0 (0)	NR	5 (18.5)	8 (25.8)
Penta-refractory, n (%)		70 (25.4)	0 (0)	70 (100)	73 (29.1)	22 (81.5)	23 (74.2)
Exposed, n (%)	Daratumumab	at least 256 (93.1)	at least 138 (93.2)	at least 68 (97.1)	251 (100)	NR	NR
	Lenalidomide	270 (98.2)	146 (98.6)	70 (100)	244 (97.2)	27 (100)	31 (100)

Trial/Study		MAMMOTH[7]			Mehra 2020[31]	Goldsmith 2020[30]	
Arms		Overall	Triple/Quad-refractory	Penta-refractory	Triple-refractory	BP	DCEP
	Bortezomib	271 (98.6)	146 (98.6)	69 (98.6)	226 (90.0)	27 (100)	31 (100)
	Pomalidomide	189 (68.7)	91 (61.5)	69 (98.6)	173 (68.9)	27 (100)	31 (100)
	Carfilzomib	178 (64.8)	85 (57.4)	68 (97.1)	145 (57.8)	27 (100)	31 (100)
	Elotuzumab	NR	NR	NR	24 (9.6)	NR	NR
	Ixazomib	38 (13.9)	24 (16.2)	12 (17.1)	NR	NR	NR
	Thalidomide	55 (20.0)	26 (17.6)	23 (32.9)	NR	NR	NR
Refractory, n (%)	**Daratumumab**	256 (93.1)	138 (93.2)	68 (97.1)	NR	22 (81.5)	23 (74.2)
	Lenalidomide	211 (76.7)	117 (79.1)	69 (98.6)		27 (100)	31 (100)
	Bortezomib	188 (68.4)	107 (72.3)	68 (97.1)		27 (100)	31 (100)
	Pomalidomide	179 (65.1)	87 (58.8)	69 (98.6)		27 (100)	31 (100)
	Carfilzomib	130 (47.3)	57 (38.5)	67 (95.7)		27 (100)	31 (100)
	Elotuzumab	NR	NR	NR		NR	NR
	Ixazomib	34 (12.4)	23 (15.5)	10 (14.3)		NR	NR
	Thalidomide	23 (8.4)	6 (4.1)	14 (20.0)		NR	NR
Data not reported on the following baseline characteristics: Height, weight							

BP: bendamustine/prednisone, DCEP: dexamethasone, cyclophosphamide, etoposide, and cisplatin, dL: deciliter, ECOG: Eastern Cooperative Oncology Group, IQR: interquartile range, mg: milligram, n: number, N: total number, N/A: not available, NR: not reported, SCT: stem cell transplant.

* Type of SCT not specified.

† Creatinine > 2mg/dL

Table D3.20. Efficacy Outcomes: Usual Care Regimens I

Trial			MAMMOTH[7]		
Arms			Overall	Triple/Quad-refractory	Penta-refractory
N			275	148	70
Median Follow-Up, Months (Range)			10.6 (1.9-42.3)		
Median PFS, Months (95%CI or HR)	Overall		NR	NR	NR
	Received ≥ 1 Subsequent LOT†		3.4 (2.8, 4.0)		
	LOT1†	Carfilzomib-based	4.2 (HR 0.60, p=0.004); [N=68]		
		Carfilzomib + alkylator	5.7 (1.6-9.7); [N=19]		
		Daratumumab + IMiD	4.5 (2.8-6.3); [N=41]		
		Elotuzumab + IMiD	2.6 (1.1-4.1); [N=19]		
Median OS, Months (95%CI)	Overall		8.6 (7.2, 9.9)	9.2 (7.1, 11.2)	5.6 (3.5, 7.8)
	High-Risk Cytogenetics		5.6,(NR) p=0.025‡; [N=80]	NR	NR
	Impaired Renal Function*		3.7 (NR) p=0.031; [N=22]		
	Received ≥ 1 subsequent LOT		9.31 (8.1, 10.6)		
	LOT1†	Carfilzomib-based	10.9 (9.5-12.4); [N=68]		
		Carfilzomib + alkylator	12.7 (5.9-19.5); [N=19]		
		Daratumumab + IMiD	12.6 (8.5-16.6); [N=41]		
		Elotuzumab + IMiD	8.3 (1.9-14.6); [N=19]		
ORR, n (%)	Overall		116/249 (46.6)	NR	NR
	High-Risk Cytogenetics		OR=0.14 (95%CI: 0.03, 0.65)	NR	NR
	LOT1†	Overall	78/249 (31.0)	57/197 (29)	19/63 (30)
		Carfilzomib-based	22/68 (32.4)	NR	NR
		Carfilzomib + alkylator	9/19 (47.0)		
		Daratumumab + IMiD	15/41 (36.6)		
		Elotuzumab + IMiD	4/19 (21.1)		
	LOT2†		34/158 (21.5)		
	LOT3†		22/87 (25.3)		
ORR after LOT1†	sCR/CR, n (%)		5/249 (2.0)	NR	NR
	vgPR, n (%)		22/249 (8.8)		

Trial		MAMMOTH[7]		
Arms		Overall	Triple/Quad-refractory	Penta-refractory
	PR, n (%)	51/249 (20.5)		
Progressive Disease, n (%)		77 (28.0)	38 (25.7)	27 (38.6)
Patients Receiving Treatment After Becoming anti-CD38 MoAB Refractory	N	249	134	63
	Median LOT received, n (range)	2 (1-10)	NR	NR
	Carfilzomib-based Treatment, n (%)	68 (27.3)	43 (32.1)	8 (12.7)
	Elotuzumab-based Treatments, n (%)	19 (7.6)	NR	NR
	Daratumumab-based Treatments, n (%)	57 (22.9)	49 (36.6)	9 (50.9)
Data not reported for the following efficacy outcomes: LOT received (Pomalidomide-based, Bortezomib-based, Lenalidomide-based, Ixazomib-based, Thalidomide-based, Monotherapy, Doublet regimen, Triplet regimens)				

95% CI: 95% confidence interval, CR: complete response, HR: hazard ratio, IMiD: immunomodulatory drug, LOT: line of therapy (after becoming CD38 MoAB refractory), MoAB: monoclonal antibody, n: number, N: total number, NR: not reported, OR: odds ratio, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PR: partial response, sCR: stringent complete response, vgPR: very good partial response,

* Creatinine > 2mg/dl.

† First (LOT1), second (LOT2), or third (LOT3) line of therapy after becoming CD38 MoAB refractory.

‡ Versus standard risk.

Table D3.21. Efficacy Outcomes: Usual Care Regimens II

Study		Mehra 2020[31]				Goldsmith 2020[30]	
Arms		Overall	LOT1*	LOT2*	LOT3*	BP	DCEP
N		251	251	138	54	27	31
Median Follow-Up, Months (Range)		6.0 (IQR: 2.7-10.8)				NR	
Median PFS, Months (95%CI)		4.8 (3.7, 6.1)	NR	NR	NR	1.4 (1.1-1.6)	2.7 (1.5-3.8)
Median OS, Months (95%CI)		11.0 (8.7, 13.6)	NR	NR	NR	8.7 (2.3-15.0)	6.2 (4.4-7.8)
ORR, n (%)		NR	NR	NR	NR	7 (25.9)	11 (35.5)
ORR after First Subsequent Line	sCR/CR, n (%)	NR				CR: 0 (0)	CR: 1 (3.2)
	vgPR, n (%)					4 (14.8)	1 (3.2)
	PR, n (%)					3 (11.1)	9 (29.0)
Progressive Disease, n (%)		NR	NR	NR	NR	NR	NR
Median Time to Next Treatment, months (95%CI)		NR	NR	NR	NR	NR	
Receiving Treatment After Becoming Triple-refractory, n		251	251	138	54		
LOT Received After Becoming Triple-refractory, Median (Range)		2 (1-8)	NR	NR	NR		
Lines of Therapy Received, n (%)	Carfilzomib-based	111 (44.2)	81 (32.3)	25 (18.1)	12 (22.2)		
	Pomalidomide-based	98 (39.0)	76 (30.3)	37 (26.8)	9 (16.7)		
	Bortezomib-based	83 (33.1)	47 (18.7)	32 (23.2)	12 (22.2)		
	Elotuzumab-based	64 (25.5)	41 (16.3)	19 (13.8)	7 (13.0)		
	Lenalidomide-based	57 (22.7)	39 (15.5)	19 (13.8)	7 (13.0)		
	Ixazomib-based	NR	22 (8.8)	25 (18.1)	5 (9.3)		
	Thalidomide-based	NR	12 (4.8)	2 (1.4)	4 (74)		
	Daratumumab-based	NR	5 (2.0)	19 (13.8)	8 (14.8)		
	Monotherapy	NR	123 (49.0)	58 (42.0)	26 (48.1)		
	Doublet Regimen		85 (33.9)	54 (39.1)	13 (24.1)		
	Triplet Regimen		7 (2.8)	4 (2.9)	4 (7.4)		
Retreatment with	Carfilzomib	39/145 (26.9)	NR	NR	NR		
	Pomalidomide	49/173 (28.3)					

Study		Mehra 2020[31]				Goldsmith 2020[30]	
Arms		Overall	LOT1*	LOT2*	LOT3*	BP	DCEP
Previously Received Regimen, n/N (%)	Bortezomib	72/226 (31.9)					
	Elotuzumab	1/24 (4.2)					
	Lenalidomide	55/244 (22.5)					
	Ixazomib	NR					
	Thalidomide	NR					
	Daratumumab	34/251 (13.5)					

95% CI: 95% confidence interval, BP: bendamustine/prednisone, CR: complete response, DCEP: dexamethasone, cyclophosphamide, etoposide, and cisplatin, LOT: line of therapy, n: number, N: total number, NR: not reported, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PR: partial response, sCR: stringent complete response, vgPR: very good partial response

*Subgroup of patients receiving a first (LOT1), second (LOT2), or third (LOT3) line of therapy after becoming triple-class refractory.

Table D3.22. Safety Outcomes: Usual Care Regimens

Trial/Study		MAMMOTH[7]	Goldsmith 2020[30]	
Arms		Overall	BP	DCEP
N		275	27	31
Median Follow-Up, Months (Range)		10.6 (1.9-42.3)	NR	
Risk of PD or Death, HR (95%CI)	Carfilzomib-based Regimens	0.60 (0.42, 0.85)	NR	
	Daratumumab + IMiD Regimens	0.64 (0.43, 0.94)		
Neutropenia	Grade 4	NR	5 (18.5)	NR
	Neutropenic fevers		NR	5 (16.1)
Thrombocytopenia	Grade 4		9 (33.3)	NR
Tumor Lysis Syndrome			1 (3.7)	1 (3.2)
Sepsis			1 (3.7)	1 (3.2)
Safety data not reported for MAMMOTH triple/quad-refractory or penta-refractory arms, or any Mehra 2020 arm.				

95% CI: 95% confidence interval, BP: bendamustine/prednisone, DCEP: dexamethasone, cyclophosphamide, etoposide, and cisplatin, HR: hazard ratio, IMiD: immunomodulatory drug, n: number, N: total number, NR: not reported, PD: progressive disease

Table D3.23. Safety Outcomes: Additional Usual Care Regimens†

Trial/Study		ELOQUENT-3[35]	TOURMALINE-MM1[33]	Bringhen 2014[34]
Treatment		**Elo + Pom + Dex**	**Ixa + Len + Dex**	**Car + Cy + Dex**
Median Follow-up		Minimum 9.1 Months	23.3 Months	18 Months
Safety Population, N		60	361	56
Age, Median (Range)		69 (43-81)	66 (38-91)	71 (IQR: 68-75)
Prior Therapies, Median (Range)		3 (2-8)	NR	NR
Double-refractory, n (%)		41 (68)	NR	NR
AEs, n (%)		58 (96.7)	355 (98.3)	44 (78.6)*
Grade ≥3 AEs, n (%)		34 (56.7)	267 (74.0)	15 (26.8)*
SAEs, n (%)		32 (53)	168 (46.5)	NR
Mortality, n (%)	**Overall**	13 (21.7)	15 (4.2)	7 (12.5)
	Disease Progression	8 (13.3)	NR	2 (3.6)
	AE	5 (8.3)	NR	4 (7.1)
Discontinuation due to AEs, n (%)		11 (18)	60 (16.6)	8 (14)
Neutropenia, n (%)	**Overall**	14 (23.3)	118 (32.7)	20 (35.7)
	Grade 3/4	8 (13.3)	81 (22.4)	11 (19.6)
Anemia, n (%)	**Overall**	15 (25.0)	103 (28.5)	39 (69.6)
	Grade 3/4	6 (10.0)	34 (9.4)	6 (10.7)
Thrombocytopenia, n (%)	**Overall**	9 (15.0)	112 (31.0)	21 (37.5)
	Grade 3/4	5 (8.3)	69 (19.1)	2 (3.6)
Lymphopenia, n (%)	**Overall**	6 (10.0)	NR	NR
	Grade 3/4	5 (8.3)	NR	NR
Hyperglycemia, n (%)	**Overall**	12 (20.0)	NR	7 (12.5)
	Grade 3/4	5 (8.3)	NR	1 (1.8)
Infections, n (%)	**Overall**	39 (65.0)	83 (23.0)	10 (17.9)
	Grade 3/4	8 (13.3)	2 (0.6)	3 (5)
Fatigue, n (%)	**Overall**	9 (15.0)	106 (29.4)	11 (20)
	Grade 3/4	0 (0.0)	13 (3.6)	1 (1.8)
Neuropathy, n (%)	**Overall**	NR	97 (26.9)	5 (8.9)

Trial/Study		ELOQUENT-3[35]	TOURMALINE-MM1[33]	Bringhen 2014[34]
Treatment		Elo + Pom + Dex	Ixa + Len + Dex	Car + Cy + Dex
	Grade 3/4	NR	9 (2.5)	0 (0)

AEs: adverse events, Car: carfilzomib, Cy: cyclophosphamide, Dex: dexamethasone, Elo: elotuzumab, IQR: interquartile range, Ixa: ixazomib, Len: lenalidomide, n: number, N: total number, NR: not reported, Pom: pomalidomide, SEA: serious adverse events

* Hematologic adverse events.

