October 13, 2020

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

Re: Comments to Draft Scoping Document on Anti B-Cell Maturation Antigen CAR T-cell and Antibody Conjugate Therapy for Triple Class Refractory Multiple Myeloma
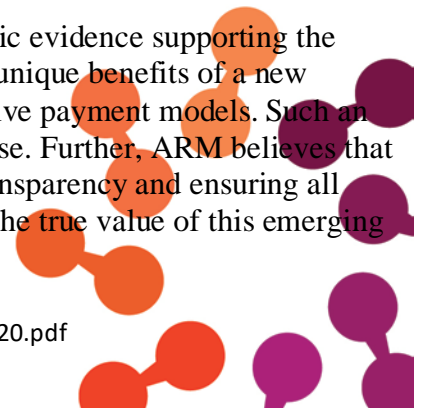
## Introduction

The Alliance for Regenerative Medicine (ARM) is pleased to provide our comments in response to the Institute for Clinical and Economic Review (ICER) September 22, 2020 draft Background and Scope Document on Anti B-Cell Maturation Antigen CAR T-cell and Antibody Conjugate Therapy for Triple Class Refractory Multiple Myeloma ("Scoping Document")[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 voice of the sector, representing the interests of 360+ members worldwide, including small and large companies, academic research institutions, major medical centers and patient groups. Although focused on one type of cancer, the Scoping Document raises critical 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 will not take into account FDA's perspective on the appropriate patient population (i.e., through the label) and that of expert providers' perspectives (i.e., through recognized compendia) and will therefore unjustifiably raise questions and doubt in the technology that could ultimately harm market access.

With the emergence of these therapies, our society is entering an unprecedented era of potentially curative treatments for patients. ICER has previously acknowledged, "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." More recently, ICER has stated, "Cell and gene therapies are starting to provide truly transformative advances for patients and their families, particularly those with conditions for which there has not been any effective treatment before." In light of these comments, ARM questions why ICER is choosing to conduct this review on therapies that have not yet even been approved by FDA. ARM believes that this assessment is premature and inappropriate, especially to include antibody drug conjugate therapy in the review because it is simply not comparable.

## Stakeholder Input

ARM believes that independent scientific evaluations of clinical and economic evidence supporting the utilization of FDA therapies is critical. However, such analyses should focus on the unique benefits of a new technology before considering issues of short-term costs and/or the need for innovative payment models. Such an approach optimizes patient access to the most appropriate therapy to treat their disease. Further, ARM believes that this initial input did not include a broad enough range of stakeholders. Increasing transparency and ensuring all stakeholders have input will allow everyone to gain a much better understanding of the true value of this emerging

[1] https://icer-review.org/wp-content/uploads/2020/08/ICER_Multiple-Myeloma_Draft-Scope_092220.pdf

technology.[2] 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[3]. These organizations have published extensively on key methodological issues in evaluating new therapies. ARM hopes that ICER will continue to seek participation from these experts when evaluating new issues.

## Report Aim

ICER states that this project will evaluate the health and economic outcomes of the therapies and will include both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and risk are considered. ARM appreciates this intention but has concerns about such comparisons being made across therapies that treat different patient populations. 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. There exists an "inherent selection bias" when physicians decide to treat with cell or non-cell therapies, which is not fully captured in patient characteristics and eligibility criteria of clinical trials and would extend to real world setting too. Further, in the case of cell therapies, patients generally have already progressed on non-cell therapies (and likely, many times) and have run out of options, which the cell therapy now provides. It would be irrelevant to use the non-cell therapy population as a comparator in that situation. This important difference should be considered in light of ICER's intentions with this review, as any comparison across these therapies would not prove useful because clinical practice patterns consider different patient types. Furthermore, the economic model as detailed in the Scoping Document does not reflect standard clinical decision-making to the disease state of interest. Should ICER proceed with this assessment ARM is concerned that it would set precedence for ICER to draw inappropriate comparisons across therapies and yield an assessment that has no relevance to clinical practice. With a flawed approach applied to therapies that treat different patient populations, the report will not be well positioned to achieve ICER's stated aim.

## Scope and Methodology of the Comparative Value Analyses

All clinical interventions should be first appraised based on their clinical merit for patients and benefits to families and caregivers, with deference to FDA's expertise and judgement. Discussions around society's willingness and ability to pay should take place subsequently and should be considered/determined by those who are directly impacted by a potential treatment choice based on the individual clinical circumstances at issue, not made in the abstract by third-party observers such as ICER. Collectively, we should make every effort to ensure patients have access to innovative new therapies in a timely manner, especially in the case of severe or life-threatening conditions, and that incentives for innovation remain in place, so that the pace of innovation is not hindered by undue challenges in market access and commercialization for this new class of transformative therapies.

In prior public statements, ARM has been clear that 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[4].

[2] https://icer-review.org/wp-content/uploads/2020/08/ICER_MM_Key_Stakeholders_092720.pdf
[3] Peter J. Neumann et al, *Cost-Effectiveness in Health and Medicine* (Oxford Scholarship Online, November 2016).
[4] See March 29, 2017 ARM letter to ICER regarding the proposed update to the ICER Value Assessment Framework.

ARM believes that ICER has a responsibility to conduct balanced evidence assessment as well as updates in economic evaluation methods that reflect the unique and broad benefits of these therapies. Reserving the public dissemination of proposed value-based payment benchmarks until a more comprehensive data set (including real world evidence) is adequate to support the validity of the underlying assessments, as well as rigorously updating assessments as evidence that reflects clinical outcomes, patient and caregiver benefits and societal impacts becomes available should be more formally reflected in ICER methods and processes.

Prematurely determining the 'fairness' of the price of highly innovative therapies for which evidence on the duration and full spectrum of benefits is not yet known does not serve patients, their families, caregivers or society, especially if it results in undue barriers to patients receiving potentially life changing treatments. ARM believes it is important to separate methodological issues from affordability and policy considerations. ICER could also play an important role in supporting industry and payer efforts to design new payment models and systems that accommodate uncertainty in long-term outcomes for newly approved innovative therapies while also rewarding unprecedented long-term performance and innovation.

ARM believes that the uniform application of cost/effectiveness thresholds in value assessments across all product and disease types is not appropriate. ICER's current approach relies largely on QALY-based cost-effectiveness models. ARM believes that the continued use of the QALY measure in ICER sensitivity analysis informing ICER's analysis is likely inappropriate given the unique nature of these therapies. ARM does not believe that the QALY is an appropriate measure of value. We furthermore believe that the evidence value of life-years gained (evLYG) approach is also a flawed way to compare different treatments within the same disease area. The evLYG does not account for differences in quality of life that may differ between treatments due to their administration routes, mechanisms of action, or other factors. This is particularly inappropriate when comparing chronically administered therapies compared to single-administration therapies. The side effects of chronic use may continuously impact patients' quality of life beyond disease-related factors. In contrast, single-administration treatments may only transiently impact quality of life while providing similar or better benefits on survival and other disease metrics over the long-term.

Rather, ARM suggests that ICER should use multi-criterion decision analysis (MCDA) to address this limitation.[5] 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. 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.

Sincerely,

Robert J. Falb,
Director, U.S. Policy and Advocacy

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**SUMMARY OVERVIEW**

Amgen appreciates the opportunity to comment on ICER's *Draft Background and Scoping Document for Anti-B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Triple Class Refractory Multiple Myeloma.* Multiple myeloma (MM) is a malignancy of the plasma cells characterized by infiltration of the bone marrow, bone destruction, and overproduction of monoclonal paraprotein. It accounts for 10% of hematologic malignancies.[1,2] Malignant plasma cells can form tumors and various other soft tissue related problems, and paraproteins can cause hyperviscosity and kidney injury, termed myeloma kidney.[3] The emergence of effective and less toxic therapies has revolutionized the prognosis and management of MM, expanding the treatment landscape to over 40 therapies since the 1960s.[4,5,6,7] Despite these effective therapies, patients often become refractory to these treatments with very few therapeutic options for heavily pretreated patients.[8] Treatment choice is informed by guidelines that aim to support an extraordinarily complex disease manifestation and significant heterogeneity in patient presentation, prognosis and tumor biology. CAR-T cell and antibody drug conjugate therapies targeting the B-cell maturation antigen (BCMA) represent new therapeutic options for triple class refractory MM patients and we would like to highlight a few important considerations for ICER:

1. **Comparator: Selection of comparators (late line therapies and palliative care) should be aligned with current National Comprehensive Cancer Network® (NCCN) guidelines and where applicable, U.S. Food and Drug Administration (FDA) approved indications.**

2. **Outcomes: Utilize an Intention To Treat (ITT) versus an "as treated" analysis by including all patients that underwent apheresis as the denominator for assessing the clinical and economic evidence for CAR-T therapies.**

3. **Adverse events: Amgen agrees with ICER that ocular toxicity is a critical outcome for belantamab mafodotin-blmf, and further suggest that ICER also consider the inclusion of costs associated with monitoring and treating patients for ocular toxicity.[9]**

A more comprehensive discussion of our recommendations is below.

