INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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

Response to Public Comments on Draft Evidence Report

April 5, 2021

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#	Comment	ICER Response
Manufacturers		
Bristol-Myers Squibb		
1.	Lack of publicly available data at the time the ICER evidence report is issued, may lead to an inappropriate assessment of value, which factors into the pricing of medicines. Today the data continue to evolve, and should ide-cel receive FDA approval, additional data will become available. Long term follow-up of the pivotal trial is expected to be reported in the following months.	*We recognize that for these treatments there are limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents right now. Two of the new therapies included in our review have been approved by the FDA. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy.* *Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness.* *This report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders.*
2.	Long-term data supporting ide-cel continues to evolve and CRB-401 data should be considered for validation and checking of clinical plausibility of survival extrapolations Ide-cel has shown deep responses and durable efficacy in both the KarMMa and CRB-401 clinical trials. Data are evolving for ide-cel in each successive data cut with longer durations of follow-up. In the KarMMa study, OS data is still maturing with data for 85 patients (66% of the total population) censored in the 12+1 dataset.1 The CRB-401 dataset has the longest duration of follow-up for ide-cel (18.1 month median follow-up), with a median OS estimated at 34.2 months across all treated patients.	*We appreciate the suggestion to use CRB-401 data. After consulting with clinical experts and reviewing available peer-reviewed data sources, we have decided to use the published results of the KarMMa trial as the main source of evidence for both the clinical section and our modeling approach, given that not all patients in CRB-401 were triple-class refractory* *In our one-way sensitivity analysis, the upper end of PFS (12 mo) and OS (33 mo) is both consistent with the higher dose from KarMMa and the listed median OS from CRB-401.* *Furthermore, we discuss CRB-401 in the revised report supplement. However, as stated above, the primary source for our evidence rating is the KarMMa study published in the New England Journal of Medicine.*

3.	Benefits of ide-cel seem to be understated both for OS and PFS, and could be improved based on incorporating feedback from long-term follow-up and consideration of clinical plausibility OS and PFS percentages at different timepoints were compared from the ICER draft report, KarMMa study, CRB-401 study and expert elicitation study (OS only), respectively. Under the ICER approach less than 10% of patients are progression-free at 18 months compared to over 20% in KarMMa and CRB-401.1,3 This underestimation of the benefit of ide-cel is also demonstrated for OS, where the ICER estimate that <2% of patients treated with ide-cel are alive at 3 years, compared to 46% in CRB-4013 and 30% from the expert elicitation study.	*Thank you for your helpful feedback on PFS and OS extrapolations. The base-case model was updated and the following percentages are reported at the time horizon you reference in your comment:* *PFS: 26% at 18 months* *OS: 37% at 3 years* *Therefore, we slightly overestimate survival for PFS as compared to KarMMa and overestimate OS at 3 years as compared to the expert elicitation study you referenced. This overestimation still provided the best fit based on AIC and was in line with clinical plausibility as noted by your clinical expert elicitation study.*
4.	Overall survival estimates for ide-cel do not align with clinical data and expert opinion There are concerns that the current approach utilized by ICER may be under-estimating the overall survival and progression-free survival of ide-cel. The ICER model generates a median overall survival (OS) of 19.4 months which falls significantly below the CRB-401 trial (overall median OS of 34.2 months [95% CI,19.2-NE months]3 across all treated patients), a trial with generally similar baseline characteristics to KarMMa (see Draft Report Table D3.2 and the table in the appendix) and a robust program of expert elicitation to estimate long-term extrapolations of the KarMMa study undertaken by BMS.	*As noted above, we agree that survival was initially underestimated, and OS estimates have been updated to better reflect the clinical plausibility of the KarMMa study.*
5.	The ICER model and draft report does not provide the statistical goodness-of-fit information (Bayesian information criterion [BIC] and Akaike's information criterion [AIC]) for any alternative parametric forms to the base case (Gompertz for OS). The use of the Gompertz distribution as the base case to extrapolate OS for ide-cel assumes the hazard will monotonically increase or decrease over time at an exponential rate yielding a projected survival that estimates almost all ide-cel patients as having died at 3 years, which is incongruous with the CRB-401 clinical trial data and clinical expert opinion.	*Thank you for these recommendations. We have included figures that display various extrapolations in the revised evidence report supplement. AIC values have also been included in the figures as well.*

	These implausible long-term survival estimates are driven by its mathematical characteristics when fitted to trial data with limited follow-up, like with ide-cel with censoring >60% at 12+1 data. Indeed, this observation is supported in a recent survival extrapolation study, co-authored by Latimer).5 Researchers fitted standard parametric and flexible parametric spline models to SEER registry cohorts with advanced cancer. The Gompertz model performed poorly when fitted to three artificially created right-censored data sets. In contrast, spline models tended to provide better visual fits to the observed data and more accurate predictions of 10-year survival. Consequently, the authors have recommended spline models be routinely included in the set of models when extrapolating cancer survival data.	
6.	Similar findings were seen in a survival extrapolation case study of nivolumab in the treatment of relapsed or refractory classical Hodgkin Lymphoma. Extended follow-up data from CheckMate 205 was used to create 3 artificial data base locks (DBL) with varying durations of follow-up. Standard parametric models (SPM) as well as more flexible extrapolation models were fitted to these DBLs to test their predictive accuracy. It was demonstrated that upon from visual inspection of the 10-year extrapolation that the Gompertz model fitted to the 12-month DBL significantly underestimates the survival benefit of nivolumab when compared to the observed data at the most recent DBL.6 Independently fitted spline models provided more consistent estimates of mean survival across the early DBLs than the best statistically fitting SPMs. The absence of external evidence to aid model selection was identified as a key limitation for this case study. In contrast to the this case study, there are long-term data available from the CRB-401 trial as well as clinical validation available to guide extrapolation; furthermore, there are real-world evidence from the control arm which can serve as a lower anchor for these analyses.	*See above for our previous response.*
7.	ICER should include a diverse group of disease area experts in developing methods, clinical	*Thank you for these recommendations. ICER is committed to open and transparent engagement with*

	assumptions and in the clinical panel at the public meeting. BMS undertook an expert elicitation program to estimate long-term extrapolations of the KarMMa study.This robust, prospective, qualitative research study was performed incorporating semi-structured interviews, adapted from the SHeffield ELicitation Framework (SHELF).8 Oncologists and haematologists (N=6) with clinical experience (including in the United States) treating triple-class exposed RRMM patients with B-cell maturation antigen (BCMA) targeted therapy (including ide-cel) were recruited. During individual interviews with experts, relevant evidence regarding patient populations and outcomes were summarized for each study of interest to provide a common basis for expert judgments. The studies of interest included the KarMMa clinical trial evaluating ide-cel (12+1 months follow-up) and the MAMMOTH study evaluating conventional care.	*all stakeholders that have an interest in each of its evidence reviews. We always reach out to a diverse group of clinical experts, payers, and patient advocacy organizations to best inform our reports; those who reviewed early drafts of our report are listed.* *We understand that at this time there are limited follow-up data available for triple-class refractory multiple myeloma. However, we have reviewed and included best available peer-reviewed published data as well as current grey literature in our report. Once important new data become available, we will of course update our assessment accordingly.*
8.	Expert consensus estimates were combined with the empirical data from each study of interest using time-to-event parametric models which produced an overall distribution of survival over time. Functional forms that align with the expert elicitation estimates at 3 and 5 years are log-normal, log-logistic, and exponential. The full report with further details on the methodology has been provided as academic-in-confidence. It is good modelling practice to undertake clinical expert validation given that the extrapolated portion of the survival model may have a very large influence on the estimated mean survival.9,10 Moreover, the NICE TSD 14, in its survival model selection algorithm recommends that when the data are not complete (significant censoring), statistical fit alone should be avoided as a means of model selection. NICE TSD 14 recommends that clinical plausibility and expert judgement, and external clinical data validation be carried out to assess the suitability of the alternative models.	*See our previous responses. The new model fit includes log-normal as the functional form in the base-case. We also note that statistical fit was not the only metric used, but rather, we took the clinical advice submitted by your elicitation exercise, along with our own clinical experts, and are now in line with clinical plausibility as compared to what was submitted by clinical experts in your elicitation study.*
9.	PFS values utilized in draft model are conservative in lieu of long-term follow-up from KarMMa and CRB-401	*See previous responses.*

	In addition to OS extrapolations, PFS extrapolations are also underestimating the value of ide-cel. No evidence has been provided for a change in hazard at 15 cycles which would justify the current modelling approach where the Weibul curve was combined with the Gompertz curve. This is not supported by the KarMMa or CRB-401 studies. In the KarMMa study, the median duration of response and median PFS in patients with CR or sCR (33% of the treated cohort) was 19.0 months (95% CI, 11.3 to could not be estimated) and 20.2 months (95% CI, 12.3 to could not be estimated), respectively	
10.	Standard parametric models may provide inaccurate estimates of long-term survival for cancer immunotherapy BMS internal modelling has identified that the goodness-of-fit across different functional standard parametric model (SPM) forms are very similar (in part due to the limited follow-up and thus information from the KarMMa study at the 12+1 month data cut: difference of 4.035 and 4.000 for Akaike information criteria [AIC] and Bayesian information criteria [BIC], respectively, between 'best' and 'worse' statistical fits in the all dose cohort for OS; difference of 23.25 for both AIC and BIC between 'best' and 'worse' statistical fits in the all dose cohort for PFS). Where statistical fit is similar, and as stated in the ICER draft report, visual inspection and validation should be used to justify curve choice. Typically, one would normally provide a series of plausible extrapolations to characterize this uncertainty, but the presented report contains no information on alternative parametric fits (neither statistical nor graphical). BMS acknowledges the challenges of choosing an appropriate functional form based on emerging data. We appreciate ICER's willingness to consider longer-term evidence (i.e., CRB-401) and clinical opinion as elicited by BMS	*We have included figures that display various extrapolations in the revised evidence report supplement. AIC values have also been included in the figures as well.*
11.	In addition to the recommended transparency in regards to the relative appropriateness of SPMs employed in the Draft report, SPMs are limited with respect to the hazards they can represent	*As noted previously, we updated our survival extrapolations and estimate similar survival to that submitted by clinical experts in your elicitation study*

	and may not accurately model survival when there are several important changes to slope of the hazard function, as could be expected with cancer immunotherapy. Beyond the evidence from longer-term clinical trial data and expert opinion, there is growing evidence that SPMs often underestimate the long-term survival benefit of cancer immunotherapies. The underlying mechanism of action of these agents gives rise to a characteristic shape in their survival curves which SPMs may struggle to capture. With sufficient follow-up, a plateau at the tail of the cancer immunotherapy survival curve may be evident with durable responses being achieved in a proportion of patients long after treatment has been discontinued. Therefore, BMS believes that these points underscore that external data, when available, together with careful consideration of clinical plausibility should be used to inform model selection.	*and when compared to actual patient data from KarMMa.*
12.	Given uncertainty around the final label, a scenario analysis focused on the 450x106 CAR+ T cells dose should be pursued Given there is not a FDA approved dose for ide-cel at this time, the source for the effectiveness and safety inputs, is across the dose evaluated in the KarMMa trial (i.e., 150-450 x 106 CAR+ T cells). A scenario analysis focused on the 450x106 CAR+ T cells dose should be pursued such that stakeholders have an appropriate understanding of the comparative effectiveness and value of ide-cel. The median PFS among the 450x106 CAR+ T cells dose cohort (n=54) in KarMMa is 12.1 months (95% CI, 8.8 to 12.3), which is higher than that of the overall treated cohort (n=128). Notably the median OS has not been reached in the 450x106 CAR+ T cells dose cohort.	*We have included one-way and probabilistic sensitivity analyses that include PFS and OS estimates similar to what was observed at the higher dose in KarMMa, i.e., median PFS of 12 months.*

