Alliance *for* Regenerative Medicine

March 8, 2021

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Comments to Draft Evidence Report on Anti B-Cell Maturation Antigen CAR T-cell and Antibody Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma

Introduction

The Alliance for Regenerative Medicine (ARM) appreciates the opportunity to submit the following comments to the Institute for Clinical and Economic Review (ICER) February 11, 2021 draft report on Anti B-Cell Maturation Antigen CAR T-cell and Antibody Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma ("Draft Evidence Report").[1]

ARM is the leading international advocacy organization dedicated to realizing the promise of regenerative medicines and advanced therapies. ARM promotes legislative, regulatory and reimbursement initiatives to advance this innovative and transformative sector, which includes cell therapies, gene therapies and tissue-based therapies. In its 11-year history, ARM has become the global voice of the sector, representing the interests of 380+ members worldwide, including small and large companies, academic research institutions, major medical centers and patient groups.

Although focused on one type of rare cancer, the Draft Evidence Report raises important issues for ARM members because of its potential negative impact on the development of the therapies under review and future therapies. 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.

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

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[1] Lee SJ, McQueen RB, Beinfeld M, Fluetsch N, Whittington MD, Pearson SD, Ollendorf DA. Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma; Draft Evidence Report. Institute for Clinical and Economic Review, February 11, 2021. https://icer.org/assessment/multiple-myeloma-2021/#timeline
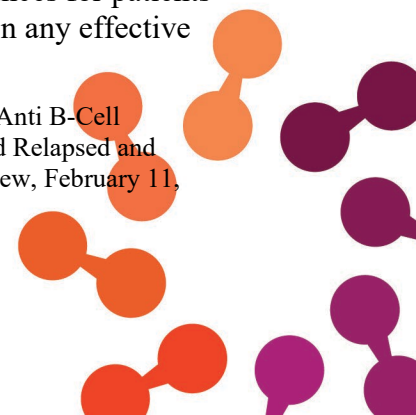
treatment before." ARM shares ICER's excitement regarding the science but is concerned ICER's review is ahead of FDA approval and post market data will lead to incomplete assessments and conclusions regarding the magnitude and cost offsets that these therapies can bring to patients and the overall healthcare system.

Draft Evidence Report Initial Conclusions

ARM appreciates the Draft Evidence Report findings that the evidence suggests that the chimeric antigen receptor T-cell therapies examined improve outcomes for triple-class refractory MM patients, with higher rates of response and longer survival than treatment with current therapies.

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[2] 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.

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.

Stakeholder Input

As stated in our initial comments to this Draft Evidence Report, ARM believes that independent scientific evaluations of clinical and economic evidence supporting the utilization of FDA approved therapies is critical, however at the appropriate time. These analyses should focus on the unique benefits of a new technology over the period of time in which its treatment effect is observed in a real-world setting post-approval before considering issues of short-term costs and/or even the need for innovative payment models, which may not be appropriate given this patient population and the longer-term efficacy readouts. Such an approach optimizes patient access to the most appropriate and innovative therapy to treat their disease.

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

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[2] See October 13, 2020 ARM letter to ICER "Comments to Draft Scoping Document on Anti B-Cell Maturation Antigen CAR T-cell and Antibody Conjugate Therapy for Triple Class Refractory Multiple Myeloma."

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true value of this emerging technology.[3] 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 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.[4] 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.

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.[5]

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.[6] 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 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.

ARM encourages ICER to continue to collaborate with the health economic field to monitor the potential future inclusion of these dimensions. ARM appreciates the opportunity to provide our perspective on these important issues. Please do not hesitate to contact me if you have any questions.

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[3] https://icer-review.org/wp-content/uploads/2020/08/ICER_MM_Key_Stakeholders_092720.pdf
[4] Peter J. Neumann et al, *Cost-Effectiveness in Health and Medicine* (Oxford Scholarship Online, November 2016).
[5] See March 29, 2017 ARM letter to ICER regarding the proposed update to the ICER Value Assessment Framework.
[6] Phelps CE, Madhavan G. Valuing Health: Evolution, Revolution, Resistance, and Reform. Value in Health. 2019 May 1;22(5):505-10

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Sincerely,

Robert J. Falb
Director, U.S. Regulatory Affairs

SUMMARY OVERVIEW

Amgen appreciates the opportunity to comment on ICER's *Draft Evidence Report for the Anti B-Cell Maturation Antigen Chimeric Antigen Receptor (CAR) T-Cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma (RRMM).*

Amgen is committed to continuing its rich history of discovery, research and development of multiple myeloma treatments and ensuring access for patients. While we are pleased that ICER's MM assessment reflects many of the complexities for patients suffering from RRMM, we would like to highlight a few essential recommendations for the Draft Report:

1. **Change the overall survival (OS) estimate for ciltacabtagene autoleucel (cilta-cel) and account for material differences across each patient population.**
2. **Re-estimate the cost-effectiveness and price threshold for CAR-T therapies using the intention to treat (ITT) population.**
3. **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.**
4. **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.**

We expand our recommendations below.

DETAILED RECOMMENDATIONS

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.[1] 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[1] 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.

ICER's analysis introduces possible bias into the model as the draft report does not account for the

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[1] Survival estimates were obtained based on the survival model parameters published in Table E.2.6. in ICER's Draft Report.

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).[2] Given these unadjusted factors across the trials, if ICER cannot obtain PFS and OS data from the manufacturers, at a minimum, add considerable discussion on the potential direction of bias throughout the report.

ICER 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.[3] Specifically, median OS and PFS decrease substantially in patients undergoing subsequent treatment lines after first-line, reflected in health utility states.[4]   We recommend adjusting health state utility values to reflect different relapsed/refractory populations.

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.[5] 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).[6] 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.[7] Notable is that ICER has not been consistent across and within appraisals in terms of approach. In ICER's 2016 MM assessment[8], ICER employed the ITT principal in the model. More importantly, within the current assessment, ICER utilized an ITT analysis for belantamab[9] 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 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.

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)[10] for those that discontinue, as equating these patients to the less refractory patients in the MAMMOTH trial (PFS = 3.4 months)[11] is underestimating the consequences of treatment delays on a sicker population.

3. **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.[12,13] In the Draft Evidence Report, ICER assumed there was <u>no retreatment due to no available data</u>. However, in the recently published Munshi *et al.*, article <u>20% of patients in the KarMMa trial underwent ide-cel retreatment</u> (28/140 total patients - 20%).[14] Furthermore, the efficacy of post-progression 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.

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.[15] 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.[16] Furthermore, patients who receive CAR-T therapy are often re-admitted to the hospital to manage complications along with follow-up care.[17] 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.[18] We recommend that ICER add all relevant real-world CAR-T treatment costs.