**KEY RECOMMENDATIONS**

1. **Comparator: Selection of comparators (late line therapies and palliative care) should be aligned with current NCCN® guidelines and where applicable, U.S. FDA approved indications.**

**The proposed comparator for CAR-Ts and belantamab mafodotin-blmf for heavily pre-treated RRMM should be selinexor in combination with dexamethasone.** This was approved by the FDA and placed in NCCN guidelines in a similar patient population as belantamab mafodotin-blmf.[10] The trial populations of CAR-T cell therapies and belantamab mafodotin-blmf that ICER will assess were studied in relapsed-refractory and heavily pretreated multiple myeloma patients who are largely resistant to available treatments.[11] The treatment paradigm in MM generally involves a combination treatment strategy, involving 2 novel agents with a steroid: an immunomodulatory (IMiD) agent (*e.g.,* lenalidomide or pomalidomide), a proteasome inhibitor

(PI) (*e.g.,* bortezomib, carfilzomib, ixazomib) or an anti-CD38 therapy (*e.g.,* daratumumab or isatuximab-irfc) with a low dose dexamethasone.[12] However, over time, multiple myeloma patients may relapse or become refractory to these established therapies, therefore limiting available treatment options in the later lines.[13] Idecabtagene, ciltacabtagene and belantamab mafodotin trials were designed to study patients who are no longer responding to or are intolerant to these classes of therapies.[14,15,16] Specifically, idecabtagene vicleucel and ciltacabtagene autoleucel trials recruited patients with a median of 6 (range 3-16)[17] and 5 (range 3-18)[18] prior lines of therapy, respectively. 84% and 86% of patients in these trials (KarMMa, CARTITUDE-1, respectively) were triple-class refractory (refractory to prior IMiD, PI and anti-CD38),[19,20] and 26% and 31% (KarMMA, CARTITUDE-1, respectively) were penta-refractory (refractory to 2 prior IMiDs, 2 prior PI's and anti-CD38).[21,22] In addition, the belantamab mafodotin-blmf trial (DREAMM-2) patients received a median of 7 prior lines of therapy (with up to 21 lines of prior therapy) with a majority of patients refractory to prior IMiD, PI and anti-CD38 monoclonal antibody.[23,24]

**Selinexor (in combination with dexamethasone) and belantamab mafodotin-blmf are the only agents approved for patients that have received at least 4 prior lines of therapy.[25,26]** NCCN guidelines and the FDA-approved indication propose that selinexor in combination with dexamethasone should be used in patients with RRMM who have received at least four prior therapies, including at least 2 PIs, 2 IMiDs, and an anti-CD38 monoclonal antibody.[27,28,29,30] In the selinexor registration trial (STORM)[31] the median number of previous regimens was 7 (range 3-18, with 59% (N=122) of the trial population having 7 or more prior regimens) which is very similar to the CAR-T and belantamab mafodotin-blmf trials described above.[32,33]

**Irradiation of bone lesions is the appropriate comparator for palliative treatment (no active treatment) for patients with triple class refractory MM in this assessment.** NCCN guidelines recommend radiation therapy (RT) for palliation in patients with MM.[34] The most common indication for RT was palliation of bone pain (42%), followed by prevention/treatment of pathological fractures (28%), spinal cord compression (10%), and involvement of vital organs/extramedullary disease (10%).[35]

2. **Outcomes: Utilize an ITT versus an "as treated" analysis by including all patients that underwent apheresis as the denominator for assessing the clinical and economic evidence for CAR-T therapies.**

**In the previous CAR-T assessment,[36] manufacturers presented data where complete response (CR) rate and overall response rate (ORR) exclude patients who receive apheresis but do not receive a CAR-T dose possibly due to manufacturing failures, death or disease progression prior to infusion, or adverse events.[37]** Specifically, the KarMMa trial's ITT population, who met the eligibility criteria, were 140 patients.[38,39] Unfortunately, 12 patients in the trial did not receive CAR-T, even though T-cells were harvested through leukapheresis. As a result, only 128 patients were ultimately treated. Similarly, in the CARTITUDE-1 trial, a total of 35 patients were enrolled, 30 patients were lymphodepleted and only 29 patients were dosed.[40] Excluding patients from the ITT population results in selection bias, where the denominator is smaller and therefore the response rate is amplified. ICER recalculated the outcomes in the prior CAR-T report based on ITT. Amgen recommends a similar approach in this assessment.[41]

Furthermore, during the manufacturing process, many patients received bridging therapy [42,43] to control their disease until infusion: ICER should consider the cost of bridging therapy into their assessment.

**3. Adverse events: Amgen agrees with ICER that ocular toxicity is a critical outcome for belantamab mafodotin-blmf, and further suggests that ICER also consider the inclusion of costs associated with monitoring and treating patients for ocular toxicity.[44]**

**Belantamab mafodotin-blmf comes with a black box warning and its use is associated with ocular toxicity, mandating ophthalmic examination at baseline, prior to each dose and prompt continuous monitoring for worsening symptoms. [45]** In the DREAMM-2 trial, ocular adverse reactions occurred in about 77% of the 218 patients in a pooled safety population: keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%).[46] These adverse reactions require continuous monitoring, increasing the cost, anxiety and burden for patients on belantamab mafodotin-blmf. They may also indirectly affect the disease outcome as some patients may choose to discontinue treatment and abrogate any potential benefit.

## CONCLUSION

There are significant nuances associated with treatment of triple class refractory MM due to the complexity in disease manifestation and heterogeneity in patient presentation and prognosis. For this reason, we recommend ICER look to the guidelines and published trial data for further direction on which late line and palliative care treatments are appropriate comparators to anti-B cell maturation antigen CAR-T cell and antibody drug conjugate therapies in triple class refractory MM. In addition, there are limitations associated with CAR-T clinical trials that make comparisons between results difficult and carefully evaluate the reported ORR and CR data for this assessment. Lastly, adverse reactions and safety risks associated with belantamab mafodotin-blmf could lead to cost and anxiety for patients and treating oncologists already dealing with a life-threatening condition.

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October 13, 2020

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

**RE: Call for Comments on ICER's Reviews of Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Triple Class Refractory Multiple Myeloma**

Dear Dr. Pearson,

Autolus appreciates the opportunity to respond to the Institute for Clinical and Economic Review's (ICER) September 22, 2020 request for input on the "Anti B Cell Maturation Antigen CAR-T cell and Antibody Drug Conjugate Therapy for Triple Class Refractory Multiple Myeloma" draft scoping document. While we do not have a current product in this space, our cell therapy candidate products are in numerous clinical trials and this tumor type is of great interest.

Autolus is a pre-commercial stage company with a broad portfolio of pipeline assets focused on chimeric antigen receptor (CAR) T-cell immunotherapy for treatment of cancer. Our lead clinical program AUTO1 for the treatment of adult acute lymphoblastic leukemia (ALL) is currently in the pivotal study phase and our additional pipeline products include AUTO3 for diffuse large B-cell lymphoma (DLBCL) and AUTO6 for GD2 positive solid tumors.

As ICER has acknowledged, "Cell and gene therapies are starting to provide truly transformative advances for patients and their families, particularly those with conditions for which there has not been any effective treatment before." We agree with this statement and believe that access to these transformative therapies will greatly improve health outcomes for patients battling cancers like multiple myeloma. With this in mind, we provide the following comments to ensure that the long-term value of CAR-T cell products are appropriately accounted for in ICER's value assessment methodology.

Methodology
Traditional heath technology assessment frameworks are not flexible enough to accommodate potentially curative therapies and do not capture the full value of these products. The short term time frame for assessing affordability versus the long-term timeframe for assessing value; variability in ability and willingness to pay based on the unmet medical need addressed; and the subjectivity of incorporating contextual considerations such as caregiver and societal impacts into a quantitative framework all fail to take into account the unique nature of CAR-T cell therapies. While we support ICER's goal to revise their traditional value assessment framework for single or short-term transformative therapies (SSTs), analyses suggest that these products would fare better if they were considered under the standard framework, implying that SSTs are less favored compared to chronic therapies like the antibody drug conjugate therapy for treatment of multiple myeloma that ICER proposes to assess along with the two CAR-Ts.