13.	Consistent Methodology across CAR T Products As noted above, given the immaturity of these data to date in RRMM, it is critical that the modelling approach used for CAR T products be consistent in order to ensure stakeholders can make reasonable inferences based upon the model outputs. Notably, across other CAR T product trials, neither median PFS nor OS have been reached. The draft report states that 'calibration techniques' were used for PFS and OS extrapolation, where PFS was calibrated based on the proportion of patients alive and progression free at 12 months. The OS curve, rather than be extrapolated based on limited data, were assumed to have the same shape parameter as the PFS curve with modification to the scale parameter. Other considerations that should be highlighted are data utilized for validation of extrapolation results that lead to potential differences from the pivotal trial including median age, prior lines of therapy, and OS results.	*As we note in many places of the report, comparisons between CAR-T products should not be made due to differential timing of clinical evidence and the populations studied. Further, we acknowledge the evidence available for modeling is limited for cilta-cel and should be interpreted with caution.*
14.	Given the methodological challenges and limitations that exist with conducting evaluations at this early stage in a product's lifecycle, BMS believes that consideration of data from similar populations and with longer follow-up information should be utilized where possible. For these reasons, BMS recommends (1) CRB-401 data should be considered for validation and checking of clinical plausibility of survival extrapolations, (2) extrapolations of both PFS and OS should incorporate feedback from longer-term follow-up studies and clinical feedback to better reflect the evidence base and demonstrated value of ide-cel, (3) ICER should include a diverse group of disease area experts when developing methods, and clinical assumptions, and in the clinical panel at the public meeting, and (4) a scenario analysis inclusive of the 450 x 106 CAR+ T cells dose should be included to inform stakeholders about ide-cel's comparative effectiveness and value.	*Thank you for your input. We have addressed each of the four specific recommendations above.*

GlaxoSmithKline		
1.	The P/I rating does not accurately or completely convey the clinical benefits and potential risk associated with belantamab mafodotin. We suggest ICER consider an evidence rating of C++, "moderate certainty of a comparable, small or substantial net health benefit, with high certainty of at least a comparable net health benefit." This is based on the data and the following points: Belantamab mafodotin is an FDA-approved and NCCN guideline-recommended regimen, having undergone FDA review including a detailed benefit-risk assessment. The Oncologic Drugs Advisory Committee voted 12 to zero to approve the product based on a complete review of the clinical benefits and risk profile, including the testimony of patients and clinical investigators regarding the net benefits to patients. • Based on the data presented in the ICER report and in the public domain, belantamab mafodotin showed a potential benefit of substantially improving OS compared to the standard of care, as well as maintaining or improving long term HRQoL in in this heavily-treated population, while having a manageable safety profile, providing high certainty of a net health benefit. This implies a C++ rating according to ICER's system.	*Our P/I evidence rating was based on several factors. First, while the OS results provide the strongest evidence of benefit, other data are more equivocal. The overall response rate of belantamab mafodotin is similar to usual care (32% vs 29%) and health-related quality of life does not improve with belantamab mafodotin treatment. Second, the harms are significant, with 18 – 30% of patients suffering significant visual toxicity with a relatively long period before resolution. Finally, there is substantial uncertainty, with HRQoL data relying on as few as 19 patients as an example.* *Thus, we feel a P/I evidence rating is appropriate since the current evidence suggests that belantamab mafodotin is comparable or has a small net benefit to available treatments. In addition, the P/I evidence rating also appropriately conveys the uncertainty of the current evidence by including small net harm.*
2.	On page 19, the draft report interprets the belantamab mafodotin 13-month DREAMM-2 ORR and OS as providing a "possible small net benefit." In a published indirect comparison of DREAMM-2 results to the relevant population from MAMMOTH, the OS benefit was statistically significant (HR 0.29, [95% CI: 0.16-0.54], p<0.001). Based on this indirect comparison study, the improvement in median OS (mOS) compared to ICER's standard of care comparator is 6.8 months. This would generally be considered clearly above the threshold of clinical significance in a population with a median OS of 6.9 months under standard of care—mOS is almost doubled. The estimated median duration of response (DOR) in DREAMM-2 was also clinically meaningful at 11 months (95% CI: 4.2-NR).5 This durable and clinically meaningful DOR	*We agree that some evidence suggests benefit. However, other data suggests minimal benefit. As noted above, while the OS results are favorable for belantamab mafodotin, the overall response rate was 32%, compared to 29% in the matched MAMMOTH cohort. In addition, there was no improvement in HRQoL with belantamab mafodotin. We strongly believe that OS data should be viewed in the context of other outcomes; viewing all available data in totality, we believe that current evidence suggests small net benefit or equivalence to currently available therapies and effectively precludes a substantial net benefit.* *We have modified in the footnote of Table ES2 to emphasize that the likelihood of slight net harm with belantamab mafodotin is small but nonzero, while the likelihood of slight net benefit is higher.*

	reflects both efficacy and safety of the regimen, as responders can continue receiving treatment and deriving the clinical benefit without discontinuing early due to safety events. Based on this data, we suggest ICER reword the evaluation of benefit to a "possible substantial net health benefit."	
3.	The HRQoL results from DREAMM-2 presented in the draft report only show data from one single time point, which is an incomplete picture. The draft report asserts "a deterioration (worsening) in the fatigue, pain, and global health sub-domain scores of the EORTC-QLQ-C30" (page 11). However, the cited poster showed that both fatigue and pain sub-domains trend towards improvement over the longer term, and global health status scores were stable over time. In addition, at 25 weeks, there were meaningful improvements in fatigue for 32% of patients, meaningful improvement in pain for 16% of patients. In addition, the EORTC-QLQ-MY20 Disease Symptoms score, describing pain in different locations, trended toward improvement over time, with clinically meaningful improvement apparent in >25% of patients receiving the indicated dosage.	*We agree that overall, the quality of life outcomes are stable for the majority of patients. For the small minority of patients who remained in the study beyond 25 weeks, we agree that there is a trend toward improvement. We have clarified these points in Section 3.2 "Benefits" of the report.*
4.	The appropriate expectation vs baseline in such a heavily pre-treated population should be one of maintenance of HRQoL7, and treatment with belantamab mafodotin meets or exceeds this expectation with stable HRQoL and improvement in some domains. We request that ICER corrects this statement on the HRQoL data, considering the following wording: "fatigue and pain sub-domains trend towards improvement over the longer term, and global health status scores were stable over time, accompanied by improvement in the EORTC-QLQ-MY20 disease symptoms score."	*We agree that in this heavily pretreated population, stable HRQoL may be an improvement over usual care. However, without data on HRQoL on a usual care comparator in DREAMM-2, this is an interesting but unproven hypothesis.* *As noted above, we agree that belantamab mafodotin improves outcomes in the minority of patients who stay on medication for >25 weeks.*

5.	In Table 3.6 a figure of "severe decline in vision in BCVA scale as 30%" is stated. However, we note that this 30% figure is based simply on a 3 line decline in Snellen visual acuity in the worse eye. GSK's recommendation for the most clinically significant indicator of change in BCVA is a decrease to worse than 20/40 in the better-seeing eye. This is how visual acuity changes are described in the Warnings & Precautions of the US Prescribing Information for Blenrep. Per the International Classification of Diseases 11, a BCVA value of "Normal" (20/20) to 20/40 is identified as having minimal to no impairment. 20/40 vision in the better seeing eye is the cut-off for an unrestricted driver's license in most states. Please note that when interpreting Snellen BCVA for an individual, the performance of the better-seeing eye can be primarily considered because that is the patient's overall vision. As per Table D3.13 on page 87, only 17.9% of patients experienced clinically meaningful changes in BCVA (defined as 20/50 or worse in the better seeing eye). We suggest ICER replace the 30% with this 17.9% figure as it is more relevant, especially to patients.	*Thank you for this clarification. We believe that both the BCVA in the more affected eye as well as the overall vision would be an important outcome for patients. Thus, we have added the overall visual decline numbers (18%) to the Executive summary, Table ES1. In addition, we now highlight Grade 2 decline in BCVA (2-3 lines in Snellen) in the more affected eye (46%)*
6.	Furthermore, these symptoms resolve quickly with dose interruption or reduction, when managed according to the recommendations in the prescribing information and the dose is held for Grade 2 or higher per the Keratopathy and Visual Acuity (KVA) scale. No permanent complete vision loss was reported in DREAMM-2 trial patients, and only 3% of patients discontinued due to corneal events.8,9 We suggest that this context should be provided in the executive summary. The BCVA decline experienced by those 17.9% of patients lasted a median duration of 21.5 days (about 1 cycle), and 82% of these patients had recovered at last follow-up.	*We agree that it is important to convey that vision loss was reversible. However, we believe that the duration of BCVA in the more affected eye (33 days) is as important the duration of overall visual decline (22 days).* *Thus, we now highlight the reversibility of visual decline (Table ES1) and note the duration as 22-33 days.*

7.	Mortality figures in Table 3.6 are presented in an inconsistent and potentially confusing manner. The presentation of mortality implies that mortality is due to treatment-related adverse events. However, across both arms of DREAMM-2 (n=196), only two deaths occurred that were identified as potentially treatment related.10 Furthermore, mortality data from the belantamab mafodotin trial is presented from a much later time point, when the disease is further advanced compared to CAR-T treatments. The mortality figure for ide-cel is reported as of 8 weeks, while the mortality figure for belantamab mafodotin is reported as of 25 weeks (approx. 6 months). We therefore suggest that the mortality column is removed from this table.	*We now list the time of mortality assessments in Table 3.6 to minimize confusion.*
8.	The comparison of belantamab mafodotin mOS and mPFS to a fixed ratio is not applicable and we request that statements making this comparison be removed from the report. Belantamab mafodotin PFS and OS data are based on clinical trial evidence, in a trial of 97 patients. We direct ICER to the 13-month curves on mOS by response as provided by GSK in the data request. The long OS demonstrated in responders (marginal response or better, mOS not yet reached) reflects the strong survival benefit for those patients who respond to belantamab mafodotin and hence the median OS observed in the trial is driven by the clinical benefit. A citation for the claimed 2.5-3.0 ratio is not referenced in the report. While the referenced publication does show an increase with median OS in accordance with an increase in median PFS, this cannot be applied to all treatments especially those with a new mechanism of action. A clinical rationale for why mPFS and mOS must be in a tight ratio in this indication is not apparent and has not been provided by ICER. This is a new mechanism of action and any existing PFS: OS ratios cannot necessarily be applied.	*We have added a meta-analysis citation which examined 22 RCTs in patients with relapsed and refractory MM. This study provided a pooled estimate suggesting that every additional month of PFS was associated with a gain of 3 months of OS. We have added details of this study in Section 2.2 of the report.* *We generally agree that given the new mechanism of action, belantamab mafodotin may have a different OS/PFS ratio than other treatments for MM. Thus, we have deleted the sentence: it is unlikely that belantamab mafodotin would increase OS dramatically without increasing PFS. We now highlight that given that the PFS/OS relationship for belantamab mafodotin is so different from other MM medications, further research is needed to confirm or refute the belantamab mafodotin OS/PFS finding.*