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.[19] 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.[20] 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.[21,22] 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.[23] 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.[24,25] Consequently, RWD costs such as those above should be the basis of CRS costs for this assessment.

4. **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.[26,27,28] 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.[29,30,31] 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 treated MM.[32] 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*).[33] Moreover, there is increasing real-world use of selinexor, as demonstrated by market share and prescription trends.[34] We recommend ICER consider selinexor as a comparator in a scenario analysis reflective of current guidance and real-world practice.

CONCLUSION

Lack of consensus and limited guidance for treating heavily pre-treated RRMM patients leaves clinicians and patients with significant challenges in identifying appropriate and optimal treatment regimens. A MM diagnosis brings substantial negative consequences and burden for patients, their families, and caregivers. We recommend that ICER mitigate the overestimation of benefit and the unquantifiable bias in the Draft Report. Additionally, incorporate comparators more reflective of real-world practice and revisit the costs related to retreatment with CAR-Ts, treatment costs, CRS, and the heterogeneous landscape of post-progression treatments for a more accurate and rigorous assessment.

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March 11, 2021

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Re: ICER's Assessment of Treatments for Multiple Myeloma

Dr. Pearson,

The American Society of Hematology (ASH) appreciates the opportunity to offer comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report: Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma.

ASH represents more than 17,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell disease, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy.

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. 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.

ASH's specific concerns with this review are outlined below.

Challenges Unique to the Multiple Myeloma Population

The Society believes that there are challenges unique to the multiple myeloma (MM) model. 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.

Additional Comments

- 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.
- Nothing is included regarding minimal residual disease responses in all three therapies and its implications.
- 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.

Thank you for the opportunity to submit comments. Should you have any questions or if you would like to discuss these comments further, please reach out to Leslie Brady, ASH Policy and Practice Manager, at lbrady@hematology.org or 716-361-2764 (cell).

Sincerely,

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March 11, 2021

RE: ICER "Anti B-cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma" Draft Evidence Report

Members of the Midwest Comparative Effectiveness Public Advisory Council:

The American Society for Transplantation and Cellular Therapy (ASTCT, formerly the American Society for Blood and Marrow Transplantation), appreciates being named as a stakeholder from whom ICER would appreciate input regarding the current Multiple Myeloma Draft Evidence Report. We commend ICER for involving an ASTCT member, Dr. Ravi Vij, as an Expert Reviewer on this assessment.

ASTCT is a professional membership association of more than 2,200 physicians, scientists and other health care professionals promoting blood and marrow transplantation and cellular therapy through research, education, scholarly publication and clinical standards. The clinical teams in our society have been instrumental in developing and implementing clinical care standards and advancing cellular therapy science, including participation in trials that led to current FDA approvals for chimeric antigen receptor T-cell (CAR-T) therapy.

COMMENTS ON THE DRAFT EVIDENCE REPORT:

Clinical Framework

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.

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 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.

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.

The ASTCT offers several additional data resources for ICER's utilization in this and future assessments related to CAR-T.

- 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

- 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 Therapy](#)[1]" 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.

- The Center for International Blood and Marrow Transplant Research (CIBMTR) was awarded a grant to operate the CIDR by the National Cancer Institute. As part of this work, the CIBMTR is collecting and analyzing extensive amounts of data related to cellular immunotherapy products, including CAR-T.

Health Disparities

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.

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 <u>reduce</u> the financial burden and access challenges associated with therapies requiring ongoing administrations,

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[1] https://www.tctjournal.org/article/S1083-8791(20)30114-2/fulltext

[2] American Cancer Society. *Cancer Facts and Figures for African Americans 2019-2021*. Atlanta: American Cancer Society, 2019. Available at: www.cancer.org.

particularly given that most therapies for Multiple Myeloma can also be categorized as 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.

Thank you for the opportunity to provide these comments on ICER's Draft Evidence Report for Multiple Myeloma. ASTCT welcomes the opportunity to discuss these recommendations in more detail or to answer any questions you may have. Please contact Alycia Maloney, ASTCT Director of Government Relations at amaloney@astct.org for any follow up issues.

Sincerely,

Stella M Davies
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Bone Marrow Transplant and Immune Deficiency
Cincinnati Children's Hospital Medical Center

March 11, 2021

RE: Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma – Draft Evidence Report

Dear Dr. Pearson,

Bristol Myers Squibb (BMS) appreciates the opportunity to respond to the Institute for Clinical and Economic Review (ICER) draft evidence report reviewing treatments for multiple myeloma posted on February 11, 2021.

BMS is focused on developing transformational medicines that improve upon the current standard of care, benefitting patients and society. BMS believes the value in healthcare should be measured by longer, healthier lives of patients, and is committed to a comprehensive, evidence-driven approach to value that incorporates patient priorities, real world data, total health system value, multi-stakeholder input and the most up-to-date clinical science. During the review of idecabtagene vicleucel (ide-cel), we respectfully believe ICER has opportunity to use more updated clinical data better account for up-to-date clinical data and, at the same time, clarify its use of the public data pertaining to patient survival extrapolated in the draft evidence report.

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.

At the same time, ICER's use of existing public data to formulate its draft evidence report recommendation contained concerning flaws from a patient survival perspective. Notably, this is especially true with ICERs estimations of survival for patients treated with ide-cel which is incongruous with the latest clinical trial data and clinical expert opinion. BMS appreciates the opportunity to constructively highlight ways in which the long-term survival estimates for ide-cel could be further evaluated to honour clinical validity and bring its findings in accordance with the longest follow-up data currently available.

BMS understands the methodological challenges associated with conducting evaluations in the early stages of a product's lifecycle (i.e., prior to regulatory approval) and recognizes the levels of uncertainty which need to be considered. There is a paucity of available evidence and data within a similar patient population and/or longer follow-up information should be utilized where possible. The relapsed / refractory multiple myeloma (RRMM) disease area is a dynamic and transformative disease area with rapidly evolving data.

Given these developments, at a minimum additional data should be considered for validation and checking of clinical plausibility. The evolving clinical data for ide-cel (i.e., KarMMa [Phase 2] and CRB-401 [Phase 1]) can help inform assumptions regarding the long-term extrapolation for overall survival (OS) and progression-free survival (PFS) for ide-cel.[1,2] In addition, there are important scenario analyses to include regarding ide-cel to help inform comparative effectiveness evaluations for stakeholders.

1. **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.[1,2] 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.[3]

2. **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-401[3] and 30% from the 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.[4]

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. 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.