† Representative prospective trials of commonly used treatments selected externally to the systematic review meant to supplement the insufficient safety data in the three retrospective studies selected to represent the effectiveness of usual care regimens.

D4. Ongoing Studies

Table D4.1. Ongoing Studies: Ide-cel

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
Study of bb2121 in Multiple Myeloma Celgene NCT02658929	Two-part, Non-randomized, Phase I Clinical Trial Actual enrollment: N = 67	**Dose Escalation Phase (Part A):** – Ide-cel (dose range: 150 – 450 x 106 CAR+ T cells) **Expansion Phase (Part B):** – Ide-cel (recommended dose)	**Inclusions:** – ECOG status of 0 or 1 – Measurable disease – Diagnosis of relapsed or refractory MM with at least 3 different prior lines of therapy including PI & IMiD, or be "double-refractory" to a PI and IMiD or previous (Part A) – Diagnosis of relapsed/refractory MM with previous PI, IMiD, and dara exposure **Exclusions:** – Known CNS disease – Inadequate renal, hepatic, bone marrow function – Significant co-morbid conditions, second malignancies, history of class III or IV congestive heart failure etc.	**Primary:** – Incidence of adverse events (including dose limiting toxicities) **Secondary:** – ORR, CR, vgPR, PR *[60 Months]*	November 30, 2023
Efficacy and Safety Study of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma (KarMMa) Celgene	Single Arm, Phase II Clinical Trial Actual enrollment: N = 149	**Intervention:** – Ide-cel (dose range: 150 – 450 x 10^6 CAR+ T cells)	**Inclusions:** – ≥3 prior MM treatments with at least 2 consecutive cycles of treatment for each regimen – Received PI, IMiD, and an anti-CD38 antibody, refractory to last treatment – ECOG status 0 or 1 – Measurable disease	**Primary***:* – ORR **Secondary:** – CR, Time to response, DOR, PFS, OS, MRD – Adverse events	November 1, 2024

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
NCT03361748			**Exclusions:** – Known CNS involvement with myeloma or presence of relevant CNS pathology – Active or history of plasma cel leukemia – Inadequate organ function – History of allogeneic hematopoietic SCT	– EORTC-QLQ-C30, EuroQol Group EQ-5D-5L, EORTC-QLQ-MY20 *[≥24 months]*	
An Efficacy and Safety Study of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma and in Subjects with High-Risk Multiple Myeloma (KarMMa-2) Celgene NCT03601078	Single Arm, Multi-cohort Phase II Clinical Trial Estimated enrollment: N = 181	**Intervention:** – Ide-cel (dose range: 150 – 450 x 10^6 CAR+ T cells)	**Inclusions:** – Measurable disease – Cohort-specific requirements: (Cohort 1) relapsed/refractory MM subjects with ≥3 prior treatment regimens; (Cohort 2) subject with 1 prior treatment regimen – ECOG status ≤1 – Grade 1 or baseline non-hematological toxicities due to prior treatments **Exclusions:** – Receiving investigational dugs, plasmapheresis, major surgery, radiation therapy, systemic anti-myeloma therapy 14 days prior to leukapheresis – History of relevant CNS pathology, CNS involvement with myeloma – Active plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome, clinically significant amyloidosis – Previous allogeneic SCT	**Primary:** – Cohort 1: ORR – Cohort 2: CR **Secondary:** – Cohort 1: CR – Cohort 2: ORR – DOR, time to response, PFS, OS, time to progression, MRD – Adverse events *[≥5 years]* – EORTC-QLQ-C30, EuroQoL Group EQ-5D-5L, EORTC-QLQ-MY20 *[≥5 years]* *[≥2 years]*	May 13, 2026

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
Efficacy and Safety Study of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3) Efficacy and Safety Study of bb2121 Versus Standard Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3) Celgene NCT03651128	Randomized, Phase III Clinical Trial Estimated enrollment: N = 381	**Intervention**: – Ide-cel (dose range: 150-450 x 10^6 CAR+ T cells) **Standard Regimens**: – Dara/Pom/Dex – Dara/Bor/Dex – Ixa/Len/Dex – Car/Dex – Elo/Pom/Dex	**Inclusions:** – Measurable disease – ECOG status of 0 or 1 – Received ≥2 but not >4 prior MM regimens – Prior treatment with dara, a PI, and an IMiD-containing regiment for ≥2 consecutive cycles – Refractory to last treatment regimen – Achieved minimal response or better to ≥1 prior treatment **Exclusions:** – Non-secretory MM – History of malignancies, history of or active plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome, amyloidosis, etc. – Subject treated with one of the comparator regimens as most-recent regimen cannot receive it again but may receive one of the others – Autologous SCT 12 weeks prior to randomization	**Primary:** – PFS **Secondary:** – OS, event-free survival, ORR, MRD, CR, DOR, time to response – Adverse events – EORTC-QLQ-C30, EuroQoL Group EQ-5D-5L, EORTC-QLQ-MY20 *[≥5 years]*	November 6, 2025
A Study to Evaluate the Safety of bb2121 in Subjects with High Risk, Newly Diagnosed Multiple Myeloma (NDMM) (KarMMa-4)	Single Group, Phase 1 Clinical Trial Estimated enrollment: N = 60	**Intervention**: – Ide-cel (dose range: 150-800 x 10^6 CAR+ T cells)	**Inclusions:** – New diagnosis of symptomatic MM – Subject has measurable disease – Subject has high-risk MM – ECOG status of ≤ 1 – Has received ≤ 3 cycles of induction anti-myeloma therapy	**Primary:** – Dose-limiting toxicity *[Up to 2 years]* – Adverse events *[Up to 5 years]*	January 15, 2025

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
Celgene NCT04196491			**Exclusions:** – Non-secretory MM – Subject received any treatments of MM other than up to 3 cycles of induction therapy – Clinically significant CNS pathology – High risk developing deep vein thrombosis/pulmonary embolus & cannot undergo anti-thrombotic therapy – Moderate or severe pulmonary hypertension – Subject has cardiac or pulmonary conditions; needs chronic immunosuppressants – History of primary immunodeficiency	**Secondary:** *[2.5 years]* – CR, ORR, DOR, PFS, OS – Time to maintenance therapy	

AE: adverse event, Bor: bortezomib, Car: carfilzomib, CNS: central nervous system, CR: complete response, Dara: daratumumab, Dex: dexamethasone, DOR: duration of response, ECOG: Eastern Cooperative Oncology Group, Elo: elotuzumab, IMiD: immunomodulatory drug, Ixa: Ixazomib, Len: lenalidomide, MM: multiple myeloma, MRD: minimal residual disease, N: total number, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PI: protease inhibitor, POEMS: polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes, Pom: pomalidomide, SCT: stem cell transplant, vgPR: very good partial response. Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Table D4.2. Ongoing Studies: Cilta-cel

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
LCAR-B38M Cells in Treating Relapsed/Refractory (R/R) Multiple Myeloma (LEGEND-2)	Single Arm Phase I/II Clinical Trial Estimated enrollment: N = 100	**Intervention**: – Cilta-cel (dose range: 0.5-5 x 10^6 CAR+ T cells/kg)	**Inclusions:** – IMWG confirmed diagnosis of active MM – Refractory MM (≥3 prior regimens, including Bortezomib) – Relapse criteria in NCCN clinical practice guidelines	**Primary:** *[1 month]* – Treatment related adverse events **Secondary:** *[36 months]*	December 31, 2021

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
Nanjing Legend Biotech Co. **NCT03090659**			**Exclusions:** – Systemic corticosteroid therapy greater than 5 mg/day prednisone or equivalent of another corticosteroid within 2 weeks of leukapheresis or chemotherapy regimen – History of allogeneic SCT (active acute or chronic GVHD or require immunosuppressant medication for GVHD within 6 months of enrollment – Active autoimmune diseases or CNS metastases or symptomatic CNS involvement	– Changes in aberrant immunoglobin in serum – Multiple myeloma cells in bone marrow	
A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-Cell Maturation Antigen (BCMA) in Participants with Relapsed or Refractory Multiple Myeloma (CARTITUDE-1) **Janssen Research & Development, LLC** **NCT03548207**	Single Arm, Phase 1b-2 Clinical Trial Estimated enrollment: N = 126	**Intervention**: – Cilta-cel (Dose: NR)	**Inclusions:** – Measurable disease – ECOG status of 0 or 1 – Received ≥3 prior therapies (including PI, IMiD, and an anti-CD38 antibody), or double refractory to IMiD and PI – Evidence of progressive disease **Exclusions:** – Prior CAR-T therapy at any target, therapy targeted to BCMA – Allogenic SCT within 6 months before apheresis; autologous SCT within 12 weeks before apheresis – Known active/prior history of CNS or meningeal involvement of MM	**Primary:** – Phase 1b: Adverse events – Phase 2: ORR **Secondary:** – Phase 2: Adverse events – vgPR or better, DOR, PFS, OS, MRD – EORTC QLQ-C30 and QLQ-MY20, EQ-5D-5L *[≥2 years]*	April 30, 2022
A Study of LCAR-B38M CAR-T Cells, a Chimeric Antigen Receptor T-cell (CAR-T) Therapy Directed Against B-cell Maturation Antigen	Single Arm, Phase II Clinical Trial Estimated enrollment: N = 60	**Intervention**: – Cilta-cel (Dose: NR)	**Inclusions:** – Measurable disease – ECOG status of 0 or 1 – Received ≥3 prior lines of MM treatment (≥1 complete cycle of treatment for each line; received a PI and IMiD)	**Primary:** – ORR **Secondary:** – vgPR or better, DOR, PFS, OS, MRD	November 30, 2022

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
(BCMA) in Chinese Participants with Relapsed or Refractory Multiple Myeloma (CARTIFAN-1) **Nanjing Legend Biotech Co.** **NCT03758417**			– Evidence of progressive disease **Exclusions:** – Prior CAR-T therapy at any target, any therapy targeted to BCMA – Allogeneic SCT for MM; Autologous SCT 12 weeks prior to apheresis – Diagnosed or treated for non-MM invasive malignancies – Prior antitumor therapy, insufficient washout period	– Adverse events *[≥2 years]*	
A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-cell Maturation Antigen (BCMA) in Participants with Multiple Myeloma (CARTITUDE-2) **Janssen Research & Development, LLC** **NCT04133636**	Single Group, single arm, Phase 2 Clinical Trial Estimated enrollment: N = 100	**Intervention**: – Cohort A: cilta-cel – Cohort B: cilta-cel – Cohort C: cilta-cel – Cohort D: cilta-cel + lenalidomide (only some participants) – Cohort E: cilta-cel + Dara/Bor/Len/Dex	**Inclusions:** – Cohort A: Received 1-3 lines of prior therapy – Cohort B: One line of therapy, early relapse – Cohort C: Treated with PI, IMiD, anti-CD38 monoclonal antibody and BCMA-directed therapy – Cohort D: Newly diagnosed MM with history of 4-8cycles initial therapy – Cohort E: Newly diagnosed, no prior therapy **Exclusions:** – Prior treatment with CAR T therapy for any target – Ongoing toxicity Grade 1 or less (except alopecia or peripheral neuropathy) – Prednisone (≥70mg) within 7 days – History of CNS or meningeal involvement of multiple myeloma	**Primary:** – MRD *[≥1 year]* **Secondary:** – ORR, vgPR or better, CBR, DOR – Adverse events *[≥2 years]*	July 25, 2024
A Study Comparing JNJ-68284528, a CAR-T Therapy Directed Against B-cell	Interventional: Randomized, Parallel Assignment,	**Intervention:**	**Inclusions:** – Measurable disease – Received 1-3 prior lines of therapy	**Primary:** – PFS	April 10, 2026