CAR-Ts, like other single administration therapies, have a clearly defined cost. To assess a CAR-T with a one-time, defined cost against therapies given for varying lengths of time based on individual patient response could be misleading across all metrics. We recommend that ICER continue to engage with stakeholders and revise the SST value framework accordingly to continue to support and not harm innovation and continued investment in these unique products.

<u>Timing of assessment</u>
Conducting value assessments on CAR-T cell therapies prior to launch, before longer term data are available in many cases, further undervalues the STT value framework. Over time, SSTs continue to provide benefits to patients and society without a continual cost incurrence like chronic cancer therapies. However, ICER has conducted several assessments prior to CAR-T product approval by the FDA—including the two CAR-Ts for treatment of multiple myeloma in this assessment—relying on early phase clinical data to determine clinical and economic value. Pricing review and speculation on the value of highly innovative products that are not yet available does not serve patients or society at large. Without evidence on the duration and full spectrum of benefits, a premature assessment of value could result in undue barriers to patient access of these potentially life-saving therapies.

We believe that public dissemination of any value assessments should be withheld until a more comprehensive data set (including real world evidence) is available and that ICER should rigorously update their assessments as additional longitudinal evidence becomes available.

Thank you for providing the opportunity to comment on ICER's methodology and draft scoping document for assessment of therapies to treat multiple myeloma. Autolus looks forward to working with ICER in the future. If there is any additional information we can provide, please do not hesitate to contact Brent Rice at b.rice@autolus.com.

Sincerely,

*Brent Rice*

Brent Rice
Chief Commercial Officer

October 13, 2020

Re: Draft Scoping Document for the Assessment of Anti B-Cell Maturation Antigen CAR T Cell and Antibody Drug Conjugate Therapy for Triple-Class Refractory Multiple Myeloma

Dear Dr. Steven Pearson,

Bristol Myers Squibb (BMS) acknowledges the importance of understanding and fully characterizing the value that innovative therapies provide to patients, and we appreciate the opportunity to respond to the Institute for Clinical and Economic Review (ICER)'s draft scoping document of *Anti B-Cell Maturation Antigen CAR T Cell and Antibody Drug Conjugate Therapy for Triple-Class Refractory Multiple Myeloma*. As a leader in the development of transformational medicines in oncology and other serious conditions, BMS appreciates the opportunity to offer recommendations to the planned scope to ensure that the review is conducted with the utmost scientific rigor.

In this document, we highlight opportunities to ensure validity and transparency of the scientific approaches so that the value of different agents for treatment of relapsed/refractory (RR) multiple myeloma (MM) patients who are triple-class exposed may be accurately reflected in the final ICER model and report. Idecabtagene vicleucel (ide-cel) is an investigational anti-BCMA CAR T cell therapy that is not approved for use in any country, and the safety or effectiveness of the therapy has not yet been established. The Food and Drug Administration (FDA) has designated a Priority Review and granted a Prescription Drug User Fee Act (PDUFA) target, or action date of March 27th, 2021.[1]

## I.    General Concerns

*Unmet Need Should Be Considered in the Assessment of Value*
BMS is pleased to read that ICER has recognized that there is a clear need for more treatment options for triple-class exposed MM patients when citing feedback from patients and clinicians. Standard-of-care (SoC) first-line chemotherapy generally involves treatment with triplet or quadruplet combinations for the treatment of MM. Despite advances in treatment over the years, RRMM is characterized by multiple periods of remission and relapse and there is no SoC for treatment beyond the initial induction regimen.[2] Most patients relapse, with worse survival outcomes seen in patients with high-risk cytogenetic profiles or treatment-refractory disease.[3-6] Depth and duration of response (DOR) as well as survival decrease with each successive treatment due to increasing resistance to available treatment options.[7,8] RRMM patients who are triple-class exposed tend to demonstrate poorer clinical outcomes across overall response rates (ORR) 26% to 31%, complete response/stringent complete response (CR/sCR) rates ($\leq$3%), median progression-free survival (PFS) of ~4 months and median overall survival (OS) of 9.3 months.[4, 10-12] Due to aggressive disease course, developing resistance and poor outcomes with currently available regimens, there is a strong need for novel treatment options for these patients who have been previously treated with immunomodulatory drugs, proteasome inhibitors (PIs), and anti-CD38 antibodies.[4, 10-12] Neither the

standard Value Assessment Framework nor the new single and short-term transformative (SST) framework include the level of unmet medical need as part of the quantitative analyses. Specifically, unmet need is not considered when evaluating the value products provide in either the comparative or cost-effectiveness analyses by ICER.

- **Recommendation**: Due to this high unmet need and currently no SoC in the triple-class exposed MM patient population, we encourage ICER to acknowledge this in the framework, and include a specific voting question asking whether the level of unmet need in this patient population has been adequately captured in the evaluation (Y/N).

*Limitations in Comparative Effectiveness Estimates Between Therapies in Scope*

There are currently no head-to-head trials to directly estimate comparative effectiveness between the treatments in scope; thus, indirect treatment comparisons will be required. It would not be accurate to try to compare the three interventions, given the single-arm nature of these studies, any indirect comparison would be limited due to insufficient data and would require making inappropriate assumptions when comparing heterogeneous trial populations, resulting in misleading conclusions about their relative value. Thus, a common comparison against standard of care is most appropriate for all treatments considered in the draft scope. It is important to recognize the trial populations of each of the listed treatments included in this scope differ in important ways across the following factors. The **number or prior regimens required**, the definitions of what constitutes a regimen and the drugs required within these regimens are highly variable across these studies. For example, while some studies require at least 3 prior lines of therapy, others allow patients to enter based upon double refractory status, as opposed to line.[13] **Refractoriness to prior regimens** also varies; for example the KarMMa study, which evaluated ide-cel, required patients to be refractory to the therapy they received directly prior to entering the study, while other studies did not.[13] The **definition of refractoriness** as some studies follow the guidelines established by the international myeloma working group (IMWG), which defines refractory as progression while on or within 60 days of completing treatment. Other studies include a broader definition of refractory, labeling patients who progressed within 6 months of completion of therapy as refractory.[13,14]**Additional factors** that differ between trials and are known to influence outcomes include but are not limited to: time since diagnosis, proportion of patients with high-risk cytogenetics, proportion who are prior refractory to bortezomib / carfilzomib / lenalidomide / pomalidomide, ISS stage, lack of overall survival outcomes and proportion with extramedullary disease.

- **Recommendation**: Given the differences in trial populations and how the results are presented for each of the CAR Ts, we believe that any indirect treatment comparisons between agents that do not address these issues with individual patient-level statistical matching will be misleading and unreliable. Therefore, in order to best provide meaningful comparisons in terms of product value, we recommend that each BCMA therapy be compared against the SoC for patients with triple-class refractory multiple myeloma.

II. **Scope of Comparative Value Analyses**

*SST Method Modifications Are Inappropriate for This Assessment*

As stated by ICER in its Draft Scoping document, their preliminary review of the current state of the evidence and conversations with several clinical experts and patient groups "indicate that CAR T therapies extend progression-free survival by a magnitude that is similar to previously-approved therapies, and their curative potential is currently unknown." Given the preliminary nature of the currently available CAR T data in RRMM, in addition to points below, we believe that use of the SST methodology is inappropriate for use in this current review.

We believe certain aspects of the methodology employed in scenarios from the SST modifications are inappropriate to assess ide-cel's value to patients in RRMM. Currently, the draft scope includes both CAR T products (e.g., ide-cel and cita-cel) as well as a chronically administered therapy (belantamab mafadotin). The SST modifications specifically note that the focus on SSTs "… implies that we do not believe that treatments taken on a chronic basis, even if they may be true cures that eradicate disease, warrant consideration of special assessment methods." Given the comparators considered within scope of this document, we believe it is critical that all therapies be evaluated with similar methodologies, such that any inferences about products can be made based on shared assumptions, methodologies, and inputs.

Obtaining deep responses over time is critically important to helping patients prolong control of their disease. Time-to-event endpoints such as PFS, ORR and DOR can be evaluated to assess clinical benefits. For example, in the pivotal KarMMa study, ide-cel demonstrated frequent, deep and durable responses in heavily pretreated, highly refractory RRMM patients. Both primary and key secondary endpoints were met with an ORR of 73% and CRR of 33%. PFS (20 months) and DOR (19 months) increased with depth of response in patients achieving CR/sCR.[14] It is important to note, however, as we have observed CAR T in clinical trials, these outcomes will continue to change with longer follow-up periods. With extended follow-up, the number of patients achieving durable long-term responses will also change. Therefore, it is important to understand that early assessment of outcomes cannot be utilized to predict true clinical impact.