Similar findings were seen in a survival extrapolation case study of nivolumab in the treatment of relapsed or refractory classical Hodgkin Lymphoma.[6] 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.[7]

3. **ICER should include a diverse group of disease area experts in developing methods, clinical 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.[4,7] 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.

The experts were asked for survival estimates at 3, 5, and 10 years for each study of interest. At each time point, experts were first asked to estimate upper and lower plausible limits and then the most likely survival value. During a follow-up consensus meeting, experts were presented with the (anonymized) individual estimates from each expert, and then were given the opportunity to discuss and provide rationales for divergent estimates.

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.

PFS values utilized in draft model are conservative in lieu of long-term follow-up from KarMMa and CRB-401

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.[1]

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.[4]

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 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.[11-14]

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.

4. **Given uncertainty around the final label, a scenario analysis focused on the 450x10^{6} 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 10^{6} CAR+ T cells). A scenario analysis focused on the 450x10^{6} 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 450x10^{6} 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 450×10^6 CAR+ T cells dose cohort.[1]

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.[15] 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.

5. BMS Recommendations

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 450×10^6 CAR+ T cells dose should be included to inform stakeholders about ide-cel's comparative effectiveness and value.

Sincerely,

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Appendix:

Baseline Characteristics of CRB-401 and KarMMa[*]

	CRB-401 Total[1] (N = 62)	KarMMa[2] (N=128)
Median age (range), yrs	61 (37-75)	61 (33-78)
Male, n (%)	39 (63)	76 (59)
Median time since diagnosis (range), yrs	5.5 (0.8-35.7)	6 (1-18)
ECOG PS 0/1, %[a]	26/71	45/53
High-risk cytogenetics, n (%)[b]	17 (27)	45 (35)
R-ISS III, n (%)	11 (18)	21 (16)
Bridging therapy, n (%)	32 (52)	112 (88)
High tumor burden, n (%)[c]	27 (44)	65 (51)
Extramedullary disease, n (%)	23 (37)	50 (39)
Median prior regimens (range)	6 (3-18)	6(3-16)
Prior ASCT, n (%)	57 (92)	120 (94)
Prior refractory, %		
Last prior therapy	75.8	100
IMiD and PI	80.6	89
IMiD, PI, and anti-CD38	69.4	84

*Inclusion criteria for: CRB-401 Dose Escalation phase: ≥ 3 prior lines of therapy including a PI and IMiD agent and Dose Expansion phase: ≥ 3 prior lines of therapy including a PI, IMiD agent, and daratumumab; Refractory to last line of therapy; explored activity in patients with low tumor B-cell maturation antigen (BCMA) expression;[1] KarMMa (Phase 2) must have received at least 3 prior MM regimens, a PI, IMiD agent, and an anti-CD38 antibody; Must be refractory to the last treatment regimen.[2]

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March 11, 2021

Steven D. Pearson, MD
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Boston, MA 02109

Re: 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 Draft Evidence Report and Voting Questions

Dear Dr. Pearson,

On behalf of the Cancer Support Community (CSC), an international nonprofit organization that provides support, education, and hope to people impacted by cancer, we appreciate the opportunity to respond to the request for comments regarding ICER's draft evidence report and voting questions regarding Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma.

I appreciated the opportunity to serve as an expert reviewer on the patient and caregiver perspectives section of the draft evidence report. Feedback included encouraging ICER to more robustly outline the process and methodology for reporting on the patient and caregiver perspectives, particularly in terms of the full breadth of qualitative findings which we believe are vital to ICER's work. We appreciate ICER's additions to this section and look forward to continuing to work with you to improve upon the process of analyzing and fully presenting patient insights.

However, as we have stated in previous letters, we believe this value assessment is premature, particularly as pricing is not yet available for the CAR T-cell therapies. We also strongly believe that ICER reports would be strengthened through additional real word data and ample patient feedback once the therapies are available outside of the clinical trial setting. Additionally, we strongly support ICER's use of real-world data and evidence in value assessments. As ICER noted in the draft 2020 framework document, "randomized controlled clinical trials have their own limitations and are often inadequate to address all questions relevant to assessments of comparative clinical effectiveness." We look forward to working with ICER as such information becomes available in order to revisit and update this report.

Patient Experience
As a leading patient advocacy organization, we are pleased to see innovative new options for patients living with multiple myeloma, particularly as the disease can cause significant quality of

life, logistical, psychosocial, and financial repercussions for many patients, survivors, and caregivers. As ICER states in this draft evidence report

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

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.

Health Equity
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.

Symptom Burden and Side Effects
Symptoms of multiple myeloma include frequent infections, calcium elevation, bone pain, fracture or damage, fatigue, impaired kidney function and kidney failure, low blood cell count, impaired immune function, anemia, weakness, difficult breathing, weight loss, loss of appetite, headaches, confusion, blurred vision, amyloidosis, and/or hypercalcemia (Mayo Clinic, 2019; International Myeloma Foundation, 2019; Cancer Support Community, 2019; Multiple Myeloma Research Foundation, n.d).

Side effects from current multiple myeloma treatments can include blood clots, peripheral neuropathy, gastrointestinal problems, myelosuppression, diarrhea, deep vein thrombosis, shingles, decreased blood counts, and other symptoms (International Myeloma Foundation, 2019; Multiple Myeloma Research Foundation, n.d). Additional complications include pain from bone destruction, height reduction and body shape changes (Kvam & Waage, 2015). These symptoms can lead to a substantially reduced health related quality of life (HRQoL) (Paul et al.,

2014). According to a recently released study conducted by researchers at CSC and leading expert in the disease:

> Patients with MM experience substantive concerns about the physical, emotional, and practical impact of the disease. Symptom burden significantly predicted poorer QoL outcomes, including depression, anxiety, and social satisfaction. Moreover, perceived lack of control over illness was associated with greater anxiety and depression among our national sample of patients with MM. As long-term survival for patients with MM improves, the need to address symptom burden, integrate palliative care, and enhance social and emotional support becomes ever more important (Zaleta et al, 2020).