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
Maturation Antigen (BCMA), Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Participants with Relapsed and Lenalidomide-Refractory Multiple Myeloma **Janssen Research & Development, LLC** NCT04181827	Phase 3 Clinical Trial Estimated enrollment: N = 400	– Cilta-cel (target dose of 0.75 * 10^6 CAR+ T cells/kg) **Standard Regimens**: – Bor/Pom/Dex – Dara/Pom/Dex	– Evidence of progressive disease – Refractory to lenalidomide – Have clinical laboratory values meeting screening phase criteria **Exclusions:** – Prior CAR T-cell therapy directed at any target – Previous therapy targeting BCMA – Ongoing toxicity from previous anticancer therapy – Monoclonal antibody treatment within 21 days; Cytotoxic therapy or Proteasome inhibitory therapy within 14 days; Immunomodulatory drug therapy within 7 days	**Secondary:** – ORR, CR/sCR, OS, MRD – Adverse events *[Up to 6 years]*	

BCMA: b-cell maturation antigen, Bor: bortezomib, CAR: chimeric antigen receptor, CBR: clinical benefit rate, CNS: central nervous system, CR: complete response, Dara: daratumumab, Dex: dexamethasone, DOR: duration of response, ECOG: Eastern Cooperative Oncology Group, GVHD: graft versus host disease, IMiD: immunomodulatory drug, IMWG: International Myeloma Working Group, Len: lenalidomide, MM: multiple myeloma, mg: milligram, MRD: minimal residual disease, N: total number, NCCN: National Comprehensive Cancer Network, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PI: protease inhibitor, Pom: pomalidomide, sCR: stringent complete response, SCT: stem cell transplant, VGPR: very good partial response
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Table D4.3. Ongoing Studies: Belantamab

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
A Study to Investigate the Efficacy and Safety of Two Doses of GSK2857916 in Participants with Multiple Myeloma	Randomized, Two-Arm Phase II Clinical Trial Actual enrollment: N = 221	**Interventions**: – Arm 1: 2.5 mg/kg frozen belantamab mafodotin every three weeks	**Inclusions:** – ECOG status of 0-2 – Histologically/cytologically confirmed MM; has undergone autologous SCT or transplant-ineligible; has failed ≥2 prior lines of therapy including IMiD and PI	**Primary:** – ORR **Secondary:** – CBR, DOR, PFS, OS	November 30, 2020

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
Who Have Failed Prior Treatment with an Anti-CD38 Antibody (DREAMM 2) **GlaxoSmithKline** **NCT03525678**		– Arm 2: 3.4 mg/kg frozen belantamab mafodotin – Arm 3: 3.4 mg/kg lyophilized belantamab mafodotin	– Measurable disease – History of autologous SCT only if 100 days prior to study enrollment & no active infections – Adequate organ system function **Exclusions:** – Systemic anti-myeloma therapy, treatment with high dose steroids, investigational drug within 14 days – Symptomatic amyloidosis, active POEMS, active plasma cell leukemia at time of screening – Prior allogeneic SCT – Current corneal epithelial disease, active renal condition, active mucosal/internal bleeding, unstable liver/biliary disease, other malignancies etc.	*[Up to 48 weeks]*	
Characterization of Corneal Epithelial Changes in Participants Treated with Belantamab Mafodotin **GlaxoSmithKline** **NCT04549363**	Parallel, Non-Randomized, Phase 3 Clinical Trial Estimated enrollment: N = 25	**Intervention:** – Arm 1: Participants undergoing Impression cytology + belantamab mafodotin – Arm 2: Participants undergoing Superficial keratectomy + belantamab mafodotin	**Inclusions:** – Age 18 years or older – Patients with relapsed/refractory MM who receives/has received treatment with Belantamab and microcyst-like epithelial changes diagnosis – If undergoing superficial keratectomy, must not pose excessive risk to patient **Exclusions:** – Serious/unstable medical or psychiatric disorder – Excess risk of delayed wound healing – Eye infections – Active uveitis – Permanent legal blindness in the non-study eye	**Primary:** – Abnormal corneal epithelium composition – Abnormal pathologic characteristics **Secondary:** – Adverse events, serious adverse events – Abnormal BCVA scores, corneal symptoms, and corneal epithelial lesions *[Up to 5 weeks]*	November 30, 2020

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
A Study of Belantamab Mafodotin to Investigate Safety, Tolerability, Pharmacokinetics, Immunogenicity and Clinical Activity in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) **GlaxoSmithKline** **NCT04177823**	Non-randomized, Single Group, Phase 1 Clinical Trial Estimated enrollment: N = 12 Actual enrollment: N = 5	**Intervention**: – 2.5 mg/kg belantamab mafodotin every 3 weeks – 3.4 mg/kg belantamab mafodotin every 3 weeks	**Inclusions:** – ECOG status of 0-2 – Histological/cytologically confirmed MM diagnosis – Has undergone stem cell transplant/stem cell transplant not deemed feasible – Failed at least 2 prior lines of anti-myeloma treatment – Refractory to an immunomodulatory drug and proteasome inhibitor – Measurable disease – Adequate organ system functions – All prior treatment-related toxicities must be ≤ Grade 1, Grade 2 peripheral neuropathy **Exclusions:** – Prior allogenic stem cell transplant – Systemic anti-myeloma therapy or investigational drugs within 14 days; plasmapheresis within 7 days – Symptomatic amyloidosis, POEMS syndrome – Active renal condition, unstable liver, or biliary disease – Malignancies other than disease under study	**Primary:** – Adverse events, serious adverse events – Dose-limiting toxicities **Secondary:** – Systolic and diastolic blood pressure – Hematology and chemistry parameters *[Up to 15 months]*	July 31, 2021
An Open-label, Dose Escalation Study in Japanese Subjects with Relapsed/Refractory Multiple Myeloma Who Have Failed Prior Anti Myeloma Treatments	Single Group, Dose-escalation, Phase I Clinical Trial Estimated enrollment: N = 14	**Part 1:** Belantamab mafodotin monotherapy **Part 2:** – Belantamab mafodotin + Bor/Dex	**Inclusions:** – Age 20 years or older – ECOG status of 0-2 – Measurable disease – Autologous stem cell transplant > 100 days prior	**Primary:** – Dose-limiting toxicities *[Day 21]* – Adverse events – Abnormal hematology, clinical chemistry, urine parameters	February 28, 2023

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
GlaxoSmithKline **NCT03828292**		– Belantamab mafodotin + Pom/Dex	– Prior toxicities ≤ Grade 1, except alopecia & peripheral neuropathy Grade 2 **Exclusions:** – Systemic anti-tumor therapy within 14 days, plasmapheresis within 7 days of first dose – Symptomatic amyloidosis, active POEMS syndrome, active plasma cell leukemia at time of screening – Allogeneic SCT – Active renal condition, corneal epithelial disease, active mucosal or internal bleeding, severe or uncontrolled systemic disease, etc.	– Abnormal vital signs, ECG, physical and ocular examination *[Up to 2.2 years]*	
A Study of Belantamab Mafodotin (GSK2857916) in Multiple Myeloma Participants with Normal and Impaired Hepatic Function (DREAMM 13) **GlaxoSmithKline** **NCT04398680**	Non-Randomized, Parallel, Phase I Clinical Trial Estimated enrollment: N = 40	**Intervention (Part 1):** – Participants with normal hepatic function: 2.5 mg/kg belantamab mafodotin every 3 weeks – Participants with moderate hepatic impairment: 2.5 mg/kg belantamab mafodotin every 3 weeks	**Inclusions:** – ECOG status of 0-2 – Histologically/cytologically confirmed MM; has undergone autologous SCT or transplant-ineligible; has failed ≥2 prior lines of therapy including IMiD and PI – Measurable disease – History of autologous SCT only if 100 days prior to study enrollment & no active infections – Adequate organ system function **Exclusions:** – Active plasma cell leukemia, symptomatic amyloidosis, active POEMS syndrome, Waldenstroem Macroglobulinemia – Prior allogeneic SCT	**Primary:** – Max observed plasma concentration – Predose plasma concentration – AUC for plasma concentration-time – AUC over the dosing interval of belantamab *[throughout 21-day cycle]* **Secondary:** – Adverse events, serious adverse events *[Up to 4 years]*	May 6, 2024

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
		Intervention (Part 2): – Patients with severe hepatic function: 2.5 mg/kg or 1.9 mg/kg belantamab mafodotin every 3 weeks	– Investigational drug or strong organic anion transporting polypeptide inhibitor received 2 weeks prior – ≥2 Grade toxicity from previous treatment except alopecia or peripheral neuropathy up to Grade 2 – Previous or concurrent malignancies unless medically stable for at least 2 years		
Study of Single Agent Belantamab Mafodotin Versus Pomalidomide Plus Low-dose Dexamethasone (Pom/Dex) in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) **GlaxoSmithKline** **NCT04162210**	Randomized, Parallel, Phase 3 Clinical Trial Estimated enrollment: N = 380	**Intervention**: – 2.5 mg/kg belantamab mafodotin every 3 weeks **Comparator**: – Pom/Dex (low dose)	**Inclusions:** – ECOG status of 0-2 – Histological/cytologically confirmed MM – Has undergone stem cell transplant/stem cell transplant not deemed feasible – Failed at least 2 prior lines of anti-myeloma treatment – Refractory to an immunomodulatory drug and proteasome inhibitor – Measurable disease – Adequate organ system functions – All prior treatment-related toxicities must be ≤ Grade 1, Grade 2 peripheral neuropathy **Exclusions:** – Prior allogenic stem cell transplant – Systemic anti-myeloma therapy or investigational drugs within 14 days; plasmapheresis within 7 days – Symptomatic amyloidosis, POEMS syndrome, plasma cell leukemia – Active renal condition, unstable liver, or biliary disease	**Primary:** – PFS *[Up to 20 months]* **Secondary:** – OS, ORR, CBR, DOR – Adverse events *[Up to 55 months]*	November 21, 2024

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
			– Malignancies other than disease under study		
A Study of Belantamab Mafodotin (GSK2857916) in Multiple Myeloma Participants with Normal and Varying Degree of Impaired Renal Function (DREAMM 12) **GlaxoSmithKline** **NCT04398745**	Non-Randomized, Phase I Clinical Trial Estimated enrollment: N = 36	**Intervention (Part 1):** – Patients with normal/mild impaired renal function: 2.5 mg/kg belantamab mafodotin every 3 weeks – Patients with severe renal impairment: 2.5 mg/kg belantamab mafodotin every 3 weeks **Intervention (Part 2):** – Patients with ESRD (not on dialysis): 2.5 mg/kg or 1.9 mg/kg belantamab mafodotin every 3 weeks – Patients with ESRD (on hemodialysis): 2.5 mg/kg or 1.9 mg/kg	**Inclusions:** – ECOG status of 0-2 – Histologically/cytologically confirmed MM; has undergone autologous SCT or transplant-ineligible; has failed ≥2 prior lines of therapy including IMiD and PI – Measurable disease – History of autologous SCT only if 100 days prior to study enrollment & no active infections – Adequate organ system function **Exclusions:** – Active plasma cell leukemia, symptomatic amyloidosis, active POEMS syndrome, Waldenstroem Macroglobulinemia – Prior allogeneic SCT – Investigational drug, belantamab mafodotin, strong organic anion transporting polypeptide inhibitor received 2 weeks prior – ≥2 Grade toxicity from previous treatment except alopecia or peripheral neuropathy up to Grade 2 – Previous or concurrent malignancies unless medically stable for at least 2 years	**Primary:** – Max. observed plasma concentration – Concentration belantamab at end of infusion – Pre-dose plasma concentration – AUC over the dosing interval of belantamab *[Up to 3 21-day cycles)* **Secondary:** – Adverse events, serious adverse events *[Up to 4 years]*	March 7, 2025