The observation that responses to ide-cel are deepening over time suggests that it is inappropriate to do this analysis now, as any assumptions regarding the long-term treatment benefit of ide-cel should be based on clinical / mechanistic inferences rather than the SST methodology which simply assumes the treatment effect stops after the duration of follow-up from the trial.

- **Recommendation**: We encourage ICER to not utilize the SST methodology for this upcoming review, given the heterogeneity between the treatments being studied (both chronic and short-term) and the need for consistency in approach between evaluations for the sake of interpretable results. In addition, we believe there are likely to be substantial survival and health gains related to the fact CAR T cell therapy would have no ongoing treatment burden from chronically administered therapy which will directly benefit patients, families, and society. The SST approach does not adequately account for the unique aspects of value that CAR T cell treatment brings to the RRMM space.

Sincerely,

Kaleen Barbary, PharmD
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Amit Agarwal, MD, PhD
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Mitch Higashi, PhD
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October 13, 2020

Steven D. Pearson, MD
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
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Re: Institute for Clinical and Economic Review—Multiple Myeloma Review Scoping Review

Dear Dr. Pearson,

On behalf of the Cancer Support Community (CSC), we appreciate the opportunity to respond to the request for comments on ICER's scoping review for the treatment of multiple myeloma. Below we are reiterating findings (those that will fit within the three-page limit) from CSC's Cancer Experience Registry Multiple Myeloma Specialty Registry. It is important to take these into account when considering treatments that could alleviate patient burdens as multiple myeloma is a chronic condition that has significant quality of life, logistical, psychosocial, and financial repercussions for many.

**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 *3*0% 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. **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. In closing, thank you for the opportunity to submit these comments. If we can serve as a resource, please reach out to me at Efranklin@cancersupportcommunity.org.

Sincerely,

Elizabeth Franklin, PhD, MSW
Executive Director, Cancer Policy Institute
Cancer Support Communtiy Headquarters

**STATEMENT OF DAVID MITCHELL, MULTIPLE MYELOMA PATIENT**

October 12, 2020

My name is David Mitchell. I was diagnosed with multiple myeloma ten years ago on November 5, 2010. At the moment my disease is under good control with drugs that carry a price of $900,000 per year.

**Importance of ICER**

I am very grateful for the work of ICER to arrive at suggested prices based on the value of a drug to patients. Approval by the FDA means a drug is safe and effective—it doesn't mean it is a good drug, especially when compared to other options.

Right now, the price set at introduction most often has little to do with the quality of the drug. Pharmaceutical corporations set prices based on what they think the traffic will bear—charging as much as they think they can get away with. ICER, on the other hand, provides an evidence-based approach to pricing using the tools of health technology assessment that are well-developed and widely employed throughout the rest of the world. No other organization in the United States plays this essential role.

**Importance of BCMA In Novel Therapies for Multiple Myeloma**

I am fortunate to have standard risk disease and have been heavily treated. I am a likely candidate for CAR-T and other drugs targeting the B-cell maturation antigen (BCMA) as their mechanism of action. I have been on a four-drug combination of pomalidomide, daratumumab, bortezomib and dexamethasone for over a year. When I fail on this regime, I will have been treated with all three of the major classes of myeloma drugs—monoclonal antibody, immunomodulatory, and proteasome inhibitor.

Having drugs with novel mechanisms of action is critical to my future health and survival. Drugs targeting BCMA could be especially important given the high expression of BCMA in all stages of multiple myeloma.

I care deeply about getting new drugs to market. But drugs don't work if people can't afford them.

**Assign a Price Based on Existing Data, Not Hoped-For Data**

When ICER conducts its analysis, I hope you will assign a price based on existing data, not hoped-for data. As a patient, I view the keys to CAR-T value to be both response rates and durability. We should establish prices based on response duration observed, and if the duration increases over time, the price can rise with the new data.

**Please Consider the Risks and Toxicities Carefully**

Extending life is clearly central for a patient like me. But the risks, toxicities and quality of life must be balanced with responses. Please weigh these carefully. Thank you.

October 13, 2020

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

**DELIVERED ELECTRONICALLY**

Dear Dr. Pearson,

On behalf of Gilead Sciences and Kite, a Gilead Company, we would like to provide input into ICER's scoping for the review of **Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Triple Class Refractory Multiple Myeloma**.

Gilead is a research-based biopharmaceutical company that discovers, develops, and commercializes innovative medicines in areas of unmet medical need. With each new discovery and investigational drug candidate, we seek to improve the care of people living with life-threatening diseases. Gilead's therapeutic areas of focus include HIV/AIDS, liver diseases, cancer, inflammatory and respiratory diseases. Our portfolio of more than 25 products contains a number of category firsts, including complete treatments for HIV and chronic HCV infection available as once-daily single-tablet regimens as well as pre-exposure prophylaxis (PrEP) for the prevention of HIV in at-risk individuals. Gilead is seeking regulatory approval for an anti-inflammatory JAK inhibitor for ulcerative colitis and rheumatoid arthritis. Through our subsidiary, Kite Pharmaceuticals (Kite), we are a leader in cell therapy and are poised to become the first cell therapy franchise with multiple approved medicines in different indications.

We encourage ICER to consider the following recommendations.

*General comments*

1. **Employ the adapted value framework for single and short-term transformative therapy (SST) due to the potential for substantial and sustained health benefits for CAR T therapy.** A significant health benefit is one that extends throughout the patient's lifetime that either is a potential cure or a transformative therapy that produces a major health benefit or stops the progression of the disease of interest.[1] CAR T therapy requires only a single infusion and the benefits of this therapy have been shown to last for years.[2,3,4,5,6] Further, CAR T was included as an SST in ICER's SST Technical Brief.[7]

*Population*

2. **Adjust the base case to reflect the trial population's age-specific variability in CAR T therapies.** Multiple myeloma (MM) primarily affects an elderly population where the median age at diagnosis is 70 years and approximately 35-40% of patients are older than 75 years.[8] However, the patients in the MM CAR T registration trials are significantly younger. From the preliminary trial results, the median age was 57 (range: 37-74)[9] and 61 (range: 50-75)[10] for the KarMMA-1 and CARTITUDE-1 trials respectively.

*Intervention*

3. **Also consider patients in the CAR T arm who have successfully received treatment, in addition to an intent-to-treat (ITT) approach.** ICER's methodology should be consistent with the scientific approach the FDA used to describe the efficacy for CAR Ts. The efficacy reported on the FDA-approved prescribing information for axicabtagene ciloleucel is based on the population <u>treated</u> with axicabtagene ciloleucel only.[11] Furthermore, for tisagenlecleucel, the efficacy reported on the FDA-approved prescribing information was based on the "<u>efficacy evaluable</u>" patients for both the relapsed or refractory pediatric B-cell acute lymphoblastic leukemia (pALL) and for the adult relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The "efficacy evaluable" patients were a subset of the patients treated with tisagenlecleucel. We recommend ICER apply the same metric for efficacy as the current FDA-approved prescribing information for current CAR T therapies.[12]

*Comparator*

4. **The comparator should be a real-world external comparator which matches the study inclusion and exclusion criteria of the intervention.** In the ICER evaluation of CAR T therapies for B-cell cancers, a basket of treatments from the SCHOLAR-1 trial were used to evaluate outcomes of alternative therapies in a similar population. Gilead recommends that a similar approach should be adopted for the evaluation of CAR T therapies in MM patients. In addition, reflective of real-world use of autologous or allogeneic stem cell transplants (SCT), SCT should also be included in the relevant comparator. NCCN guidelines include SCT as additional treatment for relapsed or progressive disease.[13,14,15,16]

*Outcomes*

5. **Incorporate Overall Response Rate (ORR) into this analysis as a "Patient-Important Outcome", rather than "Other outcomes" given that it is a meaningful outcome to providers, patients and their caregivers.** The FDA granted the CAR Ts a Breakthrough Therapy designation since there is preliminary clinical evidence that these drugs have demonstrated substantial improvement over available therapy on a clinically significant endpoint, which in this case is ORR. The FDA may approve therapies based on ORR since it provides a signal of effect earlier than mortality endpoints so that patients who are running out of treatment options have access to potentially lifesaving therapies. It also assesses the effect attributable directly to the therapeutic and not the natural history of the disease.[17]

6. **Model triple class refractory MM (TCRMM) based on a mixture cure model approach.[18,19,20]** Standard approaches for survival modelling can lead to potential bias when applied to CAR T therapies since both groups of patients, cured and uncured, are grouped together resulting in an average mean overall survival (OS). The TCRMM population represents a heterogeneous and heavily treated population with

relatively poor performers.  This is not the appropriate survival curve for CAR Ts: instead utilizing a mixture cure approach would result in greater accuracy in capturing survival gains.