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 and reiterate them here:

Physical Symptoms and Side Effects: 25% of respondents do not report their side effects to their doctor because they do not believe that anything can be done about their side effects of symptoms, however comfort levels with speaking to their doctor about side effects and symptoms were over 99% positive**.** When asked how often side effects of treatment affect their decisions about treatment for multiple myeloma, 5% said always, 9% said often, and 28% said sometimes**.** When asked how well respondents felt that their health care team prepared them to manage side effects, 33% said very much, 26% said quite a bit, and 22% said somewhat.
Kidney Disease*:* 12% of respondents had kidney disease because of their multiple myeloma
Peripheral Neuropathy*:* 24% of respondents experienced peripheral neuropathy in the past 7 days. 13% of respondents said peripheral neuropathy interfered with their lives very much; 8% said quite a bit; and 16% said somewhat. 7% of respondents said that peripheral neuropathy interfered very much with their ability to participate in social activities; 8% said quite a bit; and 14% said somewhat. **Pain and Bone Pain***:* 48% of respondents experienced bone pain in the past 7 days. 19% of respondents experienced pain always; 15% experienced pain often; and 25% experienced it sometimes. 13% of respondents said that it interfered with their lives very much; 10% said quite a bit; and 18% said somewhat. 8% of respondents said that pain interfered very much with their ability to participate in social activities; 11% said quite a bit; and 22% said somewhat. **Fatigue***:* 70% of respondents experienced fatigue in the past 7 days; 20% of respondents experienced fatigue always; 32% experienced it often; and 29% of respondents experienced it sometimes. 16% of respondents said that fatigued interfered with their lives very much; 21% said quite a bit; and 26% said somewhat. 8% of respondents said that fatigue interfered very much with their ability to participate in social activities; 19% said quite a bit; and 25% said somewhat. **Gastrointestinal Toxicity***:* 46% of respondents experienced gastrointestinal toxicity in the past 7 days. 9% of respondents experienced gastrointestinal toxicity always; 18% said often; and 20% said sometimes. 7% of respondents said that gastrointestinal toxicity interfered with their lives very much; 9% said quite a bit, and 15% said somewhat. 2% of respondents said that gastrointestinal toxicity interfered very much with their ability to participate in social activities; 7% said quite a bit; and 12% said somewhat.
Infection*:* 12% of respondents experienced infection in the past 7 days. Since being diagnosed with multiple myeloma, 31% of respondents were diagnosed with 1-2 infections, 6% were

diagnosed with 3-4 infections, and 4% were diagnosed with more than 4 infections. When asked if they were afraid of getting an infection because of their multiple myeloma diagnosis, 10% of respondents said very much, 20% said quite a bit, and 26% said somewhat. **Sleep Disturbance**:53% of respondents experienced sleep disturbance in the past 7 days. 10% of respondents experienced sleep disturbance always; 25% of respondents experienced it often; and 30% of respondents experienced it sometimes. 2% of respondents said that sleep disturbance interfered very much with their ability to participate in social activities; 8% said quite a bit; and 18% said somewhat. **Steroids**:11% of respondents experienced elevated pressure in the eyes (glaucoma) as a result of steroid use. 44% of respondents experienced flue retention, causing swelling in the lower legs as a result of steroid use. 46% of respondents experienced mood swings as a result steroid use. 66% of respondents experienced sleep disturbance as a result of steroid use. 51% of respondents experienced weight gain as a result of steroid use. 14% of respondents said that steroids and their side effects always negatively affect their ability to sleep; 25% said often; and 24% said sometimes. **General Psychosocial Impacts**: When asked how often respondents felt that it would sometimes be better if they were not around, 5% said always, 11% said often, and 17% said sometimes. When asked if they were reluctant to ask for help, 43% of respondents said yes. **Mood Swings**: 31% of respondents experienced mood swings in the past 7 days. 12% of respondents experienced mood swings very much; 24% of respondents experienced it often; and 1% of respondents said sometimes. When asked how often side effects of treatment affect their decisions about treatment for multiple myeloma, and 5% said always, 9% said often, and 28% said sometimes. **Concern about Relapse**: Regarding the impact of event scale regarding intrusive thoughts about relapse of multiple myeloma, 27% of respondents had such thoughts. **Financial Concerns**: When respondents were asked if they feel upset about money and the cost of care, 19% said always, 23% said often, and 21% said sometimes. When respondents were asked if they feel overwhelmed by the demands of paying for medical care, 8% said always, 19% said often, and 29% said sometimes. When respondents were asked if they are worried that they won't be able to leave any assets to their family when they are gone, 9% said always, 13% said often, and 22% said sometimes. 63% of respondents had received financial assistance related to their multiple myeloma. 55% of respondents said that a member of their health care team talked to them about resources related to getting financial help or financial counseling. When respondents were asked how helpful financial counseling would be for someone with multiple myeloma, 52% said very much, 29% said quite a bit, and 12% said somewhat. When asked if people in the community had donated money to them, 14% of respondents said yes. **Isolation**: When respondents were asked if they feel that they are alone, 9% said always, 22% said often, and 22% said sometimes. When respondents were asked if they feel that they have brought too much hardship on their family, 14% said always, 31% said often, and 24% said sometimes. **Relationships**: When asked how supportive their family is in respect to their cancer, 60% said very much, 25% said quite a bit, and 9% said somewhat. When asked how supportive their friends are in respect to their cancer, 37% said very much, 28% said quite a bit, and 23% said somewhat. When respondents were asked if they feel that they are not being the best spouse/partner they could be, 4% said always, 19% said often, and 19% said sometimes. When respondents were asked if they feel that they are not being the best parent they could be, 8% said always, 20% said often, and 17% said sometimes. When respondents were asked if they feel that they are not being the best friend they could be, 9% said always, 23% said often, and 25% said sometimes. When respondents were asked if their friends do not understand, 10% said always, 22% said often, and 23% said sometimes. When respondents were asked if their family

do not understand, 7% said always, 22% said often, and 23% said sometimes. When respondents were asked if they are worried that they will be a burden on their family as their disease progresses, 21% said always, 30% said often, and 19% said sometimes. When respondents were asked if they have had limited contact with friends because of their multiple myeloma, 41% said yes. When respondents were asked if they have had limited contact with family members because of their multiple myeloma, 31% said yes. When asked if they feel like they don't have enough close friends or family members, 25% of respondents said yes. When asked if they have fewer people they can rely on before cancer, 27% said yes. **Work**: When respondents were asked if they were upset because they fall behind at work and others have to fill in, 4% said always, 9% said often, and 15% said sometimes. When respondents were asked if they have forgone a job opportunity or career advancement because of multiple myeloma, 40% said yes. **Treatment Decision Making:** When respondents were asked if they feel they had a choice about where to receive medical treatment for multiple myeloma, 82% said yes. When respondents were asked how much of an impact the distance from home had on deciding where to seek medical treatment, 20% said very much, 17% said quite a bit, and 16% said somewhat. When respondents were asked how much of an impact had insurance coverage or cost had on deciding where to seek medical treatment, 33% said very much, 17% said quite a bit, and 12% said somewhat. When respondents were asked how much of an impact the sense of trust or familiarity with the doctor or the practice had on deciding where to seek medical treatment, 39% said very much, 22% said quite a bit, and 12% said somewhat. When respondents were asked how much of an impact the experience of specialization of the physician had on deciding where to seek medical treatment, 55% said very much, 24% said quite a bit, and 5% said somewhat. When respondents were asked how much of an impact access to clinical trials had on deciding where to seek medical treatment, 17% said very much, 8% said quite a bit, and 16% said somewhat.