9.	We request more consistent description of the belantamab mafodotin population in-line with the approved indication of triple-class refractory patients who have received four or more prior therapies. In some parts of the report, the population for belantamab mafodotin is accurately described as triple class refractory, who have received four or more prior therapies (in-line with the FDA approved indication statement), while in other parts of the report the population is described as quad- and penta refractory. It is also noted that the MAMMOTH population mix used as a comparator does include triple-class refractory patients, so it is inaccurate to state that a comparison was made to quad- and penta refractory patients. The places in the report with inconsistent descriptions of belantamab mafodotin's indicated population (and trial population) include but are not limited to: o p. ES1 "Belantamab mafodotin was studied in heavily pre-treated (6-7 previous lines of therapy) quad- and penta-refractory patients" o p. ES2 "Belantamab mafodotin appears to be equivalent or slightly superior to currently available treatments for quad- and penta-refractory MM patients" o p. ES4 "Belantamab appears to be equivalent or slightly superior to current treatments for quad- and penta-refractory MM patients" o Table ES1 "Belantamab Population (Quad- and Penta-Refractory)" o Table ES2 "Adults with Quad and Penta-Class Refractory MM" p. 19 "We conclude that belantamab is promising but inconclusive compared to usual care for quad- and penta- refractory MM patients"	*Thank you for this suggestion. We have made numerous changes in the Executive Summary as well as the body of the report to harmonize our description of the belantamab mafodotin population.* *We now describe it as a triple-, quad- or penta-refractory exposed to four or more prior lines of treatment.*

10.	In Table E.2.12 (page 132), belantamab mafodotin has the following monitoring information: "ophthalmic examinations at baseline, prior to each dose and weekly follow-up." This weekly follow-up is inconsistent with the monitoring strategy outlined in the belantamab mafodotin prescribing information: "Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms." The current recommended dosing in the USPI is q3 weeks.	*Thank you for pointing this out. We have fixed this in the revised report. The model does not include weekly follow-up for these examinations, only as shown in the monitoring section of the prescribing information.*
11.	In Table E.2.14 (page 134), the draft report cites Roy et al., 2015 for keratopathy, with a value of $3,400 per event. GSK was unable to find this value, or another cost value for ophthalmologic events, in that paper. This paper cannot provide a specific number for the unique MEC adverse event associated with belantamab mafodotin. Notably, while the "Source" column in Table E.2.14 says Roy et al. 2015, the cited source (#82) does not correspond to Roy in the Reference list. GSK also does not find support for the value of $3,400 in reference 82, which is listed as Brown 2013.12 GSK believes this high cost value is not likely to be justified for belantamab mafodotin, based on the minimal healthcare resource utilization associated with a management strategy that consists only of dose holds and reductions, with no intervention being used in order to resolve. Although it is possible that patients will spend some additional time consulting with physicians if they have a grade 3/4 AE, the true cost is likely to be much lower than $3,400, and closer to the cost of a few additional office visits and eye exams.	*GSK submitted a similar estimate for inclusion in the model related to keratopathy, which is why this estimate was used in the model. The revised analysis only includes the costs of examination and monitoring visits.*
12.	In order to reduce the risk of ocular toxicity, belantamab mafodotin is provided as part of a REMS program where all patients undergo ocular examinations of visual acuity testing and slit lamp exam prior to each dose; however, these are not likely to be resource intensive, as they are routine ocular examinations.	*While these are not resource intensive, they are billable in a fee-for-service health care system and therefore included in the modeling analyses, consistent with recommendations from the 2nd US Panel on Cost-Effectiveness in Health and Medicine.*

13.	The report's references to NCCN guidance should be updated, noting the inclusion of belantamab mafodotin as a recommended regimen. On page 45, the NCCN guidance referenced (V4.2020) is out of date. Please note that latest NCCN guidance (V4.2021) includes belantamab mafodotin in the "Other Recommended Regimens" for Therapy for Previously Treated Multiple Myeloma (category 2A) (Page MYEL-G 3 of 3).	*Thank you for alerting us to the updated NCCN guidelines. We now reference the 2021 Version 5 of the guidelines.*
14.	Patient and caregiver perspectives for belantamab mafodotin should be more adequately represented in the evidence report. ICER "spoke with 2 patients who had received CAR-T therapies" and "several patients who were considering CAR-T," but did not apparently speak with any belantamab mafodotin patients. We suggest that ICER consider adding belantamab mafodotin patient input, in order to fully represent the perspectives and experiences of these stakeholders.	*We completely agree that patient input is very important in informing the evidence report. Per our patient engagement guidelines, we reached out to patient advocacy organizations and with their help, sent their members a link to an online survey where they could share their experience with either belantamab mafodotin or the CAR-T therapies.* *Furthermore, we reached out to patients through patient advocacy organizations to schedule one on one interviews and we held a group interview. Unfortunately, none of the patients who signed up for the above opportunities had experience with belantamab mafodotin.* *We also reached out to patient advocacy organizations prior to the public meeting on April 16th to notify patients who have experience with belantamab mafodotin to offer a public comment at the public meeting.*
Sanofi		
1.	The scope of the ICER Draft Evidence Report is "triple-class refractory" Multiple Myeloma (TCRMM), defined as a disease that is no longer responsive to immunomodulatory drugs (IMiDs), proteasome inhibitors (PI), and anti-CD-38 monoclonal antibodies. Neither Mushtaq et al. nor Arcuri & Americo (2021) include these populations in their studies. Mushtaq et al. (2019) limit their comparison to pomalidomide-based treatments in patients with at least two prior lines of therapy but not TCRMM. Arcuri & Americo (2021) compare treatments used among patients who have received 1-3 prior treatments, regardless of treatment refractoriness. Both publications are out of scope of this Evidence Report as they capture broader patient	*We agree that the Mushtaq and Arcuri & Americo publications include a broader population than the scope of this review. This is consistent with the results of our own systematic literature review and informed our decision to include retrospective studies (Gandhi 2019) to represent the effectiveness of usual care treatments. We have therefore decided to delete these reviews in our Report Supplement and add a recent systematic review (Shah 2021) of appropriate comparison populations for CAR-T therapies. This review supported our decision to include the real world studies (Gandhi 2019) as the comparator population in the report.*

	populations than the scope of the ICER assessment and should not be included.	
2.	NMA Methodology in Arcuri & Americo (2021) The meta-analysis by Arcuri & Americo1 includes studies across different patient populations, disease severity and background therapies and ignores the concept of transitivity on which the NMA premise stands. Not only does this inappropriate application lead to misleading conclusions, it may favour less efficacious and more toxic treatments. Given ICER's emphasis for methodologic and evidence synthesis rigour, we recommend it be excluded from the final Evidence Report.	*Please see our response above for comment number 1.*
3.	One of the pillar assumptions of the NMA methodology, transitivity (or similarity), requires that trials included in the analysis are clinically and methodologically similar. In other words, it requires that all treatments are jointly randomizable (ie. that a patient from one trial could have been included in any other study) and that "the different sets of studies included in the analysis are similar, on average, in all important factors that may affect the relative effects". However, trial inclusion criteria differ significantly between the trials of the NMA, meaning that different populations and with heterogeneous disease severity are included, as shown in Table 1. Including different populations and different disease characteristics violates the transitivity assumption that underpins the premise of an NMA. No fully objective conclusion can be drawn from the study results.	*Please see our response above for comment number 1.*

4.	The studies included in the NMA1 also vary in terms of backbone therapy. Studies have either lenalidomide- or bortezomib-based regimens, except ICARIA, KEYNOTE-183, and CANDOR that have pomalidomide- or carfilzomib-based regimens. Since all backbone therapies are considered one same "control" in the NMA (see Figure 2 in original article), this implies similarity of all backbone regimens and does not consider any differences in background efficacy. For example, CANDOR and CASTOR compare daratumumab (D) in combination with carfilzomib (DKd) versus Kd, and bortezomib (DVd) versus Vd respectively, in relapsed/ refractory multiple myeloma patients. The results vary considerably, with a median progression-free survival of 15.8 months for Kd vs. 7.2 months for Vd, demonstrating it is highly inappropriate to consider these two treatments equal.	*Please see our response above for comment number 1.*
5.	In addition to the differing trial inclusion criteria mentioned previously, there is a conspicuous absence of any mention of treatment effect modifiers or assessment of balance between trials. The median number of prior treatment lines varies from 1 to 3 (see Table 1). By not accounting for these differences, the efficacy analyses are biased towards studies with fewer prior lines of therapy such as POLLUX and TOURMALINE (mean of 1 previous therapies). Similarly, treatment refractoriness results in poorer patient outcomes and is an important effect modifier. Studies that exclude bortezomib and/or lenalidomide-refractory patients or studies with lower proportions of these patients will therefore be favoured in the meta-analyses. These important treatment effect modifiers should have been accounted for as patient outcomes differ based on these characteristics.	*Please see our response above for comment number 1.*

6.	Finally, for most trials included in this analysis, serious adverse events (SAE) are used as a measure of toxicity. However, review of the meta-analysis R Code show that for CASTOR and ICARIA trials, Grade III/IV events (which are commonly exhibited in most multiple myeloma patients) were used, making those treatment combinations appear more toxic in the comparison. The Common Terminology Criteria for Adverse Events (CTCAE) definition of severe adverse events differs from Grade III/IV toxicities, and therefore cannot be compared. Adverse Events for the BOSTON trial are not included in the analysis at all, despite SAE data being reported in the referenced paper.4 The ranking results would likely be significantly different if the reported SAEs were used for all included studies, including ICARIA and BOSTON. These methodological concerns are also being raised with the Journal in which the Arcuri & Americo NMA was published.	*Please see our response above for comment number 1.*
7.	The methodological implications highlighted here are likely to lead to bias favouring studies of less pre-treated patients (with fewer lines of previous therapy or have fewer treatment-refractory patients) or lower toxicity backbone (or those using SAEs rather than Grade III/IV AEs). Rather than adjusting for differences across trials through population-adjusted comparisons (such as matching adjusted indirect comparison or simulated treatment comparison), this NMA is likely to mischaracterize and unobjectively amplify differences in efficacy and safety resulting in misleading conclusions about the treatments.	*Please see our response above for comment number 1.*
8.	The NMA does not adjust for heterogeneity in the patient populations, lines of therapy, disease severity and treatment effect modifiers. Given the scope of the ICER report, and the incorrect implementation of the NMA methodology, Sanofi recommends that the Mushtaq et al. (2019)2 and Arcuri & Americo (2021)1 papers should not be included in the final report.	*Please see our response above for comment number 1.*