7. **Consider a cut-off point where survival approximates the general population.**  Consistent with ICER's evaluation of CAR T therapies for B-cell cancers, we recommend ICER should assume a cut-off point of 4 years, after which the survival curve for CAR-T treated patients in MM should reflect survival curves of the general population.[21]

*Contextual considerations*

8. **ICER should consider racial disparities in this analysis given the unique potential of CAR T to improve health equity.**  Multiple myeloma (MM) is the second most common hematologic malignancy in the United States (US).  Specifically, African Americans have more than twice the incidence rate of multiple myeloma compared to Caucasian Americans.[22]  Moreover, there are significant disparities in outcomes for these patients, suggesting the need to incorporate a scenario analysis of this population into both the analysis and contextual criteria for this assessment.[23]

9. **Reflect the intense impact of MM on formal and informal caregiving for MM patients: this should be incorporated in ICER's formal consideration of contextual criteria as well as form a part of ICER's societal co-base case.**  ICER should include quality adjusted-life year (QALYs) and costs of formal and informal caregivers. The diagnosis of MM is a life-changing event for both the patient and the caregiver(s).[24]  MM patients of all ages require caregiver support from both formal and informal caregivers and the elderly or very sick require even more intensive caregiver support.  The impact on caregivers' quality of life is significant.  Published studies have reported that older caregivers experience greater psychological morbidity and that younger caregivers are less satisfied with their social support.[25]  Given the critical role of caregivers in patient outcomes, ICER should ensure that the impact on caregivers' quality of life and cost impact is fully incorporated in the economic model.

*Timing*

10. **Incorporate evidence on 'intervention effectiveness and harm' in the consideration of the advantages of CAR T, the relapsed or refractory nature of the disease and the unique contribution to social value derived from CAR T.**[26]  CAR T therapies offer a possible cure for patients and ICER have concluded that these therapies are cost-effective.  Snider *et. al.* measured the social value of treating pALL and DLBCL with CAR T in the United States and the social value lost from treatment delays was estimated at $6.5 billion and $34.8 billion of social value for pALL patients and DLBCL patients, respectively.  Of further note, the timing of treatments has a significant impact, with 1, 2, or 6 months of treatment delays resulting in a loss of social value up to 67% for pALL patients and up to 46% in patients with DLBCL.  Therefore, the magnitude of CAR T therapy's value depends on timely patient access.

The methodology applied to assessment and related cost-effectiveness models to capture value has evolved over time.  We believe that the proposed draft scoping document can be optimized to more accurately capture the value of CAR T therapies.  We appreciate this opportunity to make some initial comments in such a dialogue and look forward to future interactions.

Sincerely,

Bill Guyer
Senior Vice President and Head of Medical Affairs, Gilead

Ibrahim Elhoussieny
Vice President and Global Head of Oncology and Cell Therapy Medical Affairs, Kite

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October 13, 2020

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

Dear Dr. Pearson,

GlaxoSmithKline (GSK) appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Scoping Document on the assessment for treatments in triple class refractory multiple myeloma (MM).

On August 31, 2020, ICER announced an assessment of CAR-T therapies in MM. However, the draft scoping document now highlights that anti-BCMA therapies within MM are being assessed. Due to the differences in technologies and target patient population between CAR-T and non-CAR-T therapies, GSK recommends ICER consider:

- Not including belantamab mafodotin in this otherwise CAR-T-oriented assessment; *and*
- Comparing belantamab mafodotin in a later review of triple-refractory RRMM, against clinically meaningful comparators, e.g., standard of care (SoC), selinexor + dexamethasone and upcoming bispecific antibody therapies

GSK suggestions are organized into four core themes, A-D as detailed below:


**A. Please confirm that belantamab mafodotin will not be compared to CAR-T therapies, as these two treatments are used in different patient populations with distinctive characteristics in clinical practice**

We would like to confirm that it is not ICER's intention to compare belantamab mafodotin with CAR-T therapies in the review. This point was not clear in the draft scope. While belantamab mafodotin, idecabtagene vicleucel and ciltacabtagene autoleucel are all anti-BCMA therapies, the technologies are very different and will be applied to different patient populations in real-world clinical practice. Belantamab mafodotin is an antibody-drug conjugate, which is an off-the-shelf drug delivered by an intravenous infusion. By contrast, CAR-T therapy is one-time and it involves first obtaining T cells from the patient's blood, activating in vitro to facilitate gene insertion and modifying to express CAR, and reinfusing the genetically modified CAR-T cells into the body after a period of patient lymphodepletion.[1] The time from physician intent to treat to the time of actual infusion with CAR-T varies and can take up to 11 weeks.

In a disease with a short survival time (median OS of only 9.2 months for triple and quad refractory patients)[2], physicians cannot delay treating patients, particularly those patients with poor prognosis. Off-the-shelf pharmacologic treatments like belantamab mafodotin need to be administered to these patients without delay. Separately, physicians will also consider whether to give CAR-T to those who have less aggressive disease and are fitter and younger.

Not only is the comparison between belantamab mafodotin and CAR-T therapies not meaningful in clinical practice, it would also be challenging to carry out the comparison due to the differences in trial designs and patient characteristics. There are substantial differences in the patient populations in DREAMM-2 (the

pivotal trial for belantamab mafodotin)[6] compared with either KarMMa (the pivotal trial for ide-cel)[5] or CARTITUDE-1 (the pivotal trial for cilta-cel),[7] which further support that belantamab mafodotin and CAR-T therapies have different target patient populations (see Table 1 in the Appendix). We note that most patients in the CAR-T trials received bridging therapy (KarMMa 88%, CARTITUDE-1 79%)[5,7], with some already in response (4% in KarMMa)[5] by the time CAR-T infusion was received. Furthermore, a meaningful percentage of enrolled patients in the CAR-T trials did not receive infusion (KarMMa 12/140, 9%; CARTITUDE-1 6/35, 17%),[5,7] and 4/35 (11%) patients in CARTITUDE-1 died before receiving treatment[7] (KarMMa deaths were not reported). We suggest that a fair comparison should use the ITT population of the CAR-T trials instead of only the infused population.

*Based on the different technologies, uses and patient populations we wish to confirm that belantamab mafodotin will not be compared to CAR-T therapies, and request that ICER make it clear that these treatments are not comparable, either directly or indirectly via comparison of results against a 3rd treatment option in the final draft scoping document. We also request that this point be clearly stated in the final evidence report (if applicable) and results will not be presented in a way to suggest comparisons between the two types of treatments.*

## B. Belantamab mafodotin should be compared against clinically meaningful comparators in triple-refractory RRMM

The more meaningful comparators to belantamab mafodotin from the clinical perspective are other off-the-shelf pharmacologic treatments, including currently available treatments in triple-refractory RRMM, such as selinexor + dexamethasone, SoC[2], and potential upcoming treatments such as bispecific anti-BCMA antibodies. Published efficacy data for SOC in MAMMOTH[2] and ITCs may serve as references for comparisons with selinexor + dexamethasone or SoC.[9,10] The data on bispecific anti-BCMAs could be considered once available. Waiting to compare across current and upcoming treatments in triple-refractory RRMM at a slightly later time point may result in a more meaningful and comprehensive review.

*We propose that appropriate comparators should include current and upcoming off-the-shelf treatments in triple-refractory RRMM, and suggest belantamab mafodotin be assessed at a later review when data for bispecific anti-BCMAs is available*

## C. Currently proposed economic model structure is not suitable for belantamab mafodotin

We wish to point out that the proposed model structure is not suitable for belantamab mafodotin because patients do not wait to start the treatment, all patients in DREAMM-2 contributed to the efficacy evaluation and the treatment decision does not depend on response.

The proposed decision tree model structure has not been used in previously published models for RRMM. A systematic literature review (SLR) found 4 published cost-effectiveness studies in 2L+ RRMM,[11-14] including the published ICER review[11] comparing multiple treatments in RRMM. In addition, 9 NICE submissions in MM were reviewed.[15,16] None of these previous models used the proposed short-term decision tree including response to treatment.

Furthermore, we would like to specifically discuss potential limitations of linking PFS and OS to response, which is our understanding of the proposed model structure in the draft scoping document.

1. The relationship between response and PFS/OS may vary across treatments.

2. Response is a time-dependent variable. Stratification of outcomes based on best response may introduce bias because it may occur at different time points. We note that the response rate for belantamab mafodotin increased over time.

3. Most trials do not report long-term PFS and OS based on response status at a given time point. Lack of such model inputs means a decision tree model based on response is infeasible.