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion
		belantamab mafodotin every 3 weeks			
Platform Study of Belantamab Mafodotin as Monotherapy and in Combination with Anti-cancer Treatments in Participants with Relapsed/Refractory Multiple Myeloma (RRMM) (DREAMM 5) **GlaxoSmithKline** **NCT04126200**	Randomized, Sequential Assignment, Phase I/II Clinical Trial Estimated enrollment: N = 464	**Intervention**: – Substudy 1: Belantamab mafodotin + GSK3174998 – Substudy 2: Belantamab mafodotin + GSK3359609 – Substudy 3: Belantamab mafodotin + Nirogacestat – Substudy 4: Belantamab mafodotin + Dostarlimab **Active Comparator**: – Belantamab mafodotin monotherapy	**Inclusions:** – 3 prior lines of anti-myeloma treatments (including IMiD, PI, anti-CD38 monoclonal antibody) – History of autologous stem cell transplant >100 days prior to enrollment – ECOG status 0-1 – Measurable disease **Exclusions:** – Corneal epithelial disease – Prior radiotherapy within 2 weeks, prior allogenic transplant, prior CAR T therapy within 3 months, prior investigational agent treatment within 2 weeks – Delayed hypersensitivity reaction or idiosyncrasy to drugs chemically similar to Belantamab mafodotin	**Primary:** – Dose-limiting toxicities – Adverse events – Abnormality in vital signs – Changes in hematology, clinical chemistry, and urinalysis lab parameters – ORR **Secondary:** – CBR, PR, vgPR, CR, sCR, PFS, DOR, OS – Adverse events, serious adverse events *[Up to 36 months]*	February 24, 2028

AUC: area under the curve, BCVA: Best Corrected Visual Acuity, CAR: chimeric antigen receptor, CBR: clinical benefit rate, CNS: central nervous system, CR: complete response, Dex: dexamethasone, DLT: dose limiting toxicities, DOR: duration of response, ECG: echocardiogram, ECOG: Eastern Cooperative Oncology Group, ESRD: end-stage renal disease, IMiD: immunomodulatory drug, kg: kilogram, max: maximal, MM: multiple myeloma, mg: milligram, MRD: minimal residual disease, N: total number, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, PI: protease inhibitor, POEMS: polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes, Pom: pomalidomide, PR: partial response, sCR: stringent complete rate, SCT: stem cell transplant
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D5. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessment of belantamab mafodotin and one of ide-cel by the National Institute for Health and Care Excellence (NICE) summarized below. We also identified one systematic review and meta-analysis of BCMA CAR-T therapies, one systematic review and meta-analysis of pomalidomide-based regimens, and another systematic review and network meta-analysis of investigational treatments for relapsed/refractory MM.

NICE Technology Assessments

Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 3 therapies [ID2701]

NICE is currently conducting an appraisal of the clinical and cost effectiveness of belantamab mafodotin in relapsed and refractory multiple myeloma patients who have received three prior therapies. The expected publication date is to be confirmed.

Idecabtagene vicleucel for treating relapsed and refractory multiple myeloma in people who have received at least 3 prior therapies [ID1442]

NICE is currently conducting an appraisal of the clinical and cost effectiveness of ide-cel in relapsed and refractory multiple myeloma patients who have received at least three prior therapies. Comparators in the final scope include pomalidomide-dexamethasone and panabinostat-bortezomib-dexamethasone combinations, reflecting a difference in preferred treatment in England as compared to the U.S. The expected publication date is to be confirmed.

Previous Systematic Reviews

Roex G, Timmers M, Wouters K, et al. Safety and clinical efficacy of BCMA CAR-T-cell therapy in multiple myeloma. *J Hematol Oncol*. 2020;13(1):164.

This systematic review and meta-analysis assess the safety and clinical efficacy of BCMA-targeted CAR-T-cell therapies in patients with multiple myeloma. Including a total of 27 clinical studies pertaining to 23 different BCMA CAR-T-cell therapies, it is the most comprehensive review to date. One study for each of the two most advanced therapies (ide-cel and cilta-cel) were identified.

For all BCMA CAR-T patients evaluable for clinical response, high response rates were achieved. Response rates for high dose ide-cel and cilta-cel were comparable (ORR 82% and 88%, respectively). The median PFS among evaluable patients treated with high-dose ide-cel was 12.1 months (95% CI 8.8, 12.3) and 19.9 months for patients treated with cilta-cel (95% CI 9.6, 31.0). Although high response rates were achieved across BCMA CAR-T studies, toxicity was also high.

80.3% patients evaluable for safety experienced CRS with 14.1% experiencing CRS of grade ≥3. High dose ide-cel and cilta-cel had higher than average rates of CRS overall (96.3% and 89.5%, respectively) but lower rates of grade ≥3 CRS (7.0% and 5.6%, respectively). Rates of neurotoxicity differed considerably between studies. The population included in the ide-cel study was generally older and more heavily pretreated, possibly contributing to its higher neurotoxicity rate.

Overall, BCMA CAR-T-cell therapies prove to have high response rates, but equally as high toxicity. Despite toxicities, this meta-analysis provides robust evidence that BCMA CAR-T therapies are considered highly efficacious even in heavily pretreated MM patients.

Mushtaq A, Iftikhar A, Hassan H, et al. Pomalidomide-Based Regimens for Treatment of Relapsed and Relapsed/Refractory Multiple Myeloma: Systematic Review and Meta-analysis of Phase 2 and 3 Clinical Trials. *Clin Lymphoma Myeloma Leuk*. 2019;19(7):447-461.

This systematic review and meta-analysis evaluated the efficacy of various pomalidomide-based regimens in the relapsed/refractory multiple myeloma population. Investigators identified 35 phase II/III trials on a total of 4623 patients who had received two or more prior lines of therapy. Almost half of the identified trials studied the doublet regimen pomalidomide (Pom) + low-dose dexamethasone (LoDex). The remaining trials focused on triplet regimens primarily consisting of Pom + LoDex + a third drug such as cyclophosphamide, daratumumab, bortezomib, or carfilzomib.

Pooled analysis yielded an ORR of 47.1% for all identified Pom-based regimens. However, triplet regimens resulted in almost double the response rate of the doublet Pom + LoDex (pooled ORR: 61.9% vs 35.7%). Of the triplet regimens, patients on bortezomib + Pom + LoDex (BPD) and carfilzomib + Pom + LoDex (CPD) had the best responses (ORR: 83.5% and 77.1%, respectively). Although BPD has a slightly higher response, investigators suggest that patients' frequent prior exposure to bortezomib may indicate that CPD would be a superior regimen as it may be more novel to patients. As for adverse events, the most common grade 3 or higher events among Pom-based regimens were neutropenia, anemia, and thrombocytopenia. Common grade 3 or higher nonhematologic AEs were infections, pneumonia, and fatigue. The rates of adverse events are considered acceptable for Pom.

Overall, three-drug regimens of Pom achieve twice the response of two-drug Pom regimens with BPD and CPD producing better outcomes. Trials for various Pom-containing triplet regimens are ongoing and prospective head-to-head trials may be required to identify the best RRMM treatment option.

Arcuri LJ, Americo AD. Treatment of relapsed/refractory multiple myeloma in the bortezomib and lenalidomide era: a systematic review and network meta-analysis. *Ann Hematol*. Published online January 11, 2021. doi: 10.1007/s00277-021-04404-3.

This systematic review and network meta-analysis compared efficacy and safety of various combinations of novel treatments in relapsed/refractory MM (RRMM). The investigators sought to indirectly compare and rank different treatment regimens: daratumumab, isatuximab, carfilzomib, pomalidomide, elotuzumab, panobinostat, venetoclax, ixazomib, Selinexor, vorinostat, pembrolizumab, and high-dose chemotherapy. 18 phase III randomized controlled trials, most with a control arm of lenalidomide or bortezomib, in previously treated RRMM patients were included in the quantitative analysis.

Patients receiving triplet regimens containing daratumumab and pegylated liposomal doxorubicin had the highest probabilities of achieving a better PFS over the other previously listed therapies (0.924 and 0.735, respectively). Pembrolizumab, vorinostat, and high-dose chemotherapy ranked as the least effective therapies based on PFS, with pembrolizumab performing worse than control. In terms of safety, isatuximab, panobinostat, and pomalidomide were found to be the most toxic therapies, followed by pembrolizumab, daratumumab, elotuzumab, and carfilzomib. Toxicity profiles for the other treatment regimens were found to be comparable to placebo.

Overall, daratumumab- or pegylated liposomal doxorubicin-containing treatments may be preferred over other investigational therapies evaluated in this analysis. A meta-analysis of overall survival showed that, generally, adding a third drug or substituting carfilzomib for bortezomib in RRMM patients can likely improve disease control and survival.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E.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	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	X	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
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[70]

Detailed Description of Curve Digitization

Kaplan-Meier curves from the evidence were digitized using the algorithm by Guyot and colleagues to impute patient-level time-to-event data.[71] Base-case survival was derived from parametric fits to each intervention's available PFS and OS Kaplan-Meier curves.[19,44,45] Table E2.5 delineates the evidence that was used to calculate transition probabilities. The comparator PFS and OS evidence was derived from the MAMMOTH study using triple- and quad-refractory curves (for comparison to CAR-Ts) and a weighted average of triple-/quad-refractory and penta-refractory curves (for comparison to belantamab mafodotin).[7,45] Given we did not have an available PFS curve for the comparator population exposed to four or more lines of therapy (i.e., penta-refractory in Gandhi et al.), we assumed a similar shape to the PFS curve in the triple- and quad-refractory population in the Shah et al. conference proceeding[45] and adjusted the curve to fit a consistent PFS to OS relationship as observed in a recent meta-analysis.[47]

The model curves considered included distributional forms Weibull, exponential, log-normal, log-logistic, and Gompertz. The base-case distributional form was selected separately for each curve based on the best model fit using the Akaike information criterion (AIC) values and visual comparison. Monthly transition probabilities were then calculated using the model with the best fit. Beyond AIC and visual inspection, we assessed model fit based on percentage of the cohort alive and in the PFS state along with the percentage of the cohort alive overall at various time points and calibrated the model as needed. We also used piecewise modeling techniques to fit survival distributional forms at different time points after examining hazard functions.[48] For example, in the comparator population exposed to three or more lines of therapy, we first fit a log-normal distribution for all cycles less than 15 and then used the next best fit parametric distribution (Gompertz) after cycle 15. This piecewise approach improved the fit of median PFS and the percentage of the cohort in the PFS state at various time points when compared to the source of data used.

Target Population

The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients 1) no longer responsive to immunomodulatory agents, proteasome inhibitors, and anti CD38 monoclonal

antibodies (referred to as 'triple-class refractory' multiple myeloma) and exposed to three or more prior lines of therapy being treated with ide-cel and cilta-cel, and 2) those who were previously exposed to four or more lines of therapy being treated with belantamab mafodotin, entering the model. Cohort characteristics for each treatment group are described in E.1.2 and E.1.3.

Table E.1.2. Baseline Population Characteristics: Triple-Class Refractory

Triple-Class Refractory MM	Idecabtagene vicleucel	Ciltacabtagene autoleucel	Triple and Quad-Refractory Therapies
Median Age	61	61	60
Percent Male	59%	59%	57%
Refractory Status, %	Anti-CD38 Ab-refractory: 94% Triple-refractory: 84%	Triple-refractory: 88%	Anti-CD38 Ab-refractory: 100%
Median Prior Lines of Treatment	6	6	4
Source	Munshi et al, 2020[5]	Madduri et al, 2020[19]	Gandhi et al, 2019[7]

Table E.1.3. Baseline Population Characteristics: Penta-Refractory

Penta-Refractory MM	Belantamab mafodotin	Triple/Quad/Penta-Refractory Therapies
Median Age	65	59
Percent Male	53%	56%
Refractory Status, %	Anti-CD38 Ab-refractory: 100% in 2.5 mg/kg dose	Anti-CD38 Ab-refractory: 100%
Median Prior Lines of Treatment	7	5
Source	Lonial et al, 2020[44]	Gandhi et al, 2019[7]

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Idecabtagene vicleucel (Bristol Myers Squibb, Bluebird bio, Inc.)
- Ciltacabtagene autoleucel (Janssen, Legend Biotech)
- Belantamab mafodotin-blmf (Blenrep®, GlaxoSmithKline)

Comparators

The primary comparator for each type of therapy is listed below. Because of differences in population indications, interventions were not compared to each other. Given the numerous available therapies used by clinicians at various lines of therapy, a market basket approach was used to compare to each intervention based on line of therapy using the MAMMOTH study.[7] The market basket composition was approximated by both broad-therapy and specific-therapy estimations. For belantamab, we used a weighted average of MAMMOTH subcohorts so that the proportion of penta vs triple/quad refractory patients from the MAMMOTH comparator cohort matched that in the DREAMM-2 study. MAMMOTH results for these cohorts were used to inform comparator PFS and OS in the model. Specific regimens that are commonly employed in the relevant populations were also identified for the purpose of estimating market basket costs. For CAR-Ts, the comparator market basket included (sub-population within belantamab also compared using this market basket):

- Carfilzomib + cyclophosphamide + dexamethasone (KCd)
- Pomalidomide + cyclophosphamide + dexamethasone (PCd)
- Carfilzomib + pomalidomide + dexamethasone (KPd)
- Elotuzumab + pomalidomide + dexamethasone (EPd)
- Ixazomib, lenalidomide, and dexamethasone (IRd)

Comparator market basket for population exposed to four or more lines of therapy (used in weighted average comparator basket for belantamab):

- Carfilzomib + cyclophosphamide + dexamethasone (KCd)
- Pomalidomide + cyclophosphamide + dexamethasone (PCd)
- Ixazomib, pomalidomide, and dexamethasone (IPd)
- Elotuzumab + pomalidomide + dexamethasone (EPd)
- Ixazomib, lenalidomide, and dexamethasone (IRd)
- Bendamustine, prednisone, dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP)

Within each progressed state, we also applied a proportion of patients on palliative chemotherapy consistent with current evidence. Tables E.2.2 and E.2.3 provide dosing, administration schedules, and costs for each market basket of comparators.

