PATIENTS RISING NOW

March 11, 2021

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

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

Dear Dr. Pearson:

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

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

People-Centered Perspectives

We again appreciate the outreach that ICER did to patient groups and the information shared in the draft report's Section 2: "Patient and Caregiver Perspectives." ICER's decision to use a structured discussion guide for collecting information from the relevant patient groups is an important step forward for ICER, as it represents a more rigorous approach to evaluating and incorporating patient perspectives into its analyses. However, as we pointed out before, conducting a focus group is not just bringing people together for a discussion, and a gathering of just four people can hardly be considered sufficient for a meaningful focus group.[i]

As ICER is aware, and discusses in some ways in the draft report, multiple myeloma is a very complicated type of cancer that often recurs, resulting in people (and their families) having to experience many different types of treatments. This relapsing type of cancer means that people with multiple myeloma experience a very tumultuous disease course over many years that includes not only the problems from the underlying cancer, but the side effects and logistical complications of the different treatment regimens. To make good decisions, ICER, policy makers, and payers must understand and appreciate the complicated pathways that people with multiple myeloma take through their treatments, and that those paths often vary greatly from person to person – a point that is clear in the materials from the National Comprehensive Cancer Network's (NCCN) information for both clinicians and patients.[ii] The NCCN recognizes the

variety of treatments that someone with multiple myeloma may receive – ranging from several types of stem cell transplants, to general or targeted chemotherapies, to clinical trials. This complexity is noted in the draft report, i.e., "there is no widely accepted preferred ordering of lines of therapy for TCRMM patients."[iii]

We were a dismayed that the draft report's discussion of treatment options essentially ignores stem cell transplantation, even omitting stem cell transplantation from its description of "mainstays of current MM treatments."[iv] We realize that ICER's draft report is tightly focused on three new treatment options (only one of which is approved), but failing to provide the appropriate context for understanding those new treatment options compared to the array already available – and how they could be chosen or used during the course of multiple treatment failures or relapses for individual patients – does a disservice to patients, clinicians, policy makers, payers, and society. This too-narrow focus and lack of contextualization is an ongoing problem that ICER seems unable to rectify and ignores the real-world movement toward better patient-clinical team communications and shared decision-making.

In that vein, we noted that stem cell transplantation was a specific exclusion criterion for all the trials used as data sources in the draft report,[v] but in the ongoing studies (summarized in the draft report),[vi] stem cell transplantation is a reason for exclusion in only <u>some</u> of the trials. If there are clinical or scientific reasons that stem cell transplant recipients face contraindications to any of the treatments, that information should be included in the draft report. The draft report's failure to discuss stem cell therapies leaves many unanswered questions and is another example of ICER's limited perspective regarding very complex clinical conditions.

The clinical trials reviewed in the draft report attempted to include patient reported outcomes and quality of life metrics in their protocols. While those metrics were not consistent across trials, as the report notes, at least this represents an attempt to assess how the experimental treatments affected patients. Overall, from the information in the draft report, it seems that the CAR T-cell therapies were more positive in improving patients' lives than belantamab mafodotin. That insight, albeit very preliminary, is quite encouraging since CAR T-cell therapies are a new treatment approach that provide hope across a range of serious diseases and conditions. We also were encouraged by the draft report's statement that "while there is interest in utilizing CAR T-cell therapies earlier in the MM disease course, studies are needed to determine whether these therapies are superior to current therapies for first or second relapse of MM."[vii]

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

<u>Data, Modeling, Projections, Assumptions, and Uncertainties</u>

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

- The draft report utilizes unpublished or unreviewed presentations or papers as data sources. For example, one of the sources for the baseline population characteristics is a paper that was presented at a conference rather than published after peer review.[ix] We note that this data source was used for modeling the baseline population for one of the three treatments in the draft report, while the other two had their own citations – both published papers.[x] We would like ICER to explain – in doing the baseline modeling – why it was appropriate to develop different population characterization for each of the three therapies, particularly since it is expected that the usage of the new therapies will evolve in the future, with the likelihood that they will be used earlier in the course of patients' illnesses.
- In the draft report's listing of Categories of Contextual Considerations[xi] it states that concerning the context for "the magnitude of the lifetime impact on individual patients" that the "Relevant Information" is that multiple myeloma "has a moderate lifetime impact on individual patients. Many patients present with pre-symptomatic disease. While the disease becomes the primary focus of medical care for the heavily pre-treated subpopulation that is the focus of this review, this represents a relatively short proportion of the patient's lifespan." We are very concerned about that characterization, and how it dramatically ignores the effects that multiple myeloma has on the individual, their family, and others in their lives. While people with multiple myeloma who are in the "heavily pre-treated subpopulation" – meaning that they have already undergone several (or possibly many), different treatments, which likely occurred over the course of many years – ICER's characterization discounts the importance of their lives, perhaps because these individuals are likely older. We strenuously urge this characterization be a primary topic of discussion at the Midwest CEPAC meeting scheduled for April 16th; for example, during the discussion of the prioritization for question #6 "Magnitude of the lifetime impact of the condition being treated." While ICER's "Relevant Information" statement might be accurate in sterile economic terms, we find it both callous and offensive from the patients' perspective.
- The draft report repeatedly states that it is looking at the use of these treatments in people who have had at least three prior lines of therapy, but one of the cited data sources is a phase 1 trial where the patients had 1-9 prior therapies.[xii] In contrast to that reality of the underlying data, the Long-Term Cost-Effectiveness section of the draft report explicitly states, "The CAR T trial's enrollment criteria required patients to have been treated with 3 previous lines of therapy."[xiii] This is another example where ICER states parameters for its modeling, and then ignores or misrepresents the actual data it uses. At some level, ICER must have realized this discordance, since the draft report also notes that the data from this trial should be "approached with caution" because the participants were "less heavily pre-treated."[xiv]
- CAR T-cell therapy is only performed at select locations, such as inpatient facilities of academic medical centers, because it is a relatively new type of treatment that involves not just drug injection, but also requires a sequence of procedures to procure, purify, modify, and infuse the patient's own T-cells. However, while this is a technologically complex process requiring a variety of skilled teams, it is clear that the treatment is expected to expand to additional care settings, including outpatient facilities.[xv] This transition of new treatments from being used in the most constrained or intensive settings to less acute or technologically sophisticated facilities is a well-known evolution in medical care. Because these factors have such direct implications for patients, health care delivery, payers, policy makers and society – as well as costs and access – ICER should include such perspectives in its draft report.