*Given that belantamab mafodotin will not be compared to CAR-T, we believe there is no reason to assess belantamab mafodotin under this proposed model structure. We suggest that belantamab mafodotin be assessed using a conventional RRMM model design instead, which means that a separate model needs to be developed for belantamab mafodotin. This further supports our suggestion that it would be more meaningful to remove belantamab mafodotin from this review, and to include belantamab mafodotin with appropriate and upcoming off-the-shelf comparators in triple-refractory RRMM at a later review.*

**D. Suggestions for the CAR-T assessment**

Additionally, for the CAR-T assessment, we wish to highlight a few areas to consider. Firstly, the proposed decision tree structure may have to rely on strong assumptions for ide-cel as the outcomes of the 12 patients who did not receive transfusion was not reported. Secondly, we would like to confirm that cure assumptions will not be included in the model. There is no plateau in the OS curve in the KarMMa trial.[5] In fact, the OS curve dropped substantially at the tail (Figure 1 in the Appendix).

*In summary, GSK would like to confirm belantamab mafodotin will not be compared to CAR-T either directly or indirectly, given the two types of treatments have different usages and patient populations. Given that CAR-T and belantamab mafodotin would be analyzed using different model structures, we recommend removing belantamab mafodotin from the current review. Consideration of belantamab mafodotin would be more appropriate in a future review along with current and upcoming off-the-shelf therapies when data for bispecific anti-BCMAs is available and has been reviewed.*

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

matthew.d.rousculp@gsk.com

**Appendix 1: Comparison of patient characteristics in DREAMM-2, KarMMa, and CARTITUDE-1**

| | DREAMM-2 (n = 97)[1] ITT | KarMMa (n = 128)[2] Treated patients | CARTITUDE-1 (n = 29)[3] Treated patients |
|---|---|---|---|
| Age, median, years | 65 | 61 | 60 |
| Previous LOT, median (range) | 7 (3-21) | 6 (3-16) | 5 (3-18) |
| R-ISS stage III, % | 25[4] | 16 | NR |
| High-risk cytogenetics, % | 42[a] | 35 | 27 |
| ECOG PS 2, % | 16[5] | 2 | NR (excluded) |
| Refractory to anti-CD38 mAb, % | 100 | 94 | 93 |

a. DREAMM-2 trial included 1q21+
1. Lonial et al. Lancet Oncol 2020;21(2):207-211.[6]
2. Munshi et al. 2020 ASCO Annual Meeting.[5]
3. Berdeja et al. 2020 ASCO Annual Meeting.[7]
4. Suvannasankha et al. 2020 ESMO Virtual Congress.[10]
5. GSK Data on File.

**Appendix 2: Overall survival of the infused patients in KarMMa**
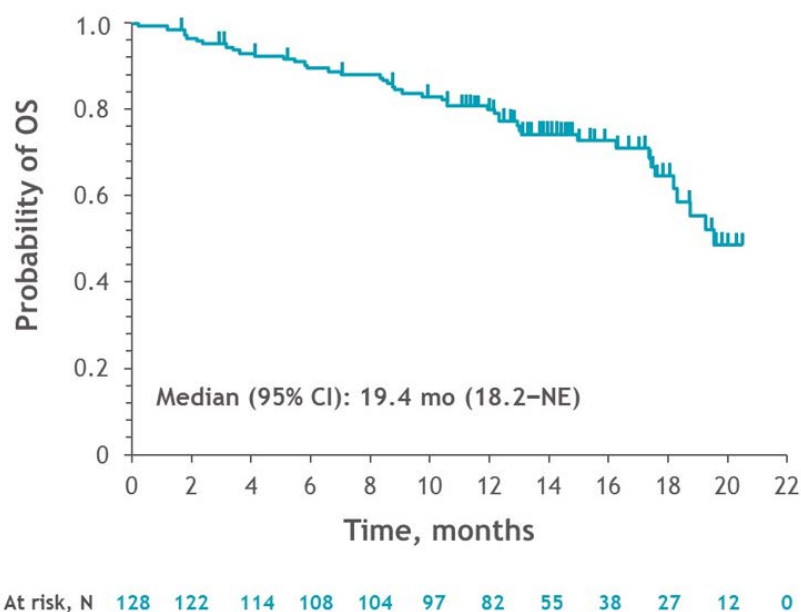


Munshi et al. 2020 ASCO Annual Meeting.[5]

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October 13th, 2020

Steven D. Pearson, MD, MSc, FRCP
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Dear Dr. Pearson,

The International Myeloma writes in regards to ICER's draft scoping document outlining the planned analysis of CAR-T Cell Therapies for Multiple Myeloma. Founded in 1990, the International Myeloma Foundation (IMF) is the oldest and largest myeloma-specific patient advocacy organization in the world. We appreciate the opportunity to respond, although we ultimately believe this review is premature due to the lack of relevant data currently available and the additional reasons we highlight below.

**Review is Premature**

We ultimately believe this review is premature due to the lack of data. Of the drugs mentioned for review, GSK's Blenrep is currently the only (and very recently) FDA approved agent via the FDA's accelerated review process included in this scoping document. Both CAR-T therapies included in the draft scope are still in the process of seeking FDA approval. While we understand it is the goal to provide payers with information surrounding cost effectiveness as early as possible, ICER should seriously consider postponing this assessment until more conclusive information surrounding these therapies is available. Otherwise it risks harming myeloma patients by limiting their access to needed therapies due to a premature assessment.

**Issues with Usage of Survival Modeling**

We first wish to raise concern with the appropriateness of using survival modeling in this scenario. The most striking reason for our opposition to this approach is how premature the data is surrounding these drugs and the difficulty of developing a strong empirical picture of potential survival attributes this early in the process. We also feel it is important to note that overall survival by itself is not a simple measure of drug efficacy in myeloma. Again, we feel this is another compelling reason to delay this review.

**Disease Heterogeneity**

As we mentioned in our previous correspondence, myeloma is a heterogeneous cancer. We stated "The treatment and progression of the disease differs from person to person. While there are many examples of how myeloma differs between individuals, one of the most basic examples of the heterogeneity of the disease we want to highlight is the many different types and subtypes of myeloma. Indeed, the genetic and molecular abnormalities in this disease are highly diverse and result in a wide range of presentations and outcomes for patients." The draft "Background and Scope" document does not seem to reflect this and it should be acknowledged that a uniform approach does not reflect the realities of the disease and how myeloma is treated.

**Underserved populations**

We also believe it is of the upmost importance for ICER to take into account the burden that multiple myeloma has on underserved populations, particularly the African American community. Multiple myeloma has a much higher prevalence in African Americans making up about 20% of the patient population. It should also be noted

that African Americans are significantly underrepresented in clinical trials, making up only 6% of patients in clinical trials.[1] Our organization has done extensive research on health disparities in this population and because African Americans are underrepresented in trials, conducting this review at this time could inadvertently hinder access and efficacy in the future. We acknowledge that ICER states that "Data permitting, we will consider evidence across relevant subgroups, such as patients with genetic factors that put them at particularly high risk as well as subgroups defined by race," however, we do not believe the review should move forward without this information as it is extremely relevant when treating myeloma patients both presently and in the future.

**BCMA Targeting Agents/Blenrep/Why Multiple Agents Could be Needed**

We question ICER's decision to examine Blenrep in this review. While Blenrep is also a BCMA targeting drug, it has a completely different mechanism of action. As background, Blenrep is not comparable because it produces ongoing deeper response over the sequential three week cycles of therapy rather than a dramatic response with a single upfront does. These drugs not only differ vastly in terms of mechanism, they also present different toxicities and accessibility among the myeloma patient population. Each of the drugs under review may provide benefits to different individual patients. This further highlights the lack of the available data necessary to determine which individuals could benefit from a particular drug. Additionally, while each of these drugs is a BCMA targeting agent, it is expected that patients in the future will be treated with more than one BCMA targeting agent during the course of their treatment. As you can see, antibody drug conjugates, CAR T-cell therapies and bi-specific T Cell engagers are vastly different drugs and it is very clear to the myeloma community that all of these therapies will have a significant role in treating myeloma patients in the future.

**Limited Therapeutic options for TRMM**

As you are likely aware, there are currently limited therapeutic options available to myeloma patients who would be a candidate eligible to receive CAR T-cell therapy treatment or any BCMA targeting drug. Many value assessment bodies all over the world, consider this factor to be important and prioritize setting medical innovation above the estimation of the cost-effectiveness ratio.