Amgen, Inc.		
1.	Change the overall survival (OS) estimate for cilta-cel and account for material differences across each patient population. The methodology for calculating cilta-cel's OS assumption should more accurately represent model approaches used for other CAR-Ts. The meta-regression of Dimopoulos et al. that ICER applied to the PFS data of cilta-cel appears to yield overly optimistic OS estimates. First of all, Dimopoulos et al.'s analysis was based on 18 RCTs predominantly in less heavily pretreated patient populations, which is considerably different from the heavily pretreated patients in CARTITUDE-1. While the meta-regression relationship may be generalizable to earlier line settings where patients still have meaningful treatment options after they progress, in this very late-line setting, the PFS-OS relationship is likely to be different given few efficacious treatment options are available after CAR-Ts. Consequently, the predicted median OS for cilta-cel is about five years vs. less than the two years for ide-cel. Such difference is unlikely to be clinically plausible. We recommend that ICER request manufacturer data to revise this analysis or conduct a scenario analysis utilizing the requested data. Failing this, we suggest 1) employing the Gompertz model approach that was used to estimate the OS for ide-cel and calibrate the scale parameter such that the 12-month OS matches the published data for cilta-cel, or 2) maintain a similar PFS-OS relationship for cilta-cel as estimated for ide-cel.	*We agree that survival extrapolations produce a wide range of potential outcomes. In our revised supplement, we provide both figures showing our extrapolations and scenario analyses that display percentage changes in ICERs based on different functional forms for both PFS and OS. PFS and OS in the revised report are in line with clinical expert elicitation and what has been observed from trial evidence at this point in time.* *Furthermore, there are two different meta-analyses (Felix et al. and Dimopoulos et al.) both suggesting the PFS to OS relationship is approximately 2.5-3.0 months of OS gained for every month gain in PFS. The modeling for all active interventions and comparators is in line with this relationship.*
2.	ICER's analysis introduces possible bias into the model as the draft report does not account for the patient populations' differences across the clinical trials. Specifically, the LEGEND-2 population (median age: 54.0-55.1 years) was younger and had fewer prior lines of therapy (median number of prior lines: 3-4) compared to all the other trials (median age: 61-65 years, median number of prior lines: 6-7). Given these unadjusted factors across the trials, if ICER cannot obtain PFS and OS data from the manufacturers, at a minimum, add considerable	*We agree that the LEGEND-2 population is substantially different from that of the other CAR-T studies. We have therefore moved discussion of that trial to the report supplement and focus on CARTITUDE-1 as the pivotal trial for cilta-cel in the main report.*

	discussion on the potential direction of bias throughout the report.	
3.	CER should adjust health state utility values: the current model used the same utility values for patient populations receiving three previous lines of therapy as those receiving four or more lines of therapy. Patients refractory to more lines of therapy tend to be older, less fit, and have shorter OS. Specifically, median OS and PFS decrease substantially in patients undergoing subsequent treatment lines after first-line, reflected in health utility states. We recommend adjusting health state utility values to reflect different relapsed/refractory populations.	*Unfortunately, data on health state utility values is very limited at later lines of therapy. The KarMMa trial provides the best available evidence on utilities for triple-class refractory populations.*
4.	2. Re-estimate the cost-effectiveness and price threshold for CAR-T therapies using the ITT population. ICER's base case analyses utilize an "as-treated" population which is likely overly optimistic and unrealistic given that the real outcome of non-infused patients is expected to be worse. The "as-treated" approach that was taken instead of an ITT approach misses a substantial portion of patients who enrolled in the CAR-T trials but did not undergo infusion, accounting for 14% of patients in the KarMMA trial (128/149 patients) and 23% of patients in the CARTITUDE-1 trial (97/126 patients). Furthermore, recently published KarMMA trial results indicate that one out of 12 patients who discontinued the study before idecabtagene vicleucel (ide-cel) infusion, did so due to manufacturing failure, which arguably should be included as part of the efficacy profile. Notable is that ICER has not been consistent across and within appraisals in terms of approach. In ICER's 2016 MM assessment , ICER employed the ITT principal in the model. More importantly, within the current assessment, ICER utilized an ITT analysis for belantamab which is in stark contrast to the "as-treated" approach of the CAR-Ts. Lastly, ICER used the ITT approach for the clinical comparative effectiveness portion of the assessment, but not for the long-term comparative-effectiveness section. Transparency on the use of ITT is essential as excluding patients	*The model does rely on an ITT approach and we agree that an ITT approach is more appropriate. While manufacturing problems led to a substantial percentage of patients being unable to receive CAR-T therapy in 2016, our current review revealed only 1 manufacturing failure (1 in KarMMa and none in CARTITUDE-1).* *Thus, the overwhelming majority of patients who were leukapheresed but not infused had more severe and progressive disease. Using an as-treated approach in this situation would lead to biased, overly optimistic results. Thus, we agree that it is critical to focus on ITT results and we highlight throughout the report.*

	who "discontinue" treatment between enrollment and infusion introduces real consequences due to the treatment delays and potential bias into the efficacy analysis in favor of the CAR-T treatments.	
5.	In the proposed model, CAR-T patients who discontinued before infusion, but did not receive treatment, received the cost, benefits, and risks of the market basket comparators/usual care. The negative impact on overall outcomes represented by these patients who discontinue in the few weeks between enrollment and infusion should not be neglected as these patients are often sicker, frailer, suffer from intolerable adverse events (AEs), experience disease progression, and/or may have sadly died. We strongly recommend that ICER request progression-free survival (PFS) and OS data from the manufacturers and use the full ITT population in the base case. If data cannot be obtained, another approach is to assume the outcomes of non-responders (PFS = 1.8 months) for those that discontinue, as equating these patients to the less refractory patients in the MAMMOTH trial (PFS = 3.4 months) is underestimating the consequences of treatment delays on a sicker population.	*We agree that an ITT analysis is most appropriate. We have highlighted the importance of ITT results in the report.* *The model does use an ITT approach and as explained in the main report, patients not infused but still alive receive the comparator therapy benefits and costs.*
6.	Update the cost of in-patient treatment administration, post-progression treatment (including cost of CAR-T retreatment), and adverse events into the model to reflect recently published trial results and real-world cost estimates. Considering newly published data, retreatment assumptions with CAR-T therapy should be included in the model. A multitude of factors including mechanism of action (MOA), associated adverse reaction profiles, and costs associated with each therapy, substantially influence the choice of subsequent therapies. In the Draft Evidence Report, ICER assumed there was no retreatment due to no available data. However, in the recently published Munshi et al., article 20% of patients in the KarMMa trial underwent ide-cel retreatment (28/140 total patients - 20%). Furthermore, the efficacy of post-progression	*We acknowledge there was no available data on re-treatment at the start of this review. However, this has been changed with the publication of the KarMMa results and we now include the cost of re-treatment in the base-case.*

	treatments can confound the already contorted OS estimate discussed above. We recommend that ICER incorporate a post-progression treatment mix, including CAR-T retreatment costs, into the economic analysis: in the absence of these data, use scenario analyses to assess the impact of different subsequent treatment costs.	
7.	Treatment costs for CAR-T's in MM are significantly higher than the values in the Draft Report. ICER uses a cost of $11,094 for ide-cel and $11,086 for cilta-cel for administration, monitoring, and AE management (except CRS). In contrast, a real-world study by Vizient estimated a median hospital stay of 15 days, with a total median cost of hospitalization to be $85,726 (about $5,700/day) from a cohort of 1,856 CAR-T patients in the US. CAR-T treatment is intensive. For an MM patient to successfully undergo treatment, they must typically stay in the hospital for infusion and monitoring for several days to weeks for adverse reactions (AEs). Patients remain in hospital an average of three days for lymphodepletion, two to seven days for CAR-T infusion, and seven days for AE monitoring, or until oncologists judge AEs to be fully managed. Furthermore, patients who receive CAR-T therapy are often re-admitted to the hospital to manage complications along with follow-up care. Currently approved CAR-T products have risk evaluation and mitigation strategies (REMS) programs where they require patients to remain within proximity (within 2 hours) of a certified CAR-T administration facility for at least four weeks following CAR-T infusion. We recommend that ICER add all relevant real-world CAR-T treatment costs.	*Thank you for noting this point of confusion. Those estimates were not inputs but weighted inputs by those that were infused and did not have adverse events such as CRS. All patients, regardless of CRS, spent a minimum of 6 days in inpatient settings (as observed in KarMMa) and a maximum of 26 days. All patients not experiencing CRS were assigned inpatient and ICU days consistent with previous evidence on CAR-Ts. Furthermore, the costs from KarMMa evidence were inclusive of additional therapies used such as tocilizumab.*

8.	Real-World Evidence (RWE) suggests that the cost of cytokine release syndrome (CRS) is higher than the value in the Draft Report. ICER based the CRS cost on 128 patients from the KarMMa trial, which produced a value of up to $121,535 for grade ≥3 CRS. In contrast, Lin et al. estimate Grade 4 CRS, the most severe grade, can ramp up total hospital costs to a range of $86,500 to $250,000. CRS patients who require IV fluid resuscitation, any vasopressors, and/or oxygen regardless of CRS severity, typically require ICU stay with hospital stay primarily driving CRS cost. Harris et al. also report higher RWD costs from a retrospective cohort of 1,570 CAR-T infusion encounters. This study indicates that patients treated for CRS who only received steroids have a mean cost of $394,113, while those who received just tocilizumab have a mean cost of $409,142. Patients who received both tocilizumab and steroids have a mean cost of $429,415. Furthermore, tocilizumab, used in 52% of patients in KarMMa and 69.1% of patients in CARTITUDE-1, is accompanied by a black box warning for the risk of serious infections. , Consequently, RWD costs such as those above should be the basis of CRS costs for this assessment.	*We agree with using the best available evidence, and where possible the use of RWE is preferred in modeling analyses on costs. The best available evidence in this case is the direct cost estimation from the KarMMa trial rather than simulation models or analyses among patients without multiple myeloma. All patients not experiencing CRS were assigned inpatient and ICU days consistent with previous evidence on CAR-Ts.*
9.	Include scenarios with selinexor as a relevant comparator for belantamab in light of new evidence from the National Comprehensive Cancer Network® (NCCN®) guidelines and uptake. Selinexor with dexamethasone (dex) has been FDA approved since July 2019, well after the MAMMOTH study publication: with the recently updated NCCN guidelines, selinexor is a relevant comparator for belantamab. , , In selinexor's pivotal STORM trial, the population was similar to the DREAMM-2 trial concerning the refractory population and inclusion criteria; therefore allowing for its ease of application in a pooled-analysis. Supporting this point, in December 2020, the NCCN® guidelines updated 3 different selinexor combination regimens to include 1) selinexor/bortezomib/dex (SVd); 2) selinexor/daratumumab/dex (SDd); and 3) selinexor/pomalidomide/dex (SPd) for previously	*In our conversations with our clinical experts, we explored potential appropriate comparator therapies including selinexor. Our clinical experts felt that selinexor was not widely used and therefore an inappropriate real-world comparator. We also examined sales data for selinexor, which confirmed that selinexor was not commonly used.* *Our clinical experts pointed to the MAMMOTH cohort as a multi-site real-world observational cohort that would most accurately approximate what patients would receive if they did not choose anti-BCMA therapies.*