Recent research from CSC also shows that, among patients with multiple myeloma, poorer physical function and greater symptom burden are associated with worse depression, anxiety, and social satisfaction (Zaleta et al., 2020), underscoring the critical connection between patients' experience of burden and their quality of life.

We appreciate the opportunity to provide these comments and would be pleased to continue to serve as a resource to your work. I can be reached at efranklin@cancersupportcommunity.org.

Sincerely,

Elizabeth F. Franklin, PhD, MSW
President
Cancer Support Community Headquarters

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March 11, 2021

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Re: ICER's Assessment of Treatments for Multiple Myeloma: Draft Evidence Report

Dear Dr. Pearson,

GlaxoSmithKline (GSK) appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on the assessment for treatments in heavily pre-treated relapsed and refractory multiple myeloma (MM). GSK would also like to acknowledge ICER's responsiveness in this process to date. However, GSK has concerns over ICER's evaluation of belantamab mafodotin in this Draft Evidence Report, and we summarize our specific suggestions for improvement as follows:

- **We ask ICER to change the evidence rating for belantamab mafodotin to C++, based on a more complete and accurate representation of the significant clinical benefits and manageable risks.**
- **Specifically, we ask ICER to recognize the clinical evidence around overall survival and duration of response for belantamab mafodotin, provide a more complete and accurate picture on HRQoL, and more accurately characterize the nature of ocular adverse events.**
- **In addition, we identified certain other inconsistencies and inaccuracies and provide suggestions to address these: consistently describe the patient population for belantamab mafodotin throughout the report, revise the estimate of adverse event costs based on likely resource utilization, and include patient and caregiver perspectives for belantamab mafodotin.**

GSK comments, with supporting rationale, references and additional context, are organized into five areas, A-E, as detailed below.

A. 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.[1,2] 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.

- o On page 19, the draft report interprets the belantamab mafodotin 13-month DREAMM-2 ORR and OS as providing a "possible small net benefit."[3] 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).[4] 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 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."
- o 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).[3] 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.[6]
    - ▪ The appropriate expectation vs baseline in such a heavily pre-treated population should be one of maintenance of HRQoL[7], and treatment with belantamab mafodotin meets or exceeds this expectation with stable HRQoL and improvement in some domains.[6]
    - ▪ 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."
- o The severity, impact, and resolution of vision-related adverse events should be further clarified to avoid misinterpretation of these events. We request that the below points are noted by ICER, to give readers a more complete understanding of these events.
    - ▪ In Table 3.6 a figure of "severe decline in vision in BCVA scale as 30%" is stated.[3] 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).[3] We suggest ICER replace the 30% with this 17.9% figure as it is more relevant, especially to patients.

- 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.[8]

- 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.

- 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.

B. 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:

- p. ES1 "Belantamab mafodotin was studied in heavily pre-treated (6-7 previous lines of therapy) quad- and penta-refractory patients"
- p. ES2 "Belantamab mafodotin appears to be equivalent or slightly superior to currently available treatments for quad- and penta-refractory MM patients"
- p. ES4 "Belantamab appears to be equivalent or slightly superior to current treatments for quad- and penta-refractory MM patients"
- Table ES1 "Belantamab Population (Quad- and Penta-Refractory)"
- 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"

We believe that it is important to keep a consistent and accurate description of the indicated population for belantamab mafodotin so that users of the ICER report will not be confused about the appropriate patient population for treatment with belantamab mafodotin. We would kindly ask ICER to review the report and update the description of the population wherever applicable, including but not limiting to the above examples.

C. ICER's references for the resource use requirements of ocular adverse events of belantamab mafodotin appear to be inaccurate, and this is likely to result in an overestimate of adverse event costs.

- 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."[3] 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."[1] The current recommended dosing in the USPI is q3 weeks.
- 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.[11] 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.[3] 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.
- 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.

D. 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).[2]

E. 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.

In summary, we would like to request that ICER fairly reflect the clinical evidence of potential significant and substantial benefit in belantamab mafodotin's indicated population and characterize the target population consistently and accurately in the document. At the same time, ICER should accurately report the impact of ocular adverse events, where evidence shows that severe impact on vision is relatively uncommon and short-lived.

Please feel free to contact us should you wish to discuss these recommendations in further detail.

Sincerely,

Matthew D. Rousculp, Ph.D., M.P.H.

Head, U.S. Value, Evidence and Outcomes

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March 11, 2021

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RE: Draft Evidence Report "Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma"

Dear Dr. Pearson:

Patients Rising Now advocates for patients with serious and chronic conditions to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, clinicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's February 11th Draft Evidence Report, "Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma." Our comments about the draft report are organized below into sections about People-Centered Perspectives; Data, Modeling, Projections, Assumptions and Uncertainties; and Additional Points.

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.[i]

As ICER is aware, and discusses in some ways in the draft report, multiple myeloma is a very complicated type of cancer that often recurs, resulting in people (and their families) having to experience many different types of treatments. This relapsing type of cancer means that people with multiple myeloma experience a very tumultuous disease course over many years that includes not only the problems from the underlying cancer, but the side effects and logistical complications of the different treatment regimens. 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.[ii] The NCCN recognizes the

variety of treatments that someone with multiple myeloma may receive – ranging from 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."[iii]

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."[iv] 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 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,[v] but in the ongoing studies (summarized in the draft report),[vi] 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.

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."[vii]

Lastly, we too are very concerned about financial toxicity of health care for individuals but wonder why ICER didn't expand upon – or explore further – the statement by a patient who stated that their drugs "were about $250,000 a year."[viii] As ICER surely knows, for almost all non-Medicare insurance there is an annual out-of-pocket limit on patient costs, and many people with Medicare also have an annual limit through a Medicare Advantage plan or a Medigap policy. The patient's statement would have been an ideal opportunity for ICER to explore (or explain) the financial protection gaps in the U.S. health care system.

Data, Modeling, Projections, Assumptions, and Uncertainties
We have noted data and related problems in other ICER work products, but the current draft report has many more errors and obfuscations than have appeared in other reports. For example:

- 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.[ix] 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.[x] 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.

- In the draft report's listing of Categories of Contextual Considerations[xi] 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.

- 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.[xii] 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."[xiii] This is another example where ICER states parameters for its modeling, and then ignores or 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."[xiv]

- 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.[xv] 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.