**Misunderstandings about Myeloma**

When reviewing ICER's Draft Scope Document surrounding CAR T-Cell Therapies for the treatment of myeloma, we believe ICER may have misconstrued several details about myeloma and how it is treated. First and foremost, there is inaccuracy in ICER's statement in the scope's section surrounding adaptable framework adaptations stating "Our preliminary review of the current state of the evidence and conversations with several clinical experts and patient groups indicate that CAR-T therapies extend progression-free survival by a magnitude that is similar to previously-approved therapies, and their curative potential is currently unknown." This particular statement is perplexing. While we are currently uncertain about the full potential of CAR T-cell therapies due to the fact the data surrounding these drugs is incomplete, we do know that CAR T-cell therapies provide progression free survival that is much longer than many other therapies available. To elaborate, CAR T-cell therapies have shown progression free survival at least double, if not triple that of other triple class refractory agents. Furthermore, while there has been a hope to achieve cure in some patients with CAR T-cell therapy, a majority of patients in the relapse/refractory category have progressive disease.

We also feel it is important to note that up to date interpretation of the achieved remission durations (progression free survival/PFS) and overall survival (OS) is necessary. The PFS is a more direct reflection of the true impact of the administered treatment. Presently, multiple factors influence the overall survival since so many rescue therapies are available for patients. Recent publications by the International Myeloma Working

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[1] https://www.myeloma.org/african-american-initiative

Group provide excellent comparators for anticipated PFS and overall survival for relapse refractory patients and we believe these expert opinions should be properly reviewed and utilized during this process.[2]

**Suboptimal Quality of Life**

Lastly, we take issue with the way ICER generalizes about and presents patient quality of life. We acknowledge that many patients are concerned about the cost of their care and face life altering side effects. That said, ICER's overly simplified and subjective statement on the time gained between treatments as suboptimal again highlights the fine line between useful metrics and the unquantifiable desire to live. There appears to be misunderstandings about the magnitude and quality of life appreciated by myeloma patients. Through contacts with myeloma patients in over 160 myeloma support groups across the United States, the feedback has been striking. Many patients achieve deep responses with CAR T-cell therapy and can function without treatments.

We also know that many patients have taken offense to the categorization of their time gained as suboptimal; time spent with loved ones and as a part of major life events like weddings, graduations, births and holidays should be called anything but when the alternative is death. We sincerely hope that ICER takes better care in their descriptions of a patient's quality of life, and that ICER is made aware that the QALY, is no substitute for someone's will to live even if the time gained is not quite like it was prior to their myeloma diagnosis.

CAR T-cell therapies and BCMA targeting drugs present great promise to patients. In the past decade, new treatments for multiple myeloma can been seen as a guide for progress in scientific research to find ways to turn some once fatal cancers into chronic illnesses that can be managed. While myeloma patients may have side effects from both their disease and treatments, new and promising therapies are helping extend their lives and these promising new therapies designed for people who previously had little hope should be accessible to patients.

We appreciate the opportunity to engage with ICER and offer the expertise of our organization to you as this process moves forward. It is our understanding that ICER's assessment of CAR T-cell therapies for myeloma has the opportunity to influence both coverage decisions from payers as well as public policy in the future. We hope the expertise of patients and myeloma specialists are taken into account as this review continues to ensure patients are able to access this transformative therapy. If you wish to discuss this matter further, please feel free to contact me at rlevy@myeloma.org.

Sincerely,

Robin Roland Levy
Senior Director, Public Policy and Advocacy

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[2] https://www.myeloma.org/imwg-publications

Some background: I'm a 25-yr Multiple Myeloma survivor, diagnosed stage 3 in 1995. My treatments have included 3 transplants, 2 autologous and 1 allogeneic. I mention these particular treatments because they are more similar to CAR-T therapy than any other current myeloma treatment. I also facilitate our large SF Bay Area Myeloma support group, where we've had several patients go through CAR-T and BlenRep treatments. To date, CAR-T patients have seen responses lasting from 0 mos to 2.5 yrs. However, patients have had different CAR-T regimens, e.g. bb2121, bb21217, Juno, and others, while this scope is only considering 2 CAR-T indications. BlenRep experience in our support group is very early with one patient achieving an early remission as well as eye toxicity forcing her to stop treatment. She may re-continue at a lower dosage.

I have several overall concerns with the ICER review being proposed that fall into the area of 1) lack of data, 2) "suboptimal" quality of life, and 3) assumptions. I'll describe my concerns in each of these areas and then follow with specific concerns/questions in the document.

Having both short and long-term data are critical to providing accurate assessments of treatments. In the case of BlenRep, it's been just recently approved to be used alone but is in trials to be used with other myeloma drugs (e.g. Velcade, Revlimid) with only early results for few patients being made available. And while there are more CAR-T results, the sample sizes are still relatively small. At present, these treatments have typically been tested in triple relapsed/refractory patients but they are looking to be used earlier in treatment lines, which most experts believe will enhance their long-term efficacy. And what do we know about treatment efficacy for high-risk MM?

Patients always hope that treatments they are receiving will results in long-term efficacy and quality of life with minimal side effects. However, QoL can also be very subjective. Treatment for me resulted in nerve and muscle damage making it very difficult to walk. I wasn't able to continue working and had to go on medical disability. But would I consider that suboptimal? Absolutely not compared to the 2-3 year expected survival I was given at diagnosis. I haven't been on Myeloma treatment since 2002. And I can't imagine having missed walking (aka "limping") two daughters down the wedding aisle and bouncing 4 grandkids on my lap, which are all were very "optimal"!

As a result of missing data, there are many assumptions you need to make. We don't know which CAR-T or BlenRep will be the most effective treatment for MM patients. We don't know if both can be used or perhaps, since they both go after the BCMA target, that using one will make the other less effective. We don't know what combination therapy will work best with BlenRep or if using these treatments earlier in a patient's treatment history will result in better results. So, assumptions will need to be made…based on what?

The following remarks are identified by Page # and "Starting paragraph text" as well as some identifying text in the sentence being referred to:

- Page 2: "Unfortunately, MM cannot be cured…"

"…combination treatment (*refractory*)." Patients can become refractory to initial treatment OR later treatments as well. Fortunately, new treatments are initiated when patients become either refractory or relapse.

- Page 2: "Three new treatments,…"

"…into the patient intraveneously." You may want to note that this gene modification/expansion process typically takes about 4 weeks. As such the patient may need to take other MM meds during this time period.

- Page 3: "The bone pain and fatigue…"

"…being tied to two IV pumps sucks…" I wonder what treatment requiring 2 IV pumps is being reference? You should get clarification, otherwise this would appear inaccurate or misleading.

- Page 3: "Clinical experts conveyed…"

"…population of RRMM who are triple class refractory." While "triple class refractory" is a common terminology, for a paper like this you should indicate that RRMM refers to Relapsed/Refractory and these treatments are for MM patients who have relapsed or are refractory to a PI, IMID, and mAb. Consider using TCRRMM rather than TCRMM throughout this document.

- Page 4: Applicable Framework Adaptations

"…similar to previously-approved therapies…" However, these previously approved therapies will not work as well for these triple-class RRMM patients. Ideally, however, you would have data to compare with previously approved therapies if BlenRep and CAR-T were given earlier in treatment. But we don't have that data yet either. I hope using these new interventions as earlier treatment options will be discussed as potentially further improving outcomes.

- Page 5: Comparators

There is no data comparing the CAR-T therapies to other treatments although one that just started. BlenRep is being compared in trials but again lacks data.

- Page 5: Outcomes

I'm not sure PRO data was done for trials being assessing so where will QoL, Pain & Fct, etc come from? Also, are MRD results being assessed?

- Page 6: "Table 1.1…"

"Delivery mechanism…" Delivery mechanism is an important distinction since CAR-T is limited to qualified cancer center (like a transplant) versus Blenrep. This has access issues for many patients.

This completes my public comments for Sep 22, 2020 Draft Background and Scope.  Please don't hesitate to contact me for additional information of clarification.

Jack Aiello
jackaiello@comcast.net
408-691-6999

ICER Draft Scope Public Comments
Jenny Ahlstrom / Myeloma Crowd
October 12, 2020


My name is Jenny Ahlstrom and I am a multiple myeloma patient diagnosed in 2010. I founded the CrowdCare Foundation and the Myeloma Crowd and have worked as a myeloma patient advocate for the last 10 years. I am very familiar with the past decade of research and progress in multiple myeloma and therefore have specific concerns with the ICER review for the upcoming CAR T therapies and BLENREP. My concerns with the ICER review include the following:

1. Review of different drug classes at the same time
2. Non-existing path to a cure framework
3. Establishing evaluation criteria when insufficient data exists to make a determination
4. Assumptions on QoL without sufficient data


**Review of Different Drug Classes at the Same Time**

Three new treatments targeting BCMA are the subject of this review. While two are in the same category (CAR T) and go after the same BCMA target, it should be noted that each CAR T product is unique and could provide different durability based on the construct. CAR T therapies are personalized, manufactured and then administered at specific academic centers with specialty follow-up for a longer period of time.