	treated MM. Most importantly, the SVd combination received a category one recommendation (Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate). Moreover, there is increasing real-world use of selinexor, as demonstrated by market share and prescription trends. We recommend ICER consider selinexor as a comparator in a scenario analysis reflective of current guidance and real-world practice.	
#	**Comment**	**ICER Response**
Clinical Society		
American Society of Hematology		
1.	ASH has two general concerns about ICER's draft evidence report, which assesses the clinical effectiveness and value of three treatments for multiple myeloma, idecabtagene vicleucel, ciltacabtagene autoleucel, and belantamab mafodotin. First, ASH believes that this analysis and any comparisons of these agents are premature, since there is not yet a significant patient population treated at recommended doses to fairly assess response rates, as well as median progression free survival (PFS) and overall survival (OS). Ultimately, there have been too few patients treated and limited time for follow-up for this analysis to be meaningful at this time.	*We recognize that for these treatments there is currently limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents right now. As of today, two of the therapies included in our report have been approved by the FDA. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy.* *This report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders.*
2.	Second, while ASH appreciates the need to make data-driven policies, it is difficult to quantify the "value" assigned to human suffering and the ability of a highly effective therapeutic agent to reduce the distress and suffering experienced by an ineffectively served subset of myeloma patients. While the Society appreciates the discussion in the "Contextual Considerations" chapter about the more difficult to quantify elements, ultimately these considerations are not included in the ICER's modeling in the Draft Evidence Report so they have less utility and impact.	*Although it is not possible to include all of the qualitative data we collected from patients and patient advocacy organizations into our cost-effectiveness model itself, these quantitative assessments are only one part of our report.* *We focus considerable attention on the data available, its limitations as well as key insights from all concerned groups including patients and their advocates. Presenting this data, along with the quantitative results are all necessary to inform policymakers about how best to consider new therapies. The comparative clinical effectiveness, quantitative evaluation, other benefits, and contextual considerations sections of our report all feature prominently in the ICER value framework to inform all decision making by our panels.*
3.	The Society believes that there are challenges unique to the multiple myeloma (MM) model.	*Thank you for your comments, we have answered your specific comments on the model below.*

	For example, unlike the non-Hodgkin's lymphoma (NHL) population that was used as a benchmark for the NHL assessment on chimeric antigen receptor (CAR) T-cells, the population of MM patients is more biologically diverse. This makes it much harder to make the one-to-one comparisons between different therapeutic approaches. In the domain of NHL, there is also less diversity of third- and fourth-line therapeutic regimens than there is in the domain of MM patients. Moreover, there are no real sixth line therapies for the NHL population while there are for patients with MM. This vastly complicates the economic modeling involved in estimating the differential cost between the "standard" approach and the three novel approaches that were the focus of this report. In addition, absence of a more rigorous risk segmentation model further limits the ability to adequately economically model out clearly risk-segmented populations for a reproducible "apples to apples" comparison.	
4.	The relationship between PFS and OS for belantamab mafodotin needs further study, as does the definition of the dose which can minimize keratopathy and decrease modifications in planned treatment, as occurs at present.	*We provide a scenario analysis around belantamab mafodotin that adjusts the PFS to OS relationship to what has been observed in two large meta-analyses (Felix et al. and Dimopoulos et al.).*
5.	Nothing is included regarding minimal residual disease responses in all three therapies and its implications.	*We have added MRD negativity as an outcome in the narrative of the main report as well as in the Evidence Tables of the report supplement.*
6.	Finally, patients with MM and their caregivers have the challenge of ophthalmologic evaluation – an additional time and cost burden – before each visit, which needs to be included in analysis.	*We have included transportation costs in the societal perspective section of the report.*

American Society for Transplantation and Cellular Therapy		
1.	ASTCT recommends that ICER re-consider its characterization of Multiple Myeloma as 'moderate.' ASTCT disagrees with ICER's characterization of the magnitude of lifetime impact of Multiple Myeloma on individuals as 'moderate'. Multiple Myeloma diagnosis and progression can swiftly create a significant and negative effect on an individual's quality of life, and its status as an incurable disease is what limits its impact to a 'relatively short proportion of the patient's lifespan.' ASTCT acknowledges that the typical age of onset of Multiple Myeloma is in the sixth or seventh decade of life, well into the trajectory of the typical life expectancy in the United States. However, we wish to note that the median age of diagnosis also coincides with a key time period in many individuals' lives, during which they plan to retire from paid work, spend time with family members and grandchildren, and engage in personal or community pursuits they may have been unable to participate in during prior life phases of focused economic and work force contributions. The burden of disease on the patient, their caregiver and their extended personal communities, as well as the significant loss of life years, should not be minimized without additional specificity from ICER as to what domains the 'moderate impact' represents.	*We recognize that for most myeloma patients, the disease has a huge impact on the quantity and quality of life. As noted in our explanation, our conclusion of a moderate lifetime impact was due to the fact that the median age of diagnosis is 69. Thus, unlike diseases such as cystic fibrosis, which has a large impact over the entire lifespan, myeloma has a large impact on a proportion of a patient's lifespan, with no effect for the first 5 or 6 decades (on average). We have clarified how we arrived at the 'moderate lifetime impact' assessment in Section 5.*
2.	Timing of the Report ASTCT recommends pausing the assessment until at least the time of approval and re-analyzing the data at that point. We reiterate the comments we made in reference to ICER's initial assessment of CAR-T for relapsed and refractory large B-cell lymphoma, in that we feel the timing of this assessment is premature due to the incomplete and preliminary status of the clinical information utilized for the analyses of Cilta-cel and Ide-cel. ICER notes several of the issues with using immature data, and specifically only clinical trial data, in the Uncertainty and Controversies section, thus making a strong argument for pausing the assessment for a short period of	*We recognize that for these treatments there is currently limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents. Two of the therapies included in this report have already been approved by the FDA. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy.* *This report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders.* *Per our review process, 12 months after we have published the final report, we will consider all new*

	time. We understand the need to balance the interests of various stakeholders as well as issuing an assessment as close to the relevant regulatory decision timeframes as possible. However, we feel that the benefit of having more complete access to the data that will be utilized for FDA decision-making outweighs the downside to waiting a few more months. Also, given the preliminary status of the current data, ASTCT is not able to comment further about the comparative clinical effectiveness of the products.	*relevant data and update our report accordingly if needed.*
3.	Data and Clinical Resources If ICER moves ahead with the current assessment timeline, ASTCT recommends that it revisit and update the assessment 12-18 months after FDA approval utilizing data collected through the Cellular Immunotherapy Data Resource (CIDR) and integrating any relevant recommendations from the ASTCT Clinical Practice Guidelines.	*As mentioned above, per our review process, 12 months after we have published the final report, we will consider all new relevant data and update our report accordingly if needed.*
4.	The ASTCT produces Clinical Practice Guidelines for member use, including guidelines related to the utilization of Immune Effector Cell Therapy (IECT), including CAR-T. These guidelines will be updated after the regulatory approval of new products to reflect the viewpoints of the Committee on Practice Guidelines after a thorough review of the relevant literature and data. Source: https://www.astct.org/learn/practice-guidelines	*Thank you for pointing out this resource for us. We will review the updated version after the regulatory approval.*
5.	Related to the prior resource, the ASTCT issues a document entitled “Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy1” at semi-regular intervals, which captures a consensus viewpoint about the use of HCT and IECT for specific indications. The document is publicly available and summarizes an extensive reference list.	*Thank you for pointing out this resource for us.*

6.	ASTCT encourages ICER to clarify the timing of stakeholder engagement work completed in the final evidence report. ASTCT also recommends that ICER conduct a sub-group analysis of outcomes for Black individuals given the disproportionate impact Multiple Myeloma has on this population. Multiple Myeloma disproportionately impacts people of color, as evidenced by an incidence rate of Multiple Myeloma in Black men that is more than 2x the rate of white Americans.2 The Patient Perspectives methodology portion of the report notes that ICER utilized information from prior discussions with the extended Multiple Myeloma community, and groups representing people of color, related to a previous assessment. The community engagement methodology description is unclear as to which portions of community engagement happened in 2016 and which were conducted recently in relation to the current assessment. Given the significant changes to the treatment landscape since 2016 and the increasing number of individuals who have received CAR-T treatment, a re-assessment of patient attitudes may be warranted based on the timing of the engagements.	*For each review, we seek input from the major disease-specific patient advocacy organizations and patients who are living with the condition that is the subject of our review. Our process also includes multiple opportunities for feedback from the broader patient and advocacy communities, including filling out an online survey, having one on one interviews of group discussions with the review team, submitting written feedback through a patient advocacy organization, explicit review of early drafts of our report. In addition, we invite patients to participate in our public meetings through both oral comments and formal participation throughout the meeting as part of a policy roundtable.* *For this review we first reached out to patient advocacy organizations in August of 2020 (prior to the scoping process), held individual interviews with patients throughout the scoping period, conducted a group discussion with patients in January 2021 to inform the draft evidence report. The timeline for public comment periods (and the full list of stakeholders who provided input) is available on our website.* *We completely agree with the need to address racial disparities in the treatment of (and research on) multiple myeloma within our report and we want to thank all patient advocates who provided us with relevant feedback from their community. Unfortunately, there is limited data available on access to treatments like these for certain patient populations. We recognize this and we hope to work with relevant organizations to advocate for more inclusion of Black and African American patients in ongoing research efforts.*
7.	In the Potential Other Benefits and Contextual Considerations Section (p. 33), ICER notes that anti-BCMA therapies have the potential to worsen existing health disparities due to high cost or high side effect burden, in conjunction with administration at a limited number of sites. ASTCT upholds the idea that new therapies should be evaluated through the lens of health disparities; we also note that one-time anti-BCMA therapies have the potential to reduce the financial burden and access challenges associated with therapies requiring ongoing administrations, particularly given that most therapies for Multiple Myeloma can also be categorized as	*We agree that if anti-BCMA therapies were priced to reduce the financial burden on patients, these therapies could decrease disparities. However, we observed little evidence to suggest such pricing, and there is uncertainty over whether these therapies have the potential to be "one-time." Thus, we believe that it is more likely that anti-BCMA therapies will exacerbate disparities due to high cost, specialized delivery, and high side effect burden.*

	high-cost and require access to specialized care sites. Assuming payer approval, a Multiple Myeloma patient may be able to significantly reduce their interactions with the healthcare system after the initial CAR-T treatment episode.	
#	**Comment**	**ICER Response**
Patient/Patient Groups		
Alliance for Regenerative Medicine		
1.	ARM is concerned that the timing of the review prevents ICER from taking into account the FDA's perspective on the appropriate patient population (i.e., through the label), that of expert providers' perspectives (i.e., through recognized compendia), and the technology's durability. Consequently, ARM is concerned that the Draft Evidence Report may harm market and patient access.	*We recognize that for these treatments there are limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents right now. As of today, two of the treatments included in this review have been approved by the FDA. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy.* *This report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders.* *As new data become available, per our review process we will also update our report findings if necessary.*
2.	With the emergence of these therapies, our society is entering an unprecedented era of potentially curative treatments for patients. ICER seems to agree by previously stating that , "the science is undeniably exciting" and can "reflect extreme magnitudes of lifetime health gains and cost offsets that are far beyond those generated by traditional therapies. Additionally, ICER stated, "Cell and gene therapies are starting to provide truly transformative advances for patients and their families, particularly those with conditions for which there has not been any effective treatment before." ARM shares ICER's excitement regarding the science but is concerned ICER's review is ahead of FDA approval and post market data will lead to incomplete assessments and conclusions regarding the magnitude and cost offsets that these therapies can bring to patients and the overall healthcare system.	*We have described our reasoning for the timing of this review above. Furthermore, belantamab mafodotin and the CAR-T therapies are currently available for use by patients (either commercially or through clinical trials). Therefore, we believe that initial assessments of these treatments are already needed now.*