- 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."[xvi] 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 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.
- The draft report notes that ICER was not able to conduct an intention-to-treat analysis for the CAR T-cell therapies,[xvii] 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 <u>received</u> 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.
- In selecting previous studies to model usual care etc., we note that ICER selected one from its own authors,[xviii] while a simple web search turned up several others, including more recent studies.[xix] 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.
- 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 should be used when interpreting cost-effectiveness estimates."[xx]
  - "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."[xxi]

  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.
- 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.

<u>Additional Points</u>
- 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."[xxii] 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."

<u>Conclusions</u>
Patients Rising Now is pleased that people with multiple myeloma have one new treatment option, and likely will soon have two more in the form of CAR T therapies, particularly since the CAR T therapies appear to improve quality of life metrics and hold the potential for long term benefits. We are glad that ICER's draft report reached a similar conclusion. However, we are concerned by the sloppy nature of the draft report's handling of the underlying limited data, and the other problems noted above. We hope that the true value of new treatments for multiple myeloma will be evaluated by others and that ICER's inappropriate and incomplete approach will not be a deterrent for the use of new treatments by patients and clinicians, or result in payers erecting barriers to use, coverage, or payment, since such access restrictions will harm patients and consume clinicians' limited resources. This is especially concerning now, since many clinicians are already struggling personally and professionally with the burdens of COVID-19, including providing care for people with multiple myeloma as their disease progresses and new treatments are required. 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.

Sincerely,

Terry M. Wilcox

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] "How to run focus groups," Citizens Advice is an operating name of The National Association of Citizens Advice Bureaux, 2015 notes that focus groups typically have around eight participants. And "Participantsin a Focus Group," Chapter 4 in "Focus Groups: A Practical Guide for Applied Research" states that "The ideal size of a focus group for most noncommercial topics is five to eight participants." https://us.sagepub.com/en-us/nam/focus-groups/book243860

[ii] https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf and https://www.nccn.org/patients/guidelines/content/PDF/myeloma-patient.pdf

[iii] Draft report, p. 2

[iv] Draft report, p. ES7

[v] Draft report, p. 8, Table 3.1

[vi] Draft report, Comparative Effectiveness: Supplemental Information, Section D4. "Ongoing Studies," pp 102-114

[vii] Draft report, p. 17

[viii] Draft report, p. 3

[ix] Madduri D, Berdeja J, Usmani S, et al. 177 CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma. Paper Presented presented [sic] at American Society of Hematology; December, 2020 (Ref. #19 in draft report.)

[x] Draft report, References #5, and #7.

[xi] Draft report, Table 5.1, p. 32

[xii] "The median number of prior lines of therapy was 3 (range, 1 to 9), including prior proteasome inhibitor therapy (68%), immunomodulatory agents (86%), and both proteasome inhibitors and immunomodulatory agents (60%)." Zhao et al., "A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma," Journal of Hematology & Oncology (2018) 11:141. Data included in the draft report, Table 31. Row containing data about "LEGEND-2 trial (Xi'an site), which was a Phase I, open single-arm study."

[xiii] Draft report, p. 21

[xiv] Draft report, p. 17

[xv] "Evolving the Delivery of CAR T-Cell Therapies to the Outpatient Setting," Smith, S., and Essell, J, J Clin Pathways. 2018;4(8):42-47

[xvi] Draft report, p. ES10

[xvii] Draft report, p. ES9

[xviii] Draft report, Reference #42: Carlson JJ, Guzauskas GF, Chapman RH, et al. Cost-effectiveness of Drugs to Treat Relapsed/Refractory Multiple Myeloma in the United States. J Manag Care Spec Pharm. 2018;24(1):29-38.

[xix] For example: "Development of an Initial Conceptual Model of Multiple Myeloma to Support Clinical and Health Economics Decision Making," MDM Policy & Practice, 1–22, 2019; " Value and Cost of Myeloma Therapy—We Can Afford It," 2018 ASCO Educational Book; and " A systematic review of economic evaluations of treatment regimens in multiple myeloma," Expert Review of Pharmacoeconomics & Outcomes Research, June 2020.

[xx] Draft report, p. 30

[xxi] Draft report, p. 31

[xxii] Draft report, p. 2

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Dr S D Pearson
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BOSTON MA 02109

11 March 2021

Submitted via Email

Email: publiccomments@icer.org

My dear Dr Pearson

PUBLIC COMMENT: DRAFT EVIDENCE REPORT

ANTI-B-Cell MATURATION ANTIGEN CAR T-Cell AND ANTIBODY DRUG CONJUGATE THERAPY FOR HEAVILY PRE-TREATED RELAPSED AND REFRACTORY MULTIPLE MYELOMA

Thank you for this valuable opportunity to comment on the draft evidence report for Anti-b-cell Maturation Antigen car t-cell and Antibody Drug Conjugate Therapy for Heavily Pre-treated Relapsed and Refractory Multiple Myeloma

I have corresponded with you on a number of occasions regarding the inappropriate use of multiattribute utilities in your lifetime simulation models. To date you have not provided a satisfactory response to the fact that these utility scores are simply ordinal. This means that they cannot be used to create quality adjusted life years. At the same time these utility scores, based on algorithms that attempt to combine different symptoms or attributes, lack dimensional homogeneity, are not unidimensional and fail to meet standards for construct validity. I note that your QALY claims in this case rest on the EQ-5D-5L (an unpublished poster).

1

If you are still convinced that multiattribute utilities are ratio measures in disguise (and you need a ratio measure for QALY creation), may I refer you to a recent letter in *Value in Health*:

Langley PC, McKenna SP. Fundamental Measurement and Quality Adjusted Life Years. *Value Health*. 2021:24(3)(:451

If you feel that you can justify the claim that EQ-5D-5L or other multiattribute measure is a ratio scale in disguise (even though it can generate negative utilities) I encourage you (or the model group at the University of Colorado) to respond to the letter so that a wider audience is informed.

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).

There is a further issue. With the release of the ICER Analytics platform we are now, presumably, in a position to create as many assumption driven simulation models as we wish. Potentially, formulary committees could be inundated with any number of models created to defend a manufacturer's claim for a "QALY determined social threshold price". Apart from the fact that QALY thresholds are mathematically impossible constructs, this may put formulary committees, in the absence of a referee to adjudicate competing model claims, in an odd position. They will have to decide between different simulated claims when they often lack the forensic skills to disentangle the various imaginary simulations. These two recent publications may be of interest:

Langley P. Medicaid Formulary Decisions and the Institute for Clinical and Economic Review: Abandoning Pseudoscience in Imaginary Pharmaceutical Pricing Claims. *InovPharm*. 2021;12(1):No. 11
https://pubs.lib.umn.edu/index.php/innovations/article/view/3702/2676

Langley P. Let a Thousand Models Bloom: ICER Analytics Opens the Floodgates to Cloud Pseudoscience. *InovPharm*.2021;2(1): No. 5
https://pubs.lib.umn.edu/index.php/innovations/article/view/3606/2668

Keep well

Yours sincerely

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March 11, 2021

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) draft evidence report for treatments for multiple myeloma. Multiple myeloma is a rare cancer that currently has few treatments available. It is important that ICER consider this context as they evaluate treatments for multiple myeloma. Please consider our below comments on ICER's model in the draft evidence report.

