SUMMARY OVERVIEW

Amgen appreciates the opportunity to comment on ICER’s