3.	Consistent with traditional evidence reviews, ICER raises some uncertainties and limitations to its conclusions based on clinical trial design and the selection of an appropriate comparator. ARM's initial comments raised some of these concerns and predicted these short fallings. Specifically, ARM stated that comparisons being made across therapies that treat different patient populations and that a close review of the clinical trials for the therapies included in the assessment would reveal that patients treated with cell therapies were quite different from patients treated by non-cell therapies. ARM notes that while ICER did not make these direct comparisons, the many Tables in the Draft Evidence Report could easily lead and confuse the reader towards making these inappropriate conclusions.	*Thank you for pointing this out to us. We have reviewed the language included with these Tables and we believe that the language we had provided should offer readers enough background information not to make direct comparisons between treatments.*
4.	Further, ARM requests that ICER detail the process physicians followed in making the decision to refer to a clinical trial. This information will further clarify the patient characteristics and eligibility criteria of the patients who entered the clinical trials and therefore may guide future physician decision when treating in the real world setting. Further, in the case of cell therapies, patients generally have already failed on non-cell therapies (and likely, many times) and have run out of options, which the cell therapy now provides, which is not well documented n this report. ARM remains concerned that this Draft Evidence Review sets an inappropriate precedence for ICER to draw non-evidence based comparisons across therapies that yields an assessment that is not instructional on clinical practice.	*In the Executive Summary (penultimate paragraph), we note, "Since anti-BCMA treatments represent a novel mechanism of action, these treatments may provide efficacy for patients who currently have few alternatives." This same point is made again in Table 5.1.*
5.	ARM reiterates that this initial input did not include a broad enough range of stakeholders to lead to a true assessment and understanding of the value of this technology. ICER should focus on increased transparency and broader input that will likely lead to a much better appreciation of the true value of this emerging technology. We appreciate ICER's interest in engaging with the stated experts, but we also note that broader engagement is necessary to obtain input from expert bodies, especially in	*Thank you for these suggestions. We completely agree that a broad range of expert stakeholders is necessary to best inform our report.* *For all of our assessments, we receive input via written submissions, interviews, and early reviews of our draft report from clinical experts, payers, patient advocates and manufacturers. Furthermore, the evidence authors for our reports are all experts in evidence-based medicine and have significant experience*

	the nascent field of HTA for potentially curative therapies. ARM has had interactions with experts from methodological bodies such as the International Society of Pharmacoeconomics and Outcomes Research (ISPOR), Health Technology Assessment International (HTAi) and the Second Panel on the Cost-Effectiveness in Health and Medicine. These organizations have published extensively on key methodological issues in evaluating new therapies. ARM recommends that ICER will seek participation from these experts when drafting its final report and in the future when evaluating new issues.	*systematically reviewing and synthesizing a body of evidence.* *However, specific recommendations for including other expert organizations are always welcome.*
6.	Scope and Methodology of the Comparative Value Analyses In prior public statements, ARM has been clear that current HTA frameworks are not flexible enough to accommodate potential cures and have not yet progressed to consistently capture the full product value due to issues including: the short term time frame for assessing affordability versus the long-term timeframe for assessing value; variability in ability and willingness to pay (and applicability of ICER threshold) based on degree of unmet medical need addressed; and the subjectivity of incorporating contextual considerations such as caregiver and societal impacts into a quantitative framework.	*Currently, there is insufficient data available to suggest that these treatments are curative. Hence, we did not apply this framework in this specific review.*
7.	ARM recommends that ICER incorporate updates in economic evaluation methods that reflect the unique and broad benefits of these therapies. In this regard, ARM recommends that this process leads ICER to conduct these types of review post-FDA approval and recommends the use of updated analytical tools for these emerging healthcare technologies. Specifically, when ICER conducts its review it also should include a multi-criterion decision analysis (MCDA) tool as part of its assessment. Developed from the field of systems engineering, MCDA measures how different treatments perform across a variety of attributes and explicitly asks the decision maker to weigh these different attributes. MCDA can be used to quantify these contextual considerations and decision makers can use	*Thank you for this recommendation. We agree that it is very important to capture varying priorities of different stakeholders. This is why we base specific public meeting voting questions on the potential other benefits and contextual considerations section of the report. This allows us capture specific aspects of these interventions while considering the impact on an individual patient, on their caregivers, the delivery system, other patients, or others. 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.*

	MCDA to examine how different prioritization affects treatment recommendations. MCDA may be useful when some key attributes of MCDA-informed value include cost or benefits received by society, but that are not captured by individual decision making or within ICER's CEA model. Finally, MCDA could also capture varying priorities based on stakeholder; for example, collect patient priorities versus other stakeholders, and therefore incorporate patient input more extensively than they do currently.	
Cancer Support Community		
1.	Patient Experience We believe that in addition to limited treatment options and limited survival for TCRMM patients, it is vital that ICER take into account the full spectrum of patient experience factors with current multiple myeloma treatment options which we've outlined below.	*Thank you for providing your feedback. We addressed your specific comments and recommendations below.*
2.	As we stated in our open input letter, risk factors for multiple myeloma include being older than 65 years, being male, being of African descent, family history, radiation exposure, workplace exposure, and ancestral background (Smith, Ambs, & Landgren, 2018). Obesity also appears to be a risk factor for the disease (Marinac et al., 2020). Incidence rates of both MGUS and multiple myeloma are greater among patients of African descent, with multiple myeloma rates among patients of African descent about twice those among patients of European descent (Smith, Ambs, & Landgren, 2018). Blacks are also diagnosed at younger ages (Marinac et al., 2020). We would like to reiterate that it is critical to better understand the perspectives of Black and African American multiple myeloma patients and survivors. We support equitable access for all patients to the most innovative, effective therapies that can prove lifesaving and/or improve the quality of a patient's life.	*We completely agree with the need to address racial disparities in the treatment of (and research on) multiple myeloma within our report and we want to thank all patient advocates who provided us with relevant feedback from their community. Unfortunately, there is limited data available on access to treatments like these for certain patient populations. We recognize this and we hope to work with relevant organizations to advocate for more inclusion of Black and African American patients in ongoing research efforts.*

3.	CSC's Multiple Myeloma Specialty Registry participants were asked about their experiences with the disease and subsequent treatment. We reported these findings in our open input and scoping document comments.	*Our review team appreciates all the information that the CSC provided to us throughout the review from the Multiple Myeloma Specialty Registry. This helped inform both our patient input section and the potential other benefits and contextual considerations, which will also be discussed by the independent appraisal committee at the public meeting on April 16th.* *We look forward to working with CSC in the future to collaborate on collecting patient-reported outcomes and highlighting the patients' experience in our reports.*
Partnership to Improve Patient Care		
1.	It is premature for ICER to assess these treatments. We would like to echo the statements of other advocacy groups, including the International Myeloma Foundation and Alliance for Regenerative Medicine, in noting that it is premature for this assessment to be conducted. Most of the value from oncology drugs comes from survival improvements. It is hard to develop a strong empirical picture of potential survival attributes of new therapies this early in the process. The difficulty and imprecision in capturing value when there are too few patients alive or progression free is a commonly cited shortfall of value frameworks when applied to oncology. , With this in mind, to deliver a more accurate assessment, ICER should seriously consider delaying this assessment until more conclusive evidence is available.	*We recognize that for these treatments there are limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents. Two of the treatments included in our review have already been approved by the FDA. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy.* *This report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders.* *Furthermore, all of these treatments are currently available for some patients (either commercially or through clinical trials), therefore we believe that it's important to publish initial assessments right now.*
2.	ICER's utilities do not accurately capture quality of life for multiple myeloma patients. Patients highlighted in their comments to ICER that quality of life was critically important in the evaluation of new therapies for triple class refractory multiple myeloma (TRCMM), as, frequently, the goal of these patients is to increase their quality of life as much as possible under the reality that long life extension is unlikely. CAR-T has been shown to be less toxic than more traditional oncology treatments. For this reason, the choices for utility values used to represent quality of life in the model are	*At this line of therapy for multiple myeloma, the best available evidence on health state utilities comes directly from one of the trials assessed in this report, i.e., KarMMa. Further changes to utility values are shown in the one-way sensitivity analyses and were also included in probabilistic sensitivity analyses.*

	seminally important. The health state utilities used in the QALY calculation for the model were 0.78, 0.82 and 0.71 for progression-free on therapy and responding; progression free off-therapy and responding; and progressing and not responding. This makes the difference between responding and not responding to therapy very small at 0.07 units of utility. Other studies have found that this range is much larger and that the utility for active progressing disease in MM is much lower. The same author, in a similar but larger study showed a mean active disease utility of 0.5 and a 'gain' from effective treatment of up to 0.15, and a 2014 study estimated a mean score for multiple myeloma patients in all stages of disease of 0.73 with a low of 0.62. It is imperative that the utilities used come as close to accurately capturing a multiple myeloma patient's quality of life as possible. We would posit that the current utilities to not fit the bill and encourage ICER to look to other studies, such as the two we reference above.	
3.	ICER should acknowledge that multiple myeloma is a rare disease and give weight to the limited number of treatment options for patients with TCRMM. Multiple myeloma is a rare cancer with an annual incidence of approximately 7 in 100,000 Americans. ICER should revisit its choice around having different thresholds for rare diseases as a matter of course. The use of alternate thresholds for rare diseases has become common practice in HTA organizations and value assessment bodies around the world. The benefits of such an approach in terms of getting treatments to patients more expediently by providing much needed incentive for both the pharmaceutical and biotechnology industries to invest in rare diseases have been widely acknowledged. In tandem with this, it is important for ICER to acknowledge that there are limited therapeutic options available to multiple myeloma patients, particularly those with TCRMM. Many value	*We agree that multiple myeloma is a rare disease. ICER updated and published modifications to the ICER value assessment framework for treatments for ultra-rare diseases (URD) in January of 2020. You can review the updates here.* *Per our rare disease guidelines listed above, multiple myeloma does not meet URD criteria, which specify a prevalence of <10,000 Americans and no expectation that future indications will expand the population.* *It is important to highlight that although we have assigned a specific value to establish if a disease falls under the URD category, during the scoping phase of our review, all stakeholders are invited to make a recommendation on whether the intervention should be assessed as a treatment for an URD.* *Following formal public comment on this recommendation, ICER will make a final decision on whether the treatment will be assessed under the modified methods presented in the document linked above.*