E2. Model Inputs

Model inputs were estimated from the clinical review, published literature, and information from expert stakeholders. The inputs that informed the model are described below. The base case analysis took a health care system perspective and focused on direct medical care costs only.

Outcomes were estimated over a lifetime time horizon using a monthly cycle to capture the potential impacts of short-term and ongoing morbidity and mortality. Costs and outcomes were discounted at 3% per year.

Treatment Regimen Inputs

Treatment regimens for the interventions are described in Tables E.2.2. The market basket of therapy regimens for three or more lines of therapy and four or more lines of therapy are described in tables E.2.3, and E.2.4.

Table E2.2. Treatment Regimen Recommended Dosage

Category/Therapy	Idecabtagene vicleucel	Ciltacabtagene autoleucel	Belantamab mafodotin
Brand Name	TBD	TBD	Blenrep
Manufacturer	Bristol Myers Squibb/bluebird bio	Janssen/Legend Biotech	GlaxoSmithKline
Route of Administration	Single infusion	Single infusion	Infusion once every 3 weeks
Dosing	150-450 x 10^6 CAR+ T cells	0.75 x 10 (range: 0.5 - 1.0 x10) CAR+ T cells/kg	2.5 mg/kg of body weight
Use of Lymphocyte Depleting Chemotherapy	Fludarabine (30 mg per square meter of body surface per day) and cyclophosphamide (300 mg per square meter per day) on days -5, -4, -3	Cyclophosphamide (300 mg per square meter per day) on days -5, -4, -3	N/A

Table E.2.3 Triple Class Comparator Regimen Recommended Dosage and Total Cost

Therapy Combination	Days/Cycle	Cycle 1 Dose	Admin. Days	Proportion of Patients on Each Combination	Per Cycle Cost
Carfilzomib, Cyclophosphamide, Dexamethasone				18%	$20,830
Carfilzomib	28	20 mg/m2	1, 2, 8, 9, 15, 16 (cycle 1); 1, 2, 15, 16 (remaining cycles)		
Cyclophosphamide	28	300mg/m2	1,8,15		
Dexamethasone	28	20 mg	1, 2, 8, 9, 15 and 16		
Pomalidomide, Cyclophosphamide, Dexamethasone				34%	$17,083
Pomalidomide	28	4mg/day	1-21		
Cyclophosphamide	28	300mg/day	1, 8, 15, 22		
Dexamethasone	28	40mg/day	1-4 and 15-18		
Carfilzomib, Pomalidomide, Dexamethasone				18%	$30,471
Carfilzomib	28	20mg/m2; 27 mg/m2	1, 2; 8, 9, 15, 16 (cycle 1) 1, 2, 8, 9, 15, 16 (cycles 2-12)		
Pomalidomide	28	4mg/day	1-21		
Dexamethasone	28	20 mg	1,8,15,22		
Elotuzumab, Pomalidomide, Dexamethasone				19%	$34,385
Elotuzumab	28	10 mg/kg	1, 8, 15, and 22		
Pomalidomide	28	4mg/day	1-21		
Dexamethasone	28	28mg oral+8mg iv	1,8,15,22		
Ixazomib, Lenalidomide, Dexamethasone				10%	$21,500
Ixazomib	28	4mg/day	1,8,15		
Lenalidomide	28	25mg/day	1-21		
Dexamethasone	28	40mg/day	1,8,15,22		
Weighted average administration costs					$2,961
Weighted average adverse event cost management (applied for 2 cycles)					$1,531
Weighted average dose intensity (applied after 2 cycles)					96%
Weighted average total cost					**$28,457**

*All therapies were treat to progression unless otherwise stated in package inserts

Table E.2.4 Quad and Penta-Class Class Comparator Regimen Recommended Dosage and Total Cost

Therapy Combination	Days/Cycle	Cycle 1 Dose	Admin. Days	Proportion of Patients on Each Combination	Per Cycle Cost
Carfilzomib, Cyclophosphamide, Dexamethasone				22%	$20,830
Carfilzomib	28	20 mg/m2	1, 2, 8, 9, 15, 16 (cycle 1); 1, 2, 15, 16 (remaining cycles)		
Cyclophosphamide	28	300mg/m2	1,8,15		
Dexamethasone	28	20 mg	1, 2, 8, 9, 15 and 16		
Pomalidomide, Cyclophosphamide, Dexamethasone				17%	$17,083
Pomalidomide	28	4mg/day	1-21		
Cyclophosphamide	28	300mg/day	1, 8, 15, 22		
Dexamethasone	28	40mg/day	1-4 and 15-18		
Ixazomib, Pomalidomide, Dexamethasone				9%	$21,500
Ixazomib	28	4mg/day	1,8,15		
Pomalidomide	28	4mg/day	1-21		
Dexamethasone	28	40mg/day	1,8,15,22		
Elotuzumab, Pomalidomide, Dexamethasone				13%	$34,385
Elotuzumab	28	10 mg/kg	1, 8, 15, and 22		
Pomalidomide	28	4mg/day	1-21		
Dexamethasone	28	28mg oral+8mg iv	1,8,15,22		
Ixazomib, Lenalidomide, Dexamethasone				10%	$21,500
Ixazomib	28	4mg/day	1,8,15		
Lenalidomide	28	25mg/day	1-21		
Dexamethasone	28	40mg/day	1,8,15,22		

Bendamustine, prednisone, dexamethasone, cyclophosphamide, etoposide, and cisplatin				29%	$9,783
Bendamustine	28	90mg/m2			
Prednisone			1,2,3,4		
Dexamethasone	28	40mg/day	1,2,3,4		
Cyclophosphamide	28	400mg/m2	1,2,3,4		
Etoposide	28	40mg/m2	1,2,3,4		
Cisplatin	28	10mg/m2	1,2,3,4		
Weighted average administration costs					$1,249
Weighted average adverse event cost management (applied for 2 cycles)					$1,259
Weighted average dose intensity (applied after 2 cycles)					96%
Weighted average total cost					**$21,770**

Survival

Transition probabilities were derived from KM curves in published literature. Table E2.5 presents sources for each curve.

Table E.2.5. Sources of Kaplan-Meier Curves to Calculate Transition Probabilities

Survival Estimate	Idecabtagene vicleucel	Ciltacabtagene autoleucel	Triple- and Quad-Refractory (Comparator to CAR-Ts)	Belantamab mafodotin	Penta-Refractory (Comparator to Belantamab mafodotin)
Progression-free survival	Phase II KarMMa results	CARTITUDE	Shah et al. ASH 2020 Presentation 1653	Updated DREAMM-2 PFS curve	No published PFS curve; therefore, PFS was be matched to median PFS estimate from MAMMOTH penta-refractory using a constant hazard of progression
Overall survival	Phase II KarMMa results	CARTITUDE	MAMMOTH	Updated DREAMM-2 OS curve	MAMMOTH
Sources	Shah et al, 2020[45]	Madduri et al, 2020[19]	Gandhi et al, 2019[7]	Academic in confidence	Gandhi et al, 2019[7]

Table E.2.6 presents the final distributions chosen for the model based on visual inspection and Akaike information criterion (AIC). The shape and scale parameters were used to generate time-dependent transition probabilities for each curve. This table also describes the survival curve knot location for piece-wise distributions.

Table E.2.6. Survival Curve Fit, Shape, and Scale Parameters for Final Model

	Outcome (Distribution Chose)	AIC	Shape	Scale	Source	Notes	Modeled % at 12 months
Ide-Cel	Progression Free Survival (Weibull)	472.9	1.44	12.56	Shah et al, 2020[45]	Applied < 15 cycles; Gompertz applied > 15 cycles	36%
	Overall Survival (Gompertz)	274.0	0.105	0.009	Shah et al, 2020[45]	N/A	79%
Cilta-Cel	Progression Free Survival (Weibull)	218.6	1.61	29.24	Madduri et al, 2020[19]	Median PFS not reached, therefore calibrated based on % alive and PFS at 12 months	77%
	Overall Survival (Weibull)	218.6	1.61	76.49	Madduri et al, 2020[19]	Assumed same shape as PFS curve with adjustment to scale parameter	94%
Population exposed to three or more lines of therapy	Progression Free Survival (Log-normal)	464.9	1.41	0.88	Shah et al, 2020[45]	Applied < 15 cycles; Gompertz applied > 15 cycles	10%
	Overall Survival (Weibull)	467.9	1.84	13.33	Gandhi et al, 2019[7]	N/A	39%
	Outcome (Distribution Chose)	**AIC**	**Shape**	**Scale**	**Source**	**Notes**	**Modeled % PFS at 12 Months**
Belantamab Mafodotin *	Progression Free Survival (Log-normal)	Academic in confidence					
	Overall Survival (Log-normal)	Academic in confidence					
Population exposed to four or more lines of therapy	Progression Free Survival (Log-normal)	N/A	1.0	0.71	Gandhi et al, 2019[7];Dimopoulos et al, 2017[47]	Adjusted PFS curve to fit proportional relationship reported in previous meta-analyses	1.5%
	Overall Survival (Weibull)	329.0	1.53	7.61	Gandhi et al, 2019[7]	N/A	11%

*Comparator to Belantamab weights outcomes from both populations exposed to three or more lines of therapy and populations exposed to four or more lines of therapy

Health State Utilities

The most current and best available evidence on health utilities comes from the KarMMa study, with elicitation of utilities using the European Quality of Life-5 dimensions 5 levels (EQ-5D-5L) health state classification instrument.[43] The analysis elicited utilities from the US, UK, and Canadian populations across different time points including baseline, pre-progression, and post-progression. We applied the baseline utility value to the progressed state, the highest utility value elicited for the progression-free "off therapy state, and the first month pre-progression overall utility for the progression-free on therapy state. Given feedback from RRMM patients, we applied a separate utility to the progression-free off therapy state for both ide-cel and cilta-cel to reflect the benefits of being off therapies for a disease that commonly continues patients on therapies until death. See table E.2.7 for health state utilities applied in the model.

Adverse event disutilities were applied for two cycles in the model (i.e., two months) as evidence suggested most adverse events were resolved within 1-3 cycles with additional dose adjustments. Consistent with previous health technology assessments,[72,73] a utility score of 0 was applied for grade 3 or higher cytokine release syndrome for a duration. Table E.2.9 details the disutility estimates applied for adverse event disutilities.

Table E.2.7. Utility Values for Health States

Parameter	Three or More Lines of Therapy
Progression-free on Therapy and Responding	0.78
Progression-free off Therapy and Responding	0.82
Progressed Disease/not Responding to Treatment	0.71
Source	Delforge et al, 2020[74]

Adverse Events

The model included any grade 3/4 adverse events that occur in 5% of patients in any of the treatments and comparators. Given the potentially significant impact of cytokine release syndrome on health care resource utilization and quality of life, we included all grades 1-4 for these adverse events and adjusted costs and quality of life estimates accordingly. The costs and disutility of adverse events were applied to the first two cycles for each intervention and comparator. After cycle 2 of the model, we applied a dose adjustment factor, assuming adverse events would be resolved with lower dosing of each therapy. Table E.2.8 includes the proportions of patients with adverse events applied in the model.