Adding the antibody drug conjugate to the CAR T review just because it targets the same BCMA protein will be a challenge as the treatments use completely different mechanisms of action, methods of manufacturing and administration. CAR T and BLENREP will be used in different ways and for different patients. For example, BLENREP is an off-the-shelf option and because of its easier administration, it will likely be used more often with standard myeloma treatment combinations in all areas of the country and in all oncology offices. Instead of a "one and done" approach, it will be given for longer periods of time for patients who are less likely to maintain a response while their T cells are being customized.

My point is that the two types of therapies, while all targeting BCMA, are radically different in administration, availably and in combination with other myeloma approved therapies. Grouping them together will be problematic and each needs to be considered on its own.


**Non-Existent Path to a Cure Framework**

In the Background section of your document, you state "Unfortunately, MM cannot be cured with approved therapies." I have spoken with myeloma experts from the Mayo Clinic in Scottsdale and NYU who states that there are 10-15% of myeloma patients who have likely been "functionally cured" or who have lived 20+ years without relapse off treatment. This is an

important point because we collectively have not identified ways of identifying the right treatment for the right patient at the right time. Without a data-driven path to a cure framework, we are looking at all myeloma patients in aggregate when they should be separated out into the various types of myeloma. Myeloma may have been cured in some patients with existing therapies and it could be cured in others with these new therapies. For patients whom a particular therapy functionally "cures", the value will be significant. For others whom it does not help, the value is less. We are lumping all patients into the same bucket to determine "value." This is opposed to the truths we already know about myeloma – it is a highly heterogenous disease and one that mutates over time with multiple types of genetic mutations which can be found in combination over the course of therapy. The lack of a cure framework makes value determinations inherently flawed.

**Insufficient data**

My prior point illustrates how we have insufficient data to determine the value of new therapies, particularly those in the immunotherapy category. The immunotherapy landscape is rapidly expanding in multiple myeloma, but there is so much we don't know.

For example, CAR T therapy has a 94-100% overall response rate for the patients in the early KarMMa and CARTITUDE clinical trials. We expected and hoped for more durable responses but these were heavily pre-treated patients, some having up to 18 prior lines of treatment. Genetic factors varied widely in these trials. Myeloma experts are now working to identify methods of increasing the durability of the treatments, pointing to the level of tumor burden at treatment, prior therapies received, the immune system functional T cell status at time of treatment and ideas around booster administration or maintenance therapy. We don't yet know what we don't know. Which patients have proper immune system function to maintain a T cell response? Does T cell health during the manufacturing process determine outcomes? Does tumor burden at time of treatment determine outcomes?

Once we are able to use CAR T earlier in the process, some of these important questions will be better answered. Hypothetically, if we learn that CAR T is best used for patients with a relatively healthy T cell function and a low tumor burden that can be sustained on minimal therapy, CAR T could be THE winning, curative treatment for these patients and will be of high value to this subset. It could also be increasingly valuable for MGUS or smoldering myeloma patients who are likely to progress to active myeloma. Or we may learn that booster administrations or a specific maintenance therapy will increase durability for a wider breadth of patients. So how can we determine value without knowing any of this? We have no clue what the value is yet, only that we have new and exciting innovation that appears to be incredibly promising with a new target and approach.

Today's myeloma treatments are never used alone. Can CAR T or BLENREP be used in combination with proteasome inhibitors, IMiDs, CELMODs, BITeS, chemo or steroids to achieve a functional cure? It is likely, but it's too early to know and the clinical trials have not yet been run. The data surrounding the use of CAR T therapy with other myeloma combinations is non-existent.

My point is that assessing value too early and putting arbitrary caps on cost will limit the exploration of innovative combinations that could lead to a myeloma cure for a subset of patients.

We just recently learned that immunomodulators, drugs that were approved for myeloma over a decade ago, work via the Cereblon pathway. We still don't fully understand the long-term impact of monoclonal antibodies on T cell or NK cell function, even though they have become effective staples of myeloma care. Immunotherapy is early in its development.

**Quality of Life Assessments**
 As a spokesperson of thousands of multiple myeloma patients we hear from in our advocacy efforts, all patients want the most effective treatment with the fewest side effects at the lowest cost. We are all aligned here. Patients do not want the cost or side effect accumulation in taking ineffective treatments. However, they do view quality of life differently than those without the disease.

My own selection of tandem transplants at diagnosis illustrates this point. My goal was a cure, so I was willing to endure a more difficult course of therapy with greater associated and potentially long-term side effects to achieve my best possible outcomes. That hard-hitting therapy allowed me to be without any myeloma treatment for the last 8 years. At diagnosis, the data did not exist in aggregate for me to make this treatment decision. I was fortunate enough to see a myeloma specialist who had worked at a facility with thousands of myeloma patients. His data showed that this treatment may be appropriate for a younger, high-risk patient and potentially achieve that functional cure. I trusted his judgement and chose that therapy. For me, it was the right choice although my myeloma has begun to return. For my girlfriend with triple hit myeloma, it did not provide the same outcome which emphasizes my first point. We are not all the same.

But what if we had the data in order to customize therapies? Patients could then make their own risk/benefit decisions about efficacy and the accompanying costs (side effects and financial).

Quality of life frameworks cannot be determined by someone without the disease because my view of QOL may mean attendance at a family wedding even with severe neuropathy, or anorexia/nausea but the ability to live, work and travel with high risk myeloma. Thankfully, the side effects of CAR T appear to be present in a small group of myeloma patients and the management of those side effects is now well known. Similarly, we are learning what to expect with BLENREP and plans have been put in place for their management. Patients make those QOL assessments every time they take a pill or visit the clinic for their IV infusion.

The innovations in multiple myeloma have been astounding. We hope they continue and that we as a myeloma community can put the right framework together to learn which myeloma treatments or combinations will be the right approach for the right patient at the right time. More data is needed. With that knowledge, we will be more prepared to use the innovations to achieve cures for a greater number of myeloma patients.  – Jenny Ahlstrom, jenny@crowdcare.org

October 13, 2020

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
         Scoping Document**

Dear Dr. Pearson:

The undersigned organizations appreciate the opportunity to respond to the draft scoping
document developed as part of ICER's assessment of CAR T cell therapies for the treatment of
multiple myeloma.

CAR T represents transformative therapy that substantially improves outcomes for patients with
relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) and B-cell acute lymphoblastic
leukemia (ALL) and provides hope for many more with other hard-to-treat cancers. According to
a study published in the Journal of the American Medical Association (JAMA), adults with B-
cell lymphoma have shown higher rates of survival when treated with CAR T, which was found
to be more cost-effective than chemotherapy.[i]

Importantly, CAR T also represents hope for patients and caregivers. Hope for a cure, for a
future without ongoing treatment, for longer and healthier lives with loved ones. As ICER
continues the review process and finalizes the scoping document for multiple myeloma, we urge
you to take the following into account, which could be improved upon as a result of CAR T:

- **Financial Burden:** Patients and caregivers alike shoulder significant financial burdens as
  they navigate the uncertainty of cancer care. Current non-CAR T therapy for multiple
  myeloma includes patients undergoing numerous treatments, adding additional costs to
  already strained budgets. The administration of numerous treatments also imposes a
  financial burden on caregivers, including the loss of work and/or societal contributions, in
  addition to related direct costs of caring for a loved one.

- **Quality of Life:** Multiple myeloma patients experience significant quality of life impact,
  including physical symptoms of the disease and side effects of treatment. The ongoing
  psychosocial impact on patients, caregivers, and family is equally great. Physical
  ailments include neurological damage such as peripheral neuropathy; pain management
  issues; kidney failure caused by multiple myeloma; autologous stem cell transplants;
  chemotherapy; and more have a substantial impact on quality of life.

- **Disruption to Life:** For patients and caregivers, multiple myeloma is an unending
  disruption to their daily life. This may include taking time off work to travel to, receive,

and recover from treatment; impact on relationships with friends loved ones; or isolation from society.

Many of the undersigned organizations have also submitted individual letters on behalf of their organizations, which we encourage ICER to read and consider as well. CAR T therapies represent a truly innovative product, and it our hope that this treatment will continue to yield significant benefits and outcomes for patients, providers, and hospitals nationwide.

If you have any questions, please don't hesitate to reach out to our organizations.

Sincerely,

American Cancer Society Cancer Action Network

Cancer Support Community

CLL Society

Lymphoma Research Foundation

Myeloma Crowd

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[i] Whittington MD, McQueen RB, Ollendorf DA, et al. Long-term Survival and Cost-effectiveness Associated With Axicabtagene Ciloleucel vs Chemotherapy for Treatment of B-Cell Lymphoma. JAMA Netw Open. 22 Feb. 2019.