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.[1,2] With this in mind, to deliver a more accurate assessment, ICER should seriously consider delaying this assessment until more conclusive evidence is available.

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.[3] For this reason, the choices for utility values used to represent quality of life in the model are 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

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[1] Schnipper LE, Schilsky RL. Are value frameworks missing the mark when considering long-term benefits from immuno-oncology drugs?. JAMA oncology. 2018 Mar 1;4(3):333-4

[2] Ben-Aharon O, Magnezi R, Leshno M, Goldstein DA. Association of immunotherapy with durable survival as defined by value frameworks for cancer care. JAMA oncology. 2018 Mar 1;4(3):326-32

[3] Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. Blood reviews. 2019 Mar 1;34:45-55.

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,[4] 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.[5] 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.

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.[6]

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 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.'[7] We urge ICER to follow this blueprint.

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

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[4] Delforge M, Minuk L, Eisenmann JC, Arnulf B, Canepa L, Fragasso A, Leyvraz S, Langer C, Ezaydi Y, Vogl DT, Giraldo-Castellano P. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. haematologica. 2015 Jun;100(6):826.

[5] Proskorovsky I, Lewis P, Williams CD, Jordan K, Kyriakou C, Ishak J, Davies FE. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. Health and quality of life outcomes. 2014 Dec;12(1):1-9.

[6] Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. A comparative study of European rare disease and orphan drug markets. Health Policy. 2010 Oct 1;97(2-3):173-9.

[7] Carlsson P, Hoffmann M, Levin LÅ, Sandman L, Wiss J. Prioritering och finansiering av läkemedel för behandling av patienter med sällsynta sjukdomar: Reviderad version. 2015

African-Americans. The number of cases in African-American males is expected to double over the next twenty years.[8] 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.[9] It is important that ICER undertake subgroups analyses in order to evaluate treatments' impacts for the population with significant burden.

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.[10] 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-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.[11] 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.

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.[12] We suggest ICER also look to methods that can more accurately capture the full benefit of these novel treatments.

Conclusion

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[8] Rosenberg PS, Barker KA, Anderson WF. Future distribution of multiple myeloma in the United States by sex, age, and race/ethnicity. Blood, The Journal of the American Society of Hematology. 2015 Jan 8;125(2):410-2

[9] Ailawadhi S, Jacobus S, Sexton R, Stewart AK, Dispenzieri A, Hussein MA, Zonder JA, Crowley J, Hoering A, Barlogie B, Orlowski RZ. Disease and outcome disparities in multiple myeloma: exploring the role of race/ethnicity in the Cooperative Group clinical trials. Blood cancer journal. 2018 Jul 6;8(7):1-8

[10] National Council on Disability. Quality-adjusted life years and the devaluation of life with disability. (2019).

[11] Schwappach, D. L. B. Resource allocation, social values and the QALY: a review of the debate and empirical evidence. Heal. Expect. 5, 210–222 (2002).

[12] Castro, H. et al. Advancing MCDA and HTA into coverage decision-making. in Multi-Criteria Decision Analysis to Support Healthcare Decisions 119–146 (2017). doi:10.1007/978-3-319-47540-0_8

We urge ICER to reconsider moving forward with this premature assessment. If ICER does continue its assessment, it is critical it take into consideration the need of the multiple myeloma patient population for new treatments, and the disproportionate impact this disease has on underserved populations.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

March 9, 2021

Dear ICER Review Team:

Sanofi appreciates the opportunity to comment on the ICER Draft Evidence Report.

Our comments relate to the inclusion of two of the network meta-analyses (NMA) in Section D5 of the ICER Draft Evidence Report, Mushtaq (2019) and Arcuri & Americo (2021).[1,2] These NMAs focus on broader and relatively less refractory patient populations (a median of 1-3 previous therapies) and are therefore out of scope of the ICER Report. Additionally, the study by Arcuri & Americo[1] presents serious methodological concerns that result in misleading conclusions. Specifically:

- It includes trials evaluating different populations and differing backbone therapies without any adjustment of treatment effect modifiers
- Different backbone regimens are considered a single "control" group
- Severe Adverse Events (AE) are used to quantify toxicity in most trials, although Grade III/IV events are used for others
- The assumption of transitivity (or similarity) which underpins the NMA methodology is violated

In light of these concerns, Sanofi recommends that these references be excluded from the final Draft Evidence Report.

Scope of the ICER Draft Report

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 populations than the scope of the ICER assessment and should not be included.

NMA Methodology in Arcuri & Americo (2021)

The meta-analysis by Arcuri & Americo[1] 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.

It is well documented that patient characteristics (ie age, performance statues, cytogenetic risk and comorbidities), number of prior treatment lines and type of therapies received, number of prior relapses, refractoriness to treatment options and time between relapses may act as prognostic factors and treatment effect modifiers.

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"[3]. 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.

The studies included in the NMA[1] 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.

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.

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.

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.

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.

We appreciate the opportunity to be involved in this review and look forward to a continued dialogue with ICER.

Kyle Hvidsten

Vice President

Global Health Economics & Value Assessment

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Appendix
Table 1: Overview of the studies included in the NMA by Arcuri & Americo, 2021

Study	Intervention (n)	Control (n)	Patient population	Median number of prior treatment lines	Bortezomib exposed	Bortezomib refractory	Lenalidomide exposed	Lenalidomide refractory	Refractory to lenalidomide and bortezomib	Adverse events source in NMA
VANTAGE 088[5]	VorV (n=317)	V (n=320)	1-3 prior regimens	2 prior regimens	+	-	+	-	-	SAE
POLLUX[6]	DRd (n=286)	Rd (n=283)	1+	1 (1-11)	+++*	+*	++†	+‡	-	SAE
ENDEAVOR[7]	Kd (n=464)	Vd (n=465)	1+	2 (1-2)	++	-	++	-	-	SAE
TOURMALINE-MM1[8]	NRd (n=360)	Rd (n=362)	1-3	1 prior: 62%	+++	+	+	-	-	SAE
TOURMALINE MM1-China[9]	NRd (n=57)	Rd (n=58)	1-3	1 prior: 44%	++	+	+	-	-	SAE
NCT00813150[10]	CyVd (n=46)	Vd (n=47)	1+	1 prior: 57%	NR	NR	NR	NR	NR	SAE
ELOQUENT-2[11]	ERd (n=321)	Rd (n=325)	1-3	2 (1-4)	+++	+	+	-	-	SAE
KEYNOTE-183[12]	PembroPd (n=125)	Pd (n=124)	2+ including IMiD and PIs	3 (1-3)	+++	NR	+++	+++	++§	SAE
DOXIL-MMY-3001[13]	PEG-Dox (n=324)	V (n=322)	1+	66% received 2+ therapies	-	-	-	-	-	SAE