Table E.2.8. Included Adverse Events

Parameter	Idecabtagene vicleucel [5]	Ciltacabtagene autoleucel [19]	Belantamab mafodotin[44]
Proportion with grade 1 CRS	41%	49%	N/A
Proportion with grade 2 CRS	23%	39%	N/A
Proportion with grade 3 CRS	2%	3%	N/A
Proportion with grade 4 CRS	1%	1%	N/A
Proportion with CRS and NE <=2	12%	NR	N/A
Proportion with CRS>= 3 and NE <=2	3%	NR	N/A
Proportion with CRS<=2 and NE=>3	3%	NR	N/A
Anemia	See above categories	68%	20%
Neutropenia		95%	9.5%
Thrombocytopenia		60%	20%
Lymphopenia		49%	16.8%
Leukopenia		61%	
Keratopathy		N/A	27%
Hypercalcemia		NR	7.4%
Hypophosphatemia		NR	5.3%

NR: Not reported

Adverse event disutilities or utilities are described in Table E.2.9. Adverse event disutilities were applied for two cycles in the model (i.e., two months). Consistent with previous health technology assessments, [72,73] a utility score of 0 were applied for grade 3 or higher cytokine release syndrome for 8 days in the first cycle.

Table E.2.9. Adverse Event Disutilities

Adverse Event Parameter	Disutility	Source
Anemia	-0.31	Brown et al. 2013 [75]
Neutropenia	-0.15	Brown et al. 2013 [75]
Thrombocytopenia	-0.31	Brown et al. 2013 [75]
Lymphopenia	-0.07	NICE TA 510 [76]
Cytokine release syndrome	0.00*	Hettle et al. 2017 [72]
Keratopathy	-0.05	Sullivan 2006 (ICD-9 369) [77]
Hypercalcemia	-0.04	Sullivan 2006 (ICD-9 289) [77]
Hypophosphatemia	-0.04	Sullivan 2006 (ICD-9 289) [77]

*This value corresponds to a utility, not a disutility.

Economic Inputs

Cost Inputs

All costs used in the model were updated to 2020 dollars.

Drug Acquisition Costs

For CAR-T therapies, the base-case findings use prices that meet the $100,000 per QALY threshold. For belantamab we used WAC pricing for the base-case findings. Comparator therapy prices were a function of one or more therapies on the market, inclusive of discounts, rebates (15% discount for comparator oral therapies based on FSS pricing schedule), patient assistance programs, and concessions to wholesalers and distributors. Patients that discontinued the CAR-T treatment before receiving the CAR-T infusion were not charged the CAR-T costs. Costs for subsequent therapies, including a proportion on palliative care, were assigned to the progressed state for 4 cycles using the appropriate comparator therapies for each population. The progressed state costs were consistent across treatment comparisons. Infusion therapies were subject to ASP + 6% pricing.

Table E.2.10. Drug Costs

Intervention (Dosage)	WAC/List Price per Unit or per Time Period*	Net Price per Unit or per Time Period	Source
Idecabtagene vicleucel	Estimated list price	N/A	Market analyst estimates
Ciltacabtagene autoleucel	Estimated list price	N/A	Market analyst estimates
Belantamab mafodotin	$8,277 per 100mg package		Micromedex Solutions[46]
Comparator therapies	See Table E.2.3 and Table E.2.4	See Table E.2.3 and Table E.2.4	Multiple

*WAC as of February 10, 2021

Administration and Monitoring Costs

Tables E.2.11 through E2.13 detail administration and monitoring utilization and costs applied in the model. Table E.2.11 includes pre-infusion regimens and unit prices for CAR-T therapies. Table E.2.12 includes administration and monitoring utilization applied at different stages of the model. We used recent evidence in heavily pre-treated patients with multiple myeloma to inform average utilization inputs per cycle.[78] We then applied unit prices from Table E.2.13 to each utilization parameter estimate. For hospital admissions we applied a fee-for-service approach.

Table E.2.11 Pre-Infusion Regimens for CAR-T Therapies

Treatment	Regimen	Unit Price	Source
Cyclophosphamide	300 mg/mg(2) on days -5, -4, -3	$33	Munshi et al, 2020[5]
Fludarabine	30 mg/m(2) on days -5, -4, -3	$50	
Cytarabine	500 mg/m(2) for 2 days a week, 2 weeks total	$1	
Methotrexate	1000 mg/m(2) for 1 day a week, 2 weeks total	$2	

Table E.2.12. Administration and Monitoring Utilization

Model Stage	Idecabtagene vicleucel	Ciltacabtagene autoleucel	Belantamab mafodotin	Comparator Market Basket of Therapies
Prior to and during therapy administration	• Leukapheresis • CRS-related treatment • 12 Inpatient days (2 in ICU) • Neurotoxicity adverse events	• Leukapheresis • CRS-related treatment • 12 Inpatient days (2 in ICU) • Neurotoxicity adverse events	• Ophthalmic examinations at baseline, prior to each dose and weekly follow-up • Other AE-related costs	• IV administration costs • Other AE-related costs
Post-therapy monitoring; progression-free [78]	• Complete blood count testing • Liver function testing	• Complete blood count testing • Liver function testing	• Treatment-specific outpatient visits per cycle • Complete blood count testing each outpatient visit • Liver function testing	• Treatment-specific outpatient visits per cycle • Complete blood count testing each outpatient visit • Liver function testing
Progressed disease [78]	• 4 cycles of subsequent treatment administration with market basket • Complete blood count testing • Liver function testing	• 4 cycles of subsequent treatment administration with market basket • Complete blood count testing • Liver function testing	• 4 cycles of subsequent treatment administration with market basket • Complete blood count testing • Liver function testing	• 4 cycles of subsequent treatment administration with market basket • Complete blood count testing • Liver function testing

Table E.2.13. Other Administration and Monitoring Unit Prices

	Value	Source
Cost per hospital day*	$3,190	HCUP Statistical Brief #125[79]
Cost per day in ICU	$5,563	Dasta, 2005 [80]
Office visit	$74	Physicians' Fee and Coding Guide (HCPCS code 99213)[81]
Leukapheresis (CAR-T only)	$1,323	Physicians' Fee and Coding Guide HCPCS code 36511[81]
Intravenous treatment administration (first hour)	$140	Physicians' Fee and Coding Guide (HCPCS code 96413)[81]
Intravenous treatment administration (each additional hour)	$29	Physicians' Fee and Coding Guide (HCPCS code 96415)[81]
Visual acuity test	$31	Physicians' Fee and Coding Guide (HCPCS code 99173)[81]
Complete blood count test	$44	Physicians' Fee and Coding Guide (HCPCS code 85027)[81]
Slit lamp exam	$110	Physicians' Fee and Coding Guide (HCPCS code 92285)[81]
Liver function test	$62	Physicians' Fee and Coding Guide (HCPCS code 80076)[81]

*Inflated to 2020 USD

Adverse Event Costs

The unit cost of adverse events applied to patients experiencing these events are shown in Table E.2.14. Adverse event costs were applied for the first two cycles of the model. Specific to CAR-T therapies, we relied on recent evidence that combined CRS and neurotoxicity events in different categories.[32]

Table E.2.14. Adverse Event Unit Costs

Adverse Event Parameter	Mean Cost	Source
Anemia	$2,007	Roy et al. 2015[82]
Neutropenia	$1,791	Roy et al. 2015[82]
Thrombocytopenia	$1,764	Roy et al. 2015[82]
Leukopenia	$3,045	Roy et al. 2015[82]
Lymphopenia	$3,102	Roy et al. 2015[82]
Cytokine release syndrome	$18,500 (grade 1) - $121,500 (grade 4)	Hari et al. 2020[32]
Keratopathy	$3,400	Roy et al. 2015[82]
Hypercalcemia	$193	Roy et al. 2015[82]
Hypophosphatemia	$193	Roy et al. 2015[82]

*Inflated to 2020 USD

Indirect Costs

A modified societal perspective was explored in a scenario analysis, and the below inputs informed that analysis to assess the impact on model outcomes.

Table E.2.15. Indirect Cost Inputs for Modified Societal Perspective

Category	Mean	Source
Average hourly wage	$25.72	US BLS[83]
Transportation cost per administration*	$18.52	Ailawadhi et al. Clin Ther 2019[84]
Patient workdays missed per administration	3 hours lost for each medical visit; 103 hours lost across 6 different regimens (average 17.17 hours)	Ailawadhi et al. Clin Ther 2019[84]
Employment rate	60.8%	US BLS[83]

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy. [85]

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

E3. Undiscounted Results

Tables E.3.1 – E.3.3 present undiscounted results for all interventions and comparators.

Table E.3.1. Base-Case Undiscounted Results for Ide-Cel Compared to Population Exposed to Three or More Lines of Therapy

Treatment	Intervention Cost	Other non-intervention costs	Total Cost	QALYs	Life Years	evLYGs	Incremental Results		
							Cost/QALY gained	Cost/LY gained	Cost per evLYG gained
Ide-Cel	$152,362	$165,000	$317,000	1.29	1.69	1.37	$95,000	$77,000	$84,000
CAR-T Comparator Market Basket	$141,000	$119,000	$260,000	0.69	0.95	0.69	-		

*price for ide-cel set to meet $100,000 per QALY threshold. evLYG: equal-value of life years gained, QALYs: quality-adjusted life years gained

Table E.3.2. Results for the Base-Case for Cilta-Cel Compared to Population Exposed to Three or More Lines of Therapy

Treatment	Intervention Cost	Other non-intervention costs	Total Cost	QALYs	Life Years	evLYGs	Incremental Results		
							Cost/QALY gained	Cost/LY gained	Cost per evLYG gained
Cilta-Cel	$363,000	$172,000	$536,000	3.75	5.01	4.22	$90,000	$68,000	$78,000
CAR-T Comparator Market Basket	$141,000	$119,000	$260,000	0.69	0.95	0.69	-		

*price for cilta-cel set to meet $100,000 per QALY threshold. evLYG: equal-value of life years gained, QALYs: quality-adjusted life years gained

Table E.3.3. Results for the Base-Case for Compared to Population Exposed to or More Lines of Therapy

Treatment	Intervention Cost	Other non-intervention costs	Total Cost	QALYs	Life Years	evLYGs	Incremental Results		
							Cost/QALY gained	Cost/LY gained	Cost per evLYG gained
Belantamab	$147,000	$101,000	$248,000	1.04	1.44	1.10	$93,000	$67,000	$82,000
Belantamab Comparator Market Basket	$110,000	$95,000	$204,000	0.57	0.79	0.57	-		

evLYG: equal-value of life years gained, QALYs: quality-adjusted life years gained

E4. Sensitivity Analyses

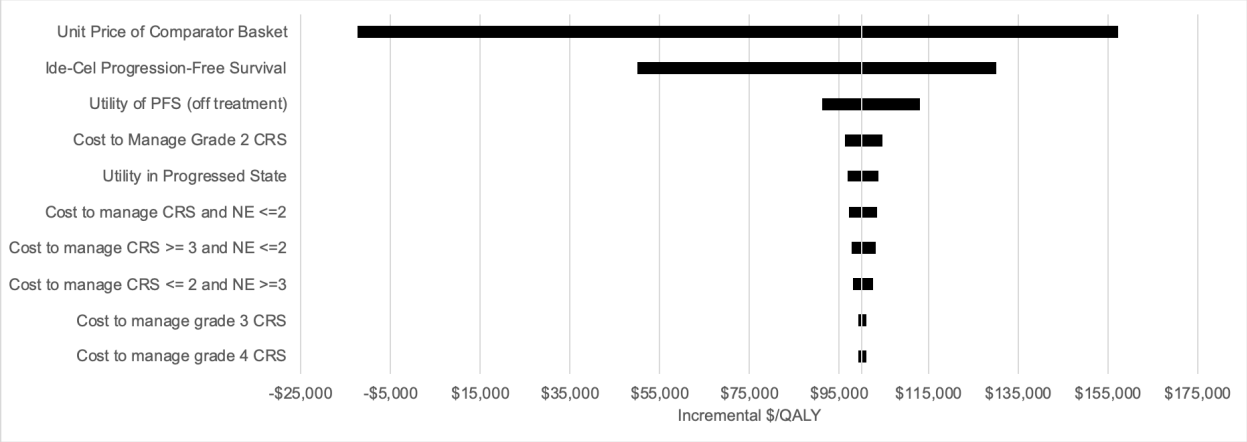
To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per QALY.

We conducted one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses were also be performed by jointly varying model parameters over 5000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We also performed threshold analyses for drug costs across a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY and evLYG).