	assessment bodies around the world consider this a key construct of priority setting in medical innovation over a therapy's cost-effectiveness ratio alone. In Norway for example, a new therapy is given greater leeway in terms of its cost-effectiveness ratio when 'no alternative treatment having a substantial effect is available.' We urge ICER to follow this blueprint.	
4.	The burden for multiple myeloma falls more acutely on under-served populations. Multiple myeloma has much higher prevalence in under-served populations. Incidence is twice as high in African-Americans than in Caucasian populations and mortality is also higher in African-Americans. The number of cases in African-American males is expected to double over the next twenty years. African-Americans are significantly underrepresented in clinical trials for treatments for multiple myeloma, and the recruitment has actually been falling over the most recent period of study. It is important that ICER undertake subgroups analyses in order to evaluate treatments' impacts for the population with significant burden.	*We completely agree with the need to address racial disparities in the treatment of (and research on) multiple myeloma within our report and we want to thank all patient advocates who provided us with relevant feedback from their community. Unfortunately, there is limited data available on access to treatments like these for certain patient populations. We recognize this and we hope to work with relevant organizations to advocate for more inclusion of Black and African American patients in ongoing research efforts.*
5.	The use of the QALY and traditional cost-effectiveness assessment (CEA) is not appropriate for evaluating novel CAR-T therapies. PIPC has made the case many times to ICER that the QALY is discriminatory and should not be used to determine coverage of and access to therapies. The shortcomings of the QALY and traditional CEA become even more prevalent when assessing novel cell and gene therapies, and we would urge ICER to reconsider using this methodology. The QALY is well known and documented to discriminate against those with disabilities and chronic illnesses. It is particularly problematic when applied to rare diseases, which many cell therapies, including the ones being studied in this review, are designed to treat. Standard, generic quality of life instruments, like the EQ-	*We appreciate the concerns about relying solely on QALYs.* *The quality-adjusted life year (QALY) is the gold standard for measuring how well all different kinds of medical treatments lengthen and/or improve patients' lives, and therefore the metric has served as a fundamental component of cost-effectiveness analyses in the US and around the world for more than 30 years. If evidence shows that a treatment helps lengthen life or improve quality of life, these benefits are comprehensively summed up to calculate how many additional QALYs the treatment provides, and this added health benefit is then compared to the added health benefit of other treatments for the same patient population.* *To complement the use of the QALY, ICER's reports also include a calculation of the Equal Value of Life Years Gained (evLYG), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. In other words, if a*

	5D, which are used as inputs to the QALY are disease agnostic and designed to measure individual preferences. In reality, research has shown that there is frequently a great societal preference to allocate resources to rare diseases. There are also less well-defined health state preference weights for these rarer conditions, which we touch on above in reference to this assessment. This makes it more likely that assessments underestimate the disease burden for patients who are not receiving the cell therapy.	*treatment adds a year of life to a vulnerable patient population – whether treating individuals with cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community.* *By understanding a treatment's cost per evLYG, as well as its traditional cost per QALY, policymakers can take a broader view of cost-effectiveness and be reassured that they are considering information that poses no risk of discrimination against any patient group.*
6.	Due to these concerns, many HTA bodies around the world have started exploring alternative and potentially more comprehensive methods of value assessment, like multi-criteria decision analysis. We suggest ICER also look to methods that can more accurately capture the full benefit of these novel treatments.	*Thank you for this recommendation. In addition to the information provided above, we have also updated our Potential Other Benefits and Contextual Considerations section to provide more insight into how these treatments might impact different stakeholders.*
Patients Rising Now		
1.	People-Centered Perspectives We again appreciate the outreach that ICER did to patient groups and the information shared in the draft report's Section 2: "Patient and Caregiver Perspectives." ICER's decision to use a structured discussion guide for collecting information from the relevant patient groups is an important step forward for ICER, as it represents a more rigorous approach to evaluating and incorporating patient perspectives into its analyses. However, as we pointed out before, conducting a focus group is not just bringing people together for a discussion, and a gathering of just four people can hardly be considered sufficient for a meaningful focus group.	*Thank you for this feedback. The goal for hosting the group discussion with these specific patients was to complement the individual patient survey responses and individual patient interviews we held earlier in the review process.* *However, we agree that there is always room for improvement and we appreciate specific feedback on how to even better incorporate patient input in our reports.*
2.	To make good decisions, ICER, policy makers, and payers must understand and appreciate the complicated pathways that people with multiple myeloma take through their treatments, and that those paths often vary greatly from person to person – a point that is clear in the materials from the National Comprehensive Cancer Network's (NCCN) information for both clinicians and patients. The NCCN recognizes the variety of treatments that someone with multiple myeloma may receive – ranging from	*Thank you for pointing this out. We have updated the NCCN guidelines in our report to the most recent version. We agree that treatment for triple-class refractory multiple myeloma is very complex and we hope to have a more detailed discussion about this at the public meeting on April 16th (in addition to addressing this in the report).*

	several types of stem cell transplants, to general or targeted chemotherapies, to clinical trials. This complexity is noted in the draft report, i.e., "there is no widely accepted preferred ordering of lines of therapy for TCRMM patients."	
3.	We were a dismayed that the draft report's discussion of treatment options essentially ignores stem cell transplantation, even omitting stem cell transplantation from its description of "mainstays of current MM treatments." We realize that ICER's draft report is tightly focused on three new treatment options (only one of which is approved), but failing to provide the appropriate context for understanding those new treatment options compared to the array already available – and how they could be chosen or used during the course of multiple treatment failures or relapses for individual patients – does a disservice to patients, clinicians, policy makers, payers, and society. This too-narrow focus and lack of contextualization is an ongoing problem that ICER seems unable to rectify and ignores the real-world movement toward better patient-clinical team communications and shared decision-making.	*In the 4th paragraph of the background section of the report, we note, "modern combination treatments and autologous stem cell transplant can often lead to effective control...of MM.".*
4.	In that vein, we noted that stem cell transplantation was a specific exclusion criterion for all the trials used as data sources in the draft report, but in the ongoing studies (summarized in the draft report), stem cell transplantation is a reason for exclusion in only some of the trials. If there are clinical or scientific reasons that stem cell transplant recipients face contraindications to any of the treatments, that information should be included in the draft report. The draft report's failure to discuss stem cell therapies leaves many unanswered questions and is another example of ICER's limited perspective regarding very complex clinical conditions.	*Unfortunately, space limitations preclude us from including inclusion and exclusion criteria of all trials.* *It seems there may have been confusion regarding autologous and allogeneic stem cell transplant. While autologous stem cell transplant is an accepted and efficacious treatment modality for MM, allogeneic stem cell transplant has high treatment-related mortality and is considered experimental. Most studies allowed inclusion of patients who had received autologous SCT but excluded patients who had received allogeneic SCT.*

5.	The clinical trials reviewed in the draft report attempted to include patient reported outcomes and quality of life metrics in their protocols. While those metrics were not consistent across trials, as the report notes, at least this represents an attempt to assess how the experimental treatments affected patients. Overall, from the information in the draft report, it seems that the CAR T-cell therapies were more positive in improving patients' lives than belantamab mafodotin. That insight, albeit very preliminary, is quite encouraging since CAR T-cell therapies are a new treatment approach that provide hope across a range of serious diseases and conditions. We also were encouraged by the draft report's statement that "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."	*Thank you for this comment.*
6.	The draft report utilizes unpublished or unreviewed presentations or papers as data sources. For example, one of the sources for the baseline population characteristics is a paper that was presented at a conference rather than published after peer review. We note that this data source was used for modeling the baseline population for one of the three treatments in the draft report, while the other two had their own citations – both published papers. We would like ICER to explain – in doing the baseline modeling – why it was appropriate to develop different population characterization for each of the three therapies, particularly since it is expected that the usage of the new therapies will evolve in the future, with the likelihood that they will be used earlier in the course of patients' illnesses.	*Thank you for this feedback. During the public comment period, more evidence was published in peer-reviewed journals and we have included these in our base-case analyses. Please see the revised report (Section 4: Long-Term Cost-Effectiveness) which should answer your questions about the data sources and baseline population.*

7.	In the draft report's listing of Categories of Contextual Considerations it states that concerning the context for "the magnitude of the lifetime impact on individual patients" that the "Relevant Information" is that multiple myeloma "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." We are very concerned about that characterization, and how it dramatically ignores the effects that multiple myeloma has on the individual, their family, and others in their lives. While people with multiple myeloma who are in the "heavily pre-treated subpopulation" – meaning that they have already undergone several (or possibly many), different treatments, which likely occurred over the course of many years – ICER's characterization discounts the importance of their lives, perhaps because these individuals are likely older. We strenuously urge this characterization be a primary topic of discussion at the Midwest CEPAC meeting scheduled for April 16th; for example, during the discussion of the prioritization for question #6 "Magnitude of the lifetime impact of the condition being treated." While ICER's "Relevant Information" statement might be accurate in sterile economic terms, we find it both callous and offensive from the patients' perspective.	*We recognize that for most myeloma patients, the disease has a huge impact on the quantity and quality of life. As noted in our explanation, our conclusion of a moderate lifetime impact was due to the fact that the median age of diagnosis is 69. Thus, unlike diseases such as cystic fibrosis, which has a large impact over the entire lifespan, myeloma has a large impact on a proportion of a patient's lifespan, with no effect for the first 5 or 6 decades (on average). We have clarified how we arrived at the 'moderate lifetime impact' assessment in Section 5.*
8.	The draft report repeatedly states that it is looking at the use of these treatments in people who have had at least three prior lines of therapy, but one of the cited data sources is a phase 1 trial where the patients had 1-9 prior therapies. In contrast to that reality of the underlying data, the Long-Term Cost-Effectiveness section of the draft report explicitly states, "The CAR T trial's enrollment criteria required patients to have been treated with 3 previous lines of therapy." This is another example where ICER states parameters for its modeling, and then ignores or	*Thank you for this comment. We have made changes in the report to harmonize our description of the populations.*