Study	Intervention (n)	Control (n)	Patient population	Median number of prior treatment lines	Bortezomib exposed	Bortezomib refractory	Lenalidomide exposed	Lenalidomide refractory	Refractory to lenalidomide and bortezomib	Adverse events source in NMA
CASTOR[14]	DVd (n=251)	Vd (n=247)	1+	2 (1-9)	++*	-	++†	+	-	Grade III/IV
OPTIMISMM[15]	PVd (n=281)	Vd (n=278)	1-3 and R-refractory	NR (1-3)	+ ++	+	+ ++	+ ++	NR	SAE
PANORAMA-1[16]	PanVd (n=387)	Vd (n=381)	1-3 treatments	1 (1-3)	++	+	+	NR	NR	SAE
ASPIRE[17]	KRd (n=396)	Rd (n=396)	1-3	2 (1-3)	+ +	-	+	-	-	SAE
BELLINI[18]	VenVd (n=194)	Vd (n=97)	1-3	NR¶	++*	NR	++	+	NR	SAE
GMMG ReLApsE[19]	ASCT-Rd (n=139)	Rd (n=138)	1-3	1 prior: 94%	+++	-	+	-	-	SAE
BOSTON[4]	SVd (n=195)	Vd (n=207)	1-3 prior regimens	2 (1-2)	+++	-	++	-	-	SAE but stated as NR
CANDOR[20]	DKd (n=312)	Kd (n=154)	1-3 prior therapies	2 (1-2)	+++	+	+ +	+	NR	SAE
ICARIA-MM[21]	IsaPd (n=154)	Pd (n=153)	2+ and have not responded to R or a PI	3 (2-4)	+++	+ + +	+++	+ + +	+ + +	Grade III/IV

+ 1-33%; ++ 34-66%; +++ 67-100%
- 0%

Study	Intervention (n)	Control (n)	Patient population	Median number of prior treatment lines	Bortezomib exposed	Bortezomib refractory	Lenalidomide exposed	Lenalidomide refractory	Refractory to lenalidomide and bortezomib	Adverse events source in NMA

[*]Based on prior exposure to a proteasome inhibitor[†] Based on prior exposure to an immunomodulatory drug [‡] Trial excluded lenalidomide refractory patients however some patients appear to have been enrolled [§]Patients were considered refractory if two (double: lenalidomide and bortezomib), three (triple: lenalidomide, bortezomib and pomalidomide or lenalidomide, bortezomib and carfilzomib) or four (quadruple: lenalidomide, bortezomib, pomalidomide and carfilzomib) previous lines of treatment were ineffective, defined as documented disease progression during or within 60 days of completing their last anti-myeloma therapy

[¶]In the VenV arm, 47% of patients received 1 prior line of therapy and 53% received 2-3 prior lines of therapy

Abbreviations: ASCT, autologous stem cell transplant; Cy, cyclophosphamide; D, daratumumab; d, dexamethasone; Dox, doxorubicin; E, elotuzumab; Isa, isatuximab; IMiD, immunomodulatory drug; K, carfilzomib; N, ixazomib; NMA, network meta-analyses, NR, not reported; P, pomalidomide; Pan, panobinostate; Pembro, pembrolizumab; PEG-Dox, pegylated liposomal doxorubicin; PI, proteasome inhibitor; R, lenalidomide; S, selinexor; SAE, serious adverse event; V, bortezomib; Ven, venetoclax; Vor, vorinostat

Attal el al. (2019)[21]; Dimopoulos et al. (2013)[5]; Dimopoulos et al. (2016)[6]; Dimopoulos et al. (2016)[7]; Dimopoulos et al. (2020)[20]; Hou et al. (2017)[9]; Goldschmidt et al. (2020)[19]; Grosicki et al. (2020)[4]; Kropff et al. (2017)[10]; Kumar et al. (2020)[18]; Lonial et al. (2015)[11]; Mateos et al (2019)[12]; Moreau et al. (2016)[8]; Orlowski et al. (2016)[13]; Palumbo et al (2016)[14]; Richardson et al. (2019)[15]; San-Miguel et al. (2014)[16]; Stewart et al. (2014)[17]

March 11, 2021

Steven D. Pearson, MD
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: **Institute for Clinical and Economic Review — Multiple Myeloma Review Draft
       Evidence Report**

Dear Dr. Pearson:

The undersigned organizations, who participate in a CAR T-cell therapy working group,
appreciate the opportunity to respond to the draft evidence report on Anti B-Cell Maturation
Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed
and Refractory Multiple Myeloma.

CAR T-cell therapy (CAR T) is a transformative therapy that can substantially improve
outcomes for patients with specific types of cancer.[1] While there are currently four approved
CAR T therapies, there are over 630 active clinical trials, including those for Multiple Myeloma,
two of which are being reviewed in this report.[2,3]

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.[4,5]

Below, we highlight several areas that we recommend ICER further consider.

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.[6] CAR T for Multiple Myeloma have demonstrated
an overall survival of over 19 months.[7] Research has also shown that the "cyclical nature" of
Multiple Myeloma can result in higher levels of anxiety, depression and fatigue.[8] 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.

Studies show that many Multiple Myeloma patients experience significant quality of life
impacts, including physical symptoms of the disease and side effects of treatment.[9] The ongoing
psychosocial impacts on patients, caregivers, and family members are also great.[10,11] 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.[12]

Health Disparities
Multiple Myeloma is twice as common in Black people.[13] 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.

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 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.[14] These challenges can be significantly disruptive to the daily life of patients and caregivers.[15]

In conclusion, thank you for the opportunity to provide comments on this draft evidence report document. We believe that innovative treatments like CAR T represent hope for patients and caregivers. If you have any questions regarding our comments, please do not hesitate to reach out to our organizations.

Sincerely,

American Society for Gene and Cell Therapy

BMT InfoNet

Cancer Support Community

CLL Society

Myeloma Crowd

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