Important input parameter drivers of model findings include the unit price of the comparator market basket of therapies, progression-free survival for the active interventions, and health state

utility values. When varying PFS, we assumed the same proportional relationship in terms of gains in OS. In the case of Ide-cel (Figure E.4.1 and Table E.4.1), when fixing the price set to meet $100,000 per QALY and changing the price of the comparator market basket to the upper range, we find increases in the ICER above commonly cited cost-effectiveness thresholds and decreases in the ICER to cost savings when the price of the comparator market basket is at the lower range. Higher PFS (and thus higher survival overall) leads to decreases in the ICER that meet commonly cited cost-effectiveness thresholds whereas lower PFS increases the ICER above commonly cited cost-effectiveness thresholds. Utility of PFS (off treatment) was also a driver that led to increases in the ICER at upper levels of the PFS utility and decreases in the ICER at lower levels of utility, however, these estimates were within commonly cited cost-effectiveness thresholds. After varying multiple inputs simultaneously while running multiple iterations of the model, we found Ide-Cel, when fixed at a price that meets the $100,000 per QALY threshold, ranged from less costly and more effective to ICERs that exceeded commonly cited cost-effectiveness thresholds (Table E.4.2). A total of 64% of iterations for ide-cel versus triple-class comparator were below a threshold of $150,000 per QALY gained (Table E.4.3 and Figure E.4.2). A total of 75% of iterations for ide-cel versus triple-class comparator were below a threshold of $150,000 per evLYG gained (Table E.4.4).

Figure E.4.1. Tornado Diagram for Ide-Cel†



† Vertical axis set at price that meets $100,000 per QALY threshold

Table E.4.1. Tornado Diagram Inputs and Results for Ide-Cel versus Population Exposed to Three or More Lines of Therapy†

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Unit Price of Comparator Basket	-$12,451‡	$157,136	$17,083	$37,508
Ide-Cel Progression-Free Survival (months)	$49,269	$130,599	6	12
Utility of PFS (off treatment)	$91,184	$113,015	0.73	0.89
Cost to Manage Grade 2 CRS	$96,342	$104,664	$13,309	$36,005
Utility in Progressed State	$96,830	$103,641	0.64	0.78
Cost to manage CRS and NE <=2	$97,280	$103,468	$18,967	$51,310
Cost to manage CRS >= 3 and NE <=2	$97,623	$103,030	$66,297	$179,348
Cost to manage CRS <= 2 and NE >=3	$98,106	$102,416	$52,845	$142,957
Cost to manage grade 3 CRS	$99,214	$101,003	$34,631	$93,685
Cost to manage grade 4 CRS	$99,253	$100,953	$69,468	$187,925

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

† Vertical axis set at price that meets $100,000 per QALY threshold

‡ Dominated (more costly, less effective) by comparator market basket

Table E.4.2. Results of Probabilistic Sensitivity Analysis for Ide-Cel versus Population Exposed to Three or More Lines of Therapy

	Ide-Cel		Comparator Basket		Incremental	
	Mean	**Credible Range**	**Mean**	**Credible Range**	**Mean**	**Credible Range**
Total						
Total Costs	$314,000	$244,000 - $347,000	$255,000	$162,000 - $398,000	$59,000	-$98,000 - $160,000
Total QALYs	1.25	1.39 – 2.11	0.68	0.63-0.72	0.57	0.72-1.41
ICER					$103,000	Less costly, more effective - $222,000

*price for ide-cel set to meet $100,000 per QALY threshold

Table E.4.3. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Ide-Cel versus Population Exposed to Three or More Lines of Therapy

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Ide-cel	26%	44%	64%	85%

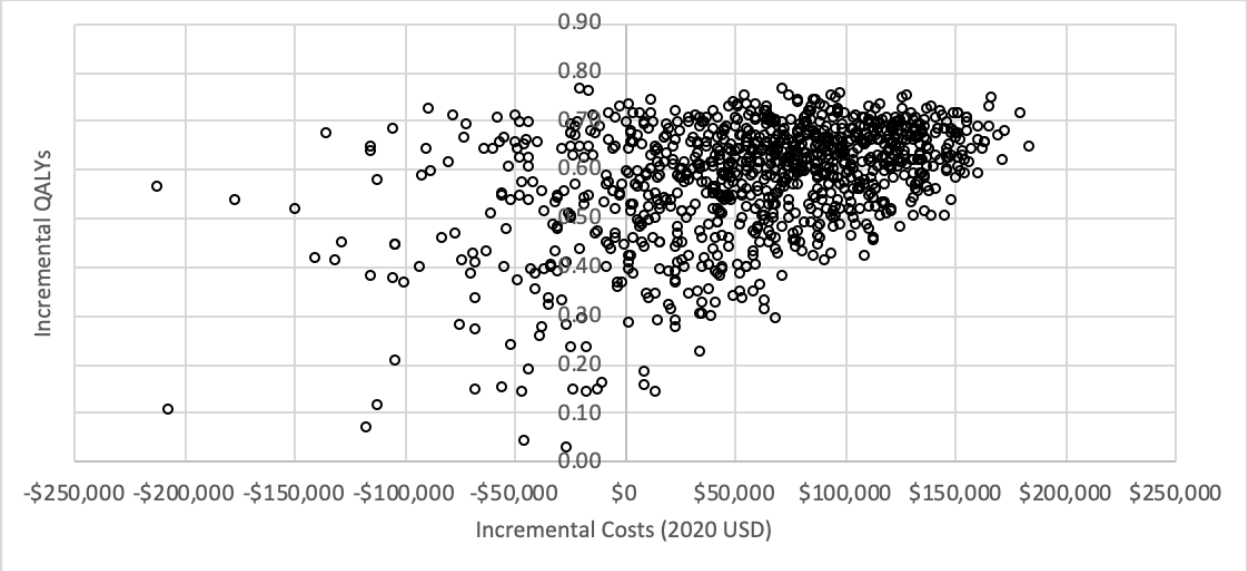
*price for ide-cel set to meet $100,000 per QALY threshold

Table E.4.4. Probabilistic Sensitivity Analysis Cost per evLYG Gained Results: Ide-Cel versus Population Exposed to Three or More Lines of Therapy

	Cost Effective at $50,000 per evLYG	Cost Effective at $100,000 per evLYG	Cost Effective at $150,000 per evLYG	Cost Effective at $200,000 per evLYG
Ide-cel	30%	49%	74%	94%

*price for ide-cel set to meet $100,000 per QALY threshold

Figure E.4.2. Incremental Cost-Effectiveness Cloud for Ide-Cel versus Comparator Market Basket

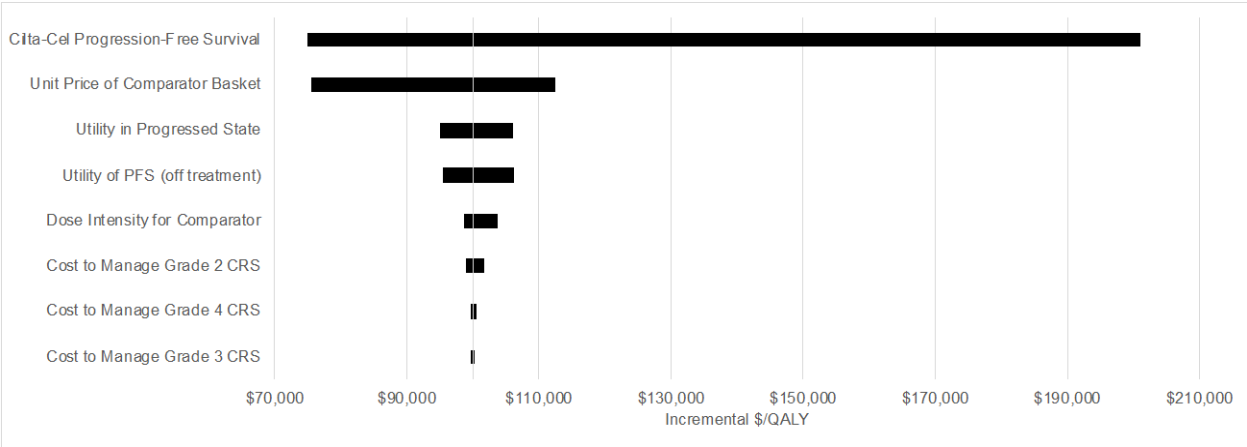


*price for ide-cel set to meet $100,000 per QALY threshold

In the case of cilta-cel (Figure E.4.3 and Table E.4.5), when fixing the price set to meet $100,000 per QALY, higher PFS (and thus higher survival overall) leads to decreases in the ICER that meet commonly cited cost-effectiveness thresholds whereas lower PFS increases the ICER above commonly cited cost-effectiveness thresholds. Changing the price of the comparator market basket to the upper range, we find increases in the ICER that fall within commonly cited cost-effectiveness thresholds and decreases in the ICER still within commonly cited cost-effectiveness thresholds when the price of the comparator market basket is at the lower range. After varying multiple inputs simultaneously while running multiple iterations of the model, we found Ide-Cel, when fixed at a

price that meets the $100,000 per QALY threshold, ranged from $50,000 per QALY to $122,000 per QALY. (Table E.4.6). Based on limited clinical evidence, 100% of iterations for ide-cel versus triple-class comparator were below a threshold of $150,000 per QALY gained and $100,000 per evLYG gained (Tables E.4.7, E.4.8, and Figure E.4.4).

Figure E.4.3. Tornado Diagram for Cilta-Cel†



† Vertical axis set at price that meets $100,000 per QALY threshold

Figure E.4.4. Incremental Cost-Effectiveness Cloud for Cilta-Cel versus Comparator Market Basket

*price for cilta-cel set to meet $100,000 per QALY threshold

In the case of belantamab (Figure E.4.5 and Table E.4.9), the model results were most sensitive to the price of the comparator market basket, specifically the market basket of triple class comparators. Higher prices for the comparator market basket drove the ICER towards zero and lower prices drove the ICER above the $100,000 per QALY threshold. Higher PFS (and thus higher

survival overall) led to decreases in the ICER whereas lower PFS only increased the ICER slightly above the base-case estimate. This is largely due to a small change in PFS from clinical studies on belantamab.

After varying multiple inputs simultaneously while running multiple iterations of the model, we found belantamab ranged from less costly and more effective to ICERs that exceeded commonly cited cost-effectiveness thresholds (Table E.4.10 and Figure E.4.6).

Table E.4.5. Tornado Diagram Inputs and Results for Cilta-Cel versus Population Exposed to Three or More Lines of Therapy

	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Cilta-Cel Progression-Free Survival	$74,815	$201,027	13	33
Unit Price of Comparator Basket	$75,534	$112,431	$17,083	$37,508
Utility in Progressed State	$94,985	$106,007	0.64	0.78
Utility of PFS (off treatment)	$95,414	$106,072	0.73	0.89
Dose Intensity for Comparator	$98,723	$103,816	0.83	1.00
Cost to Manage Grade 2 CRS	$98,748	$101,596	$13,309	$36,005
Cost to Manage Grade 4 CRS	$99,656	$100,439	$69,468	$187,925
Cost to Manage Grade 3 CRS	$99,743	$100,328	$34,631	$93,685

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

Table E.4.6. Results of Probabilistic Sensitivity Analysis for Cilta-Cel versus Population Exposed to Three or More Lines of Therapy

	Cilta-Cel		Comparator Basket		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total						
Total Costs	$525,000	$516,000 - $535,000	$257,000	$168,000 - $396,000	$267,000	$136,000 - $351,000
Total QALYs	3.12	3.12 – 3.58	0.68	0.63-0.72	2.68	2.46-2.88
ICER					$100,000	$50,000 - $122,000

*price for cilta-cel set to meet $100,000 per QALY threshold

Table E.4.7. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Cilta-Cel versus Population Exposed to Three or More Lines of Therapy

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY
Cilta-cel	3%	43%	100%	100%

*price for cilta-cel set to meet $100,000 per QALY threshold

Table E.4.8. Probabilistic Sensitivity Analysis Cost per evLYG Gained Results: Cilta-Cel versus Population Exposed to Three or More Lines of Therapy

	Cost Effective at $50,000 per evLYG	Cost Effective at $100,000 per evLYG	Cost Effective at $150,000 per evLYG	Cost Effective at $200,000 per evLYG
Cilta-cel	5%	74%	100%	100%