	misrepresents the actual data it uses. At some level, ICER must have realized this discordance, since the draft report also notes that the data from this trial should be "approached with caution" because the participants were "less heavily pre-treated."	
9.	CAR T-cell therapy is only performed at select locations, such as inpatient facilities of academic medical centers, because it is a relatively new type of treatment that involves not just drug injection, but also requires a sequence of procedures to procure, purify, modify, and infuse the patient's own T-cells. However, while this is a technologically complex process requiring a variety of skilled teams, it is clear that the treatment is expected to expand to additional care settings, including outpatient facilities. This transition of new treatments from being used in the most constrained or intensive settings to less acute or technologically sophisticated facilities is a well-known evolution in medical care. Because these factors have such direct implications for patients, health care delivery, payers, policy makers and society – as well as costs and access – ICER should include such perspectives in its draft report.	*Thank you for pointing this out. We addressed this in our patient interviews, where we had specific questions for patients about where they received CAR-T therapies. Furthermore, we spoke with relevant experts to get a better understanding of how different populations might have or have not access to novel treatments like the ones reviewed in this report. We assessed this potential discrepancy for both the CAR-Ts and Blenrep. You can find it in the report under "Uncertainties and Controversies".*
10.	Related to that point, we again find ICER's presentation of new technologies fails to model any movement forward in improvements that would facilitate delivery and access, including to patients in underserved areas. For example, the draft report states, "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." Disparities exist largely because of the historical discriminatory nature of the U.S. health care system; society's failure to address those structural and reimbursement problems perpetuate those disparities. This is another opportunity for ICER to learn from the current COVID pandemic, in which disparities in testing and care have dramatically illuminated the very real structural inequity in the U.S. health care	*We agree that the primary culprit for disparities is our imperfect healthcare system. However, since the anti-BCMA therapies will not dramatically change the structure of the US healthcare system, we are simply trying to foresee the most likely impact of these new therapies on the admittedly imperfect healthcare system we have. Thus, we stand by our conclusion; namely that the likely high costs, specialized delivery, and high side effect burden of these therapies have a high likelihood of exacerbating disparities.*

	system that existed before the pandemic. In essence, in the draft report, ICER is blaming the new tool for the outcome, rather than the system that wields the tool.	
11.	The draft report notes that ICER was not able to conduct an intention-to-treat analysis for the CAR T-cell therapies, apparently because ICER does not have access to the full data set from the clinical trials. We strongly expect that if this is an important analysis, the FDA will conduct it as part of their review prior to making an approval decision. However, we note that for individuals with multiple myeloma, they should care more about actual outcomes from people who received a line of therapy, rather than a statistical analysis of a large group that includes people who considered a treatment, but for a variety of reasons ended up not getting it. We realize that is the difference between patient perspectives and health system or regulatory concerns, but ICER should recognize and care about those differences.	*The modeling analysis uses an ITT approach. Patients not infused received comparator costs and benefits. We also account for those that died prior to receiving the infusion.*
12.	In selecting previous studies to model usual care etc., we note that ICER selected one from its own authors, while a simple web search turned up several others, including more recent studies. ICER should discuss how it selected its own study and then justify why that data is better or more appropriate than other more recent studies.	*If you are referring to the 2018 assessment of CAR-T Therapies (Tisagenlecleucel and Axicabtagene Ciloleucel) for Leukemia and Lymphoma, we refer to this previous report as one reference to a previous CAR-T assessment.* *However, this was not the only (or the main) source for data for our modeling sections. All relevant sources are cited within the modeling section and listed in the Reference section at the end of the document.* *Furthermore, both our Model Analysis Plan and Research Protocol (available on our website) will provide you a detailed overview of how we selected studies and data sources for this assessment.*
13.	In previous comments to ICER we have strongly urged that the uncertainties and limitations be expressed more strongly and sooner. This draft report is another example of the importance of doing that. For example, the draft report contains these statements: "[G]iven that the treatment landscape changes dramatically over short time periods in RRMM, and the lack of an indirect treatment comparison against each therapy, caution	*Thank you for this feedback on the template of our report. We believe that the Uncertainty and Controversies is a very important section to address the issues that you have highlighted. This is why we have included this section in the main report (and not the supplement) to highlight its importance.*

	should be used when interpreting cost-effectiveness estimates." "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." Such admissions that the economic modeling and analysis are based on flimsy and non-comparable data indicates that the conclusions may be very wrong. But yet again, ICER buries that admission in the depth of the draft report.	
14.	Given the limited data used to develop the draft report, and the unknown prices for the CAR T-cell therapies, we find discussion in the Budget Impact Section to be ludicrous but do appreciate that ICER recognizes that the same patients would not be expected to receive two different types of CAR T-cell therapies in a five-year period.	*ICER's analyses of potential budget impact are intended to provide an alert if the anticipated cost to the overall health care system has the potential to exceed specific growth targets due to high incremental costs and/or population size.* *Since ide-cel was approved by the FDA on March 27th, we have updated our analyses accordingly with new available data in the revised report.*
15.	There are many endnotes that are wrong. For example, on page 45, endnotes 54 and 55 are incorrect, with the actual references being included in endnotes 61 and 62. The reference to the NCCN's clinical guidelines is to the May 2020 version, even though there is a more recent version that was released in December 2020, and it is unclear what "Recommendation 3" is referring to since the NCCN guidelines do not use that designation. The language in the report can be somewhat technical and misleading to readers not steeped in the scientific areas. For example, with CAR T therapies, there is reference to the cells being "expanded and then infused back into patients." After doing some research, we realized that this use of the term "expanded" means to increase in number through ex-vivo multiplication, and it does not mean to increase the volume of each cell, which would be the normal meaning of the word "expanded."	*We apologize for these mistakes. We have reviewed and fixed them in the revised evidence report.* *We have also updated the NCCN clinical guidelines to the most recent version.*

	We are disappointed that ICER does not recognize the trauma that COVID-19 has caused people with multiple myeloma (and other serious health conditions) who have often faced physical access restrictions to care and potentially limited support from caregivers; and incorporate those realities in its work.	*There is no denying that the COVID-19 pandemic has impacted care for many patients with a wide variety of diseases. We did address this in our patient interviews, where we heard directly from patients how the pandemic had disrupted their treatment plans and ability to resume daily activities while in remission. We have addressed this in the Patient and Caregiver Perspectives section of the report.*
Multiple Patient Advocacy Organizations		
1.	Both idecabtagene vicleucel and ciltacabtagene autoleucel have yet to be approved and studied in real world settings. We remain concerned that the clinical and financial data utilized are premature for the evaluation of CAR-T for Multiple Myeloma. The clinical benefits to patients receiving CAR T for Multiple Myeloma are still evolving, and new studies testing these treatments in earlier lines of care explore the possibility that they may be more effective.	*We recognize that for these treatments there are limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents right now. Two of the treatments included in our review have already been approved by the FDA. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy.* *This report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of stakeholders. Per our review process guidelines, we can update our report findings after the public meeting once new relevant data emerges.*
2.	CAR T Challenges & Patient Population With the potential approval of CAR T for Multiple Myeloma approaching, there is significant excitement about the possibility to improve the lives of many patients impacted by the disease. Multiple Myeloma patients eligible for CAR T are usually at the point where they have limited alternate treatment options and a very poor chance of survival, with data showing median overall survival without CAR T at 3.4 to 9.3 months. CAR T for Multiple Myeloma have demonstrated an overall survival of over 19 months. Research has also shown that the "cyclical nature" of Multiple Myeloma can result in higher levels of anxiety, depression and fatigue. We have heard first-hand from patients about the value of hope, and that having another option can provide a mindset shift to those facing these circumstances.	*Thank you for providing us with this feedback. Your comments are very similar to the feedback we received from patients and we have incorporated these aspects into our report.*

3.	Studies show that many Multiple Myeloma patients experience significant quality of life impacts, including physical symptoms of the disease and side effects of treatment. The ongoing psychosocial impacts on patients, caregivers, and family members are also great. , Physical ailments can include neurological damage such as peripheral neuropathy; pain management issues; kidney failure caused by Multiple Myeloma; and more, having a substantial impact on quality of life. Specifically, in a survey of approximately 200 multiple myeloma patients, 65% said that fatigue interferes with their daily life, 38% were at risk for clinically significant levels of anxiety, and 33% were at risk for clinically significant levels of depression.	*Thank you for providing us with this feedback. Your comments are very similar to the feedback we received from patients and we have incorporated these aspects into our report.*
4.	Health Disparities Multiple Myeloma is twice as common in Black people. ICER addresses concerns about health disparities in the draft evidence report. Specifically, ICER suggests that complex and higher-cost therapies have been underutilized by historically disadvantaged populations, suggesting that breakthrough treatments like CAR T may worsen health disparities. We recognize the critical need to ensure that all therapies – including the most innovative – are available to all people living with multiple myeloma, particularly those from historically disadvantaged populations. We look forward to working with ICER and all relevant stakeholders to ensure equitable access.	*We completely agree with the need to address racial disparities in the treatment of (and research on) multiple myeloma within our report and we want to thank all patient advocates who provided us with relevant feedback from their community. Unfortunately, there is limited data available on access to treatments like these for certain patient populations. We recognize this and we hope to work with relevant organizations to advocate for more inclusion of Black and African American patients in ongoing research efforts.*
5.	Additional Patient Perspectives are Needed We recognize and appreciate ICER's inclusion of patient and caregiver perspectives in the report. The significant physical, emotional, and financial burden on patients being treated for Multiple Myeloma should continue to be a focal point of these analyses. ICER takes into account the impact that side effects have on patients, however it is critical that ICER understand the value of a "one and done" therapy. Numerous treatments and regular physician and hospital visits impose a	*We completely agree. We have included this perspective in our Patient and Caregiver Perspectives section since we heard directly from patients how important it is for them to reduce the number of hospital visits to minimize the disruptions to their daily life. Furthermore, we have added a more detailed overview of patient perspectives in the supplement.*

	financial burden on both patients and caregivers, including loss of work and/or societal contributions, in addition to direct costs of assuming the role of family caregiver. These challenges can be significantly disruptive to the daily life of patients and caregivers.	
#	**Comment**	**ICER Response**
Other		
Paul Langley		
	A further concern is that those building these models (in this case the group at the University of Colorado) appear not to recognize the standards of normal science. That is: claims generated for any model must be credible, evaluable and replicable. Otherwise they fail the demarcation test and are nothing more than pseudoscience (e.g., intelligent design). I realize that building model simulations has been a core belief in health technology assessment for over 30 years. This does not mean it is useful let alone valid. In building simulations that claim to project benefits for decades into the future, I fear that your model builders have failed to recognize Hume's problem of induction: Assumptions as to future events can never be secured since we cannot observe future events … it cannot be established logically from the fact that all past futures have resembled past pasts so it does not follow that all future futures will resemble future past. Creating future claims by simulation modelling of assumptions is just wrong (and don't tell me that an assumption about the future is 'realistic'). Certainly assumptions have a place in modelling and hypothesis testing – but only if the claims that rest on those assumption are empirically evaluable (i.e., falsifiable).	*Thank you for your feedback.* *ICER works with numerous clinical experts, modeling experts and academic institutions to provide a diverse and exhaustive approach to our value assessment work.* *We have developed the framework for our assessments with the help of several stakeholders in addition to the ones we have mentioned above, and we continue to welcome feedback on how to further improve our methodology.*