- Related to that point, we again find ICER's presentation of new technologies fails to model any movement forward in improvements that would facilitate delivery and access, including to patients in underserved areas. For example, the draft report states, "However, CAR T therapies are complex and high-cost with significant side effects. Historically, treatments with these characteristics are underutilized by historically disadvantaged populations, suggesting these treatments may worsen disparities."[xvi] Disparities exist largely because of the historical discriminatory nature of the U.S. health care system; **society's failure to address those structural and reimbursement problems perpetuate those disparities**. This is another opportunity for ICER to learn from the current COVID pandemic, in which disparities in testing and care have dramatically illuminated the very real structural inequity in the U.S. health care system that existed before the pandemic. In essence, in the draft report, ICER is blaming the new tool for the outcome, rather than the system that wields the tool.
- The draft report notes that ICER was not able to conduct an intention-to-treat analysis for the CAR T-cell therapies,[xvii] apparently because ICER does not have access to the full data set from the clinical trials. We strongly expect that if this is an important analysis, the FDA will conduct it as part of their review prior to making an approval decision. However, we note that for individuals with multiple myeloma, they should care more about actual outcomes from people who received a line of therapy, rather than a statistical analysis of a large group that includes people who considered a treatment, but for a variety of reasons ended up not getting it. We realize that is the difference between patient perspectives and health system or regulatory concerns, but ICER should recognize and care about those differences.
- In selecting previous studies to model usual care etc., we note that ICER selected one from its own authors,[xviii] while a simple web search turned up several others, including more recent studies.[xix] ICER should discuss how it selected its own study and then justify why that data is better or more appropriate than other more recent studies.
- In previous comments to ICER we have strongly urged that the uncertainties and limitations be expressed more strongly and sooner. This draft report is another example of the importance of doing that. For example, the draft report contains these statements:
  - "[G]iven that the treatment landscape changes dramatically over short time periods in RRMM, and the lack of an indirect treatment comparison against each therapy, caution should be used when interpreting cost-effectiveness estimates."[xx]
  - "The evidence used in the model relies on limited clinical study evidence with a PFS estimate that has yet to reach its median and no reported estimate for OS."[xxi]

  Such admissions that the economic modeling and analysis are based on flimsy and non-comparable data indicates that the conclusions may be very wrong. But yet again, ICER buries that admission in the depth of the draft report.
- Given the limited data used to develop the draft report, and the unknown prices for the CAR T-cell therapies, we find discussion in the Budget Impact Section to be ludicrous but do appreciate that ICER recognizes that the same patients would not be expected to receive two different types of CAR T-cell therapies in a five-year period.

Additional Points

- There are many endnotes that are wrong. For example, on page 45, endnotes 54 and 55 are incorrect, with the actual references being included in endnotes 61 and 62.

- The reference to the NCCN's clinical guidelines is to the May 2020 version, even though there is a more recent version that was released in December 2020, and it is unclear what "Recommendation 3" is referring to since the NCCN guidelines do not use that designation.
- The language in the report can be somewhat technical and misleading to readers not steeped in the scientific areas. For example, with CAR T therapies, there is reference to the cells being "expanded and then infused back into patients."[xxii] After doing some research, we realized that this use of the term "expanded" means to increase in number through ex-vivo multiplication, and it does not mean to increase the volume of each cell, which would be the normal meaning of the word "expanded."

Conclusions

Patients Rising Now is pleased that people with multiple myeloma have one new treatment option, and likely will soon have two more in the form of CAR T therapies, particularly since the CAR T therapies appear to improve quality of life metrics and hold the potential for long term benefits. We are glad that ICER's draft report reached a similar conclusion. However, we are concerned by the sloppy nature of the draft report's handling of the underlying limited data, and the other problems noted above. We hope that the true value of new treatments for multiple myeloma will be evaluated by others and that ICER's inappropriate and incomplete approach will not be a deterrent for the use of new treatments by patients and clinicians, or result in payers erecting barriers to use, coverage, or payment, since such access restrictions will harm patients and consume clinicians' limited resources. This is especially concerning now, since many clinicians are already struggling personally and professionally with the burdens of COVID-19, including providing care for people with multiple myeloma as their disease progresses and new treatments are required. We are disappointed that ICER does not recognize the trauma that COVID-19 has caused people with multiple myeloma (and other serious health conditions) who have often faced physical access restrictions to care and potentially limited support from caregivers; and incorporate those realities in its work.

Sincerely,

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

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

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

[iii] Draft report, p. 2

[iv] Draft report, p. ES7

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

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

[vii] Draft report, p. 17

[viii] Draft report, p. 3

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

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

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

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

[xiii] Draft report, p. 21

[xiv] Draft report, p. 17

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

[xvi] Draft report, p. ES10

[xvii] Draft report, p. ES9

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

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

[xx] Draft report, p. 30

[xxi] Draft report, p. 31

[xxii] Draft report, p. 2