*price for cilta-cel set to meet $100,000 per QALY threshold

Figure E.4.5. Tornado Diagram for Belantamab

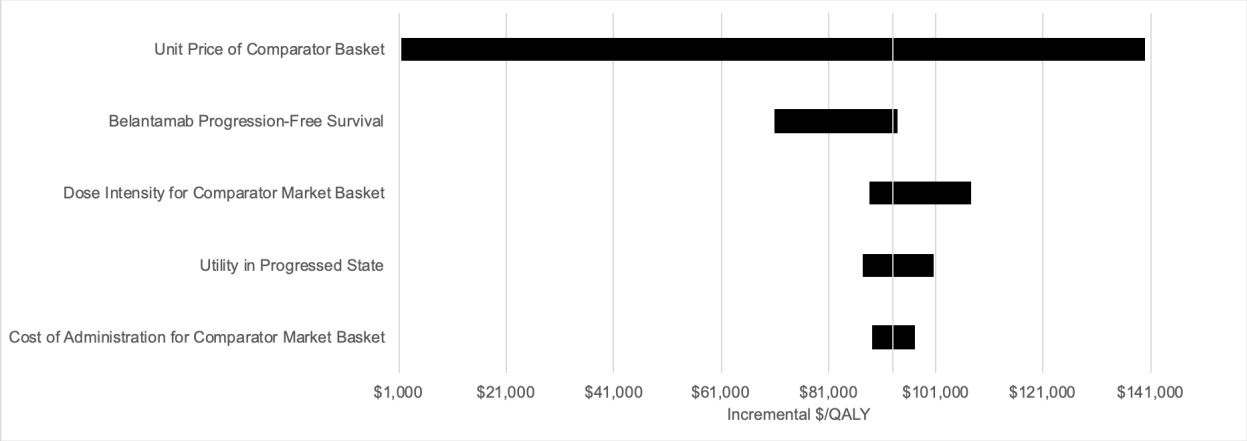


Table E.4.9. Tornado Diagram Inputs and Results for Belantamab versus Comparator

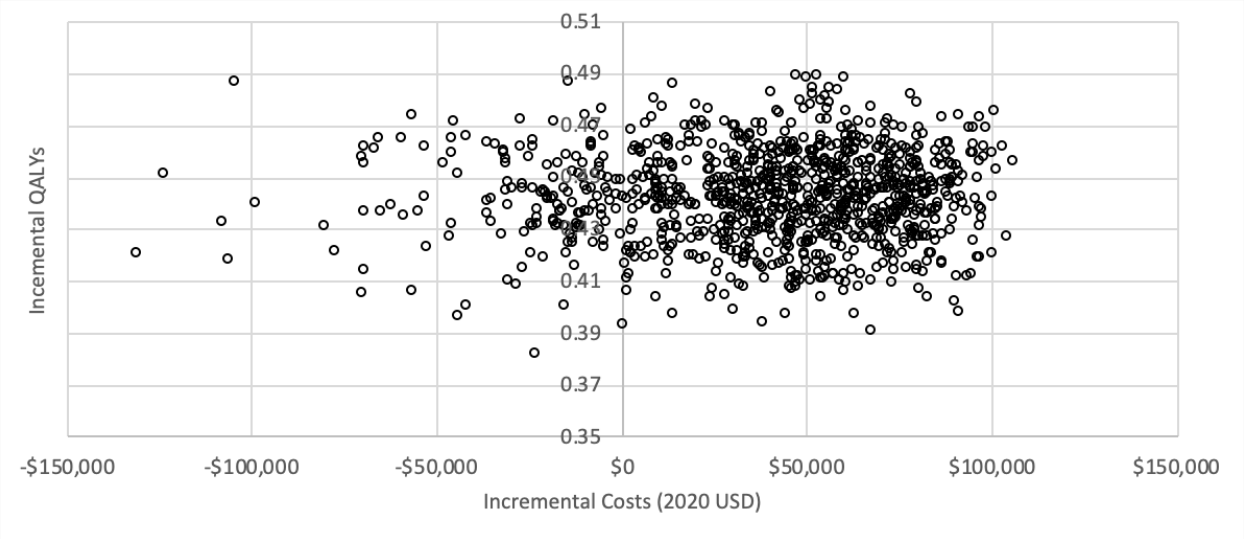
	Lower ICER	Upper ICER	Lower Input*	Upper Input*
Unit Price of Comparator Basket	$1,536	$140,010	$17,083	$37,508
Belantamab Progression-Free Survival	$94,795	$71,224	2	3
Dose intensity for comparator	$107,677	$88,565	0.83	1.00
Utility in progressed state	$100,542	$87,529	0.64	0.78
Cost of administration	$97,211	$89,113	$2,409	$3,569

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

Table E.4.10. Results of Probabilistic Sensitivity Analysis for Belantamab versus Comparator

	Belantamab		Comparator Basket		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total						
Total Costs	$243,000	$235,000 - $250,000	$203,000	$151,000 - $291,000	$40,000	-$48,000 - $93,000
Total QALYs	0.56	1.39 – 2.11	0.68	0.63-0.72	0.57	0.40-0.48
ICER					$90,000	Less costly, more effective - $196,000

Figure E.4.6. Incremental Cost-Effectiveness Cloud for Belantamab versus Comparator



E5. Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1. Modified societal perspective that includes components such as productivity losses
2. Adjusting the proportional relationship between PFS and OS for belantamab to be within a similar range as a recent meta-analyses.[47]

Scenario Analysis 1

We ran a modified societal perspective that included productivity losses and transportation time to and from health care appointments (see Table E.2.15 for unit costs). For the modified societal

perspective, we estimated the modified societal perspective incremental cost effectiveness estimates using the $100,000 per QALY threshold price from the health care sector perspective.

Table E.5.1. Incremental Cost-Effectiveness Ratios for Scenario Analysis 1

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG	Cost per Month of PFS Gained
Ide-cel	CAR-T Comparator Market Basket	$99,000	$80,000	$86,000	$12,000
Cilta-cel	CAR-T Comparator Market Basket	$100,000	$76,000	$87,000	$13,000
Belantamab mafodotin	Belantamab Comparator Market Basket	$94,000 per QALY	$67,000 per LY	$83,000	$19,000

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

Scenario Analysis 2

Recent evidence synthesis in multiple myeloma suggest a proportional relationship between PFS and OS consistent with a three month gain in OS for every one month gain in PFS.[47] While both CAR-T therapies were within the range of these proportional relationships, evidence from belantamab suggests a nearly five month gain for every one month gain in PFS. Given the evidence on belantamab is not consistent with prior multiple myeloma treatments, we ran a scenario analysis that adjusted the relationship between PFS and OS for belantamab to be consistent with this recent evidence. In this scenario, belantamab had the same PFS of 2.8 months but we adjusted the OS estimates to be set at an approximate median of 9 months. As expected, this scenario increased the cost per QALY base-case estimate over $200,000 per QALY.

Table E.5.2. Incremental Cost-Effectiveness Ratios for Scenario Analysis 2

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLYG	Cost per Month of PFS Gained
Belantamab mafodotin	Belantamab Comparator Market Basket	$209,000	$150,000	$192,000	$18,000

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

E6. Heterogeneity and Subgroups

We considered 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. Due to small patient numbers and the lack of data on survival, health-related quality of life, and health care costs stratified by these subgroups, we were not able to conduct subgroup analyses.

E7. 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 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.

We used several approaches to validate the model. First, we provided preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. We also performed calibration techniques that fit survival estimates to observed findings from trials and other evidence in MM. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also are sharing the model with the relevant manufacturers for external verification around the time of publishing the draft report for this review. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were validated against the trial/study data of the interventions and also any relevant observational datasets.

E8. Prior Economic Models

We found prior economic models in RRMM that estimated total costs and cost-effectiveness outcomes relevant to this review.[42,82,84] Carlson et al. was based on the prior ICER review in multiple myeloma and estimated the cost-effectiveness of second- and third-line therapies in RRMM. The Carlson et al. analysis had the advantage of a network meta-analysis to combine evidence on indirect comparisons across regimens of interest which was not available in this analysis. Therefore, this previous study allowed for direct application of hazard ratios to PFS and OS curves. Our analysis instead separately estimated and extrapolated survival outcomes by treatment arm in

the model given the lack of an available indirect treatment comparison. For sensitivity analyses, instead of applying a hazard ratio we varied the shape and scale parameters on the active interventions, while fixing the comparator arm. While the approach to estimate our base-case and sensitivity analyses was different than Carlson et al., both studies found considerable uncertainty on whether therapies were cost-effective at various commonly cited thresholds. It should be noted the Carlson et al. analysis was based on earlier lines of therapy than this analysis so direct comparisons on QALYs, LYs, and other outcomes should not be made between studies.

The Ailawadhi et al. and Roy et al. cost estimation analyses were informative to our market basket cost calculations.[88,90] Specifically, the approach used to identify regimen dosing each cycle along with identifying and costing adverse events informed our market basket calculation. In some cases, the combination of therapies was different so caution should be used when comparing the total cost estimates between studies. The most recent evidence from Ailawadhi et al. found total costs ranging from approximately $93,000 to $315,000 for common second-line regimens. While these estimates are for earlier line therapies, some of the reported regimens are approved for later lines of therapy and were used in our market basket calculations. For example, our total cost estimation for the CAR-T market basket of comparators was $140,000 (discounted) over a lifetime horizon which is within the range reported by Ailawadhi et al. We further varied the market basket cost and found the cost of comparators to be a key driver of model results.

F. Potential Other Benefits and Contextual Considerations

QALY Shortfalls: Comparing Multiple Myeloma to Other Severe Diseases

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions,[49] and that giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[87,88] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without any treatment.[52] The ethical consequences of using absolute QALY 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, rapidly fatal conditions of children or lifelong disabling conditions score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[53,54] The proportional QALY 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 QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For the population of adults with multiple myeloma who have been exposed to three or more lines of therapy, the absolute shortfall was estimated to be 17.79 QALYs, with a proportional shortfall of 0.96, representing a loss of 96% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition. For the population of adults with multiple myeloma who have been exposed to four or more lines of therapy, the absolute shortfall was estimated to be 17.91 QALYs, with a proportional shortfall of 0.97, representing a loss of 97% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition.

To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table F.1, using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[88]

Table F.1. League Table of Absolute and Proportional QALY Shortfalls for Selected Conditions

	From ICER Reports			From iDBC tool	
Condition	**Age**	**% Male**	**Total Undiscounted QALYs with Standard of Care**	**Absolute Shortfall**	**Proportional Shortfall**
Multiple Myeloma, Exposed to Three or More Lines of Therapy (>80% triple-class refractory)	60	50	0.69	17.79	0.96
Multiple Myeloma, Exposed to Four or More Lines of Therapy (100% triple-class refractory)	60	50	0.57	17.91	0.97
Cystic Fibrosis	2	52	25.8	42.3	0.62
Secondary Progressive Multiple Sclerosis	48	39	3.0	24.5	0.89
Hemophilia A	18	100	38.6	13.3	0.26
Treatment-Resistant Major Depression	46	33	20.5	8.7	0.30
Moderate-to-Severe Ulcerative Colitis	40	59	27.4	6.2	0.19
BCG-Unresponsive High-Risk NMIBC	72	80	4.94	5.7	0.54

QALY: quality-adjusted life year

G. Potential Budget Impact: Supplemental Information

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[92,93] The intent of our revised approach to potential 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.

Briefly, we evaluate whether a new drug would take market share from one or more existing treatments, and calculate the blended potential budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that patients eligible for the interventions under review in this analysis would otherwise have been treated with the comparator treatment(s).

Using this approach to estimate potential budget impact, we then compared 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 (https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/), 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 reports begun in 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $819 million per year for new drugs.

All costs used in the potential budget impact model were undiscounted and estimated over a five-year time horizon. This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment described earlier in the report. We assumed 20% of these patients would initiate treatment in each of the five years

In the final evidence report, ICER will include an "affordability and access alert" if discussion among clinical experts at the public meeting of ICER's independent appraisal committees suggests that full, "clinically optimal" utilization at estimated net pricing (or at the $150,000 per QALY threshold price if estimated net price is not available) would exceed the ICER annual potential budget impact threshold, without active intervention by insurers and others to manage access to the treatment.

Results

Table G.1. Cumulative Net Cost per Patient Treated with Belantamab mafodotin at Wholesale Acquisition Cost Over a Five-Year Time Horizon

	Belantamab mafodotin	
Year	**Additional Costs per Year (non-cumulative)**	**Cumulative Cost**
Year 1	$2,654	$2,654
Year 2	$24,098	$26,752
Year 3	$11,792	$38,544
Year 4	$3,689	$42,233
Year 5	$1,187	$43,420

Table G.2. Cumulative Net Cost per Patient Treated with Ide-cel at Price to Achieve $100,000 per QALY

	Ide-cel	
Year	**Additional Costs per Year (non-cumulative)**	**Cumulative Cost**
Year 1	$60,071	$60,071
Year 2	$18,375	$78,446
Year 3	$4,665	$83,111
Year 4	$222	$83,333
Year 5	$0	$83,333

Table G.3. Cumulative Net Cost per Patient Treated with Cilta-cel at Price to Achieve $100,000 per QALY

	Cilta-cel	
Year	**Additional Costs per Year (non-cumulative)**	**Cumulative Cost**
Year 1	$225,174	$225,174
Year 2	$9,255	$234,429
Year 3	$23,655	$258,084
Year 4	$15,997	$274,081
Year 5	$9,638	$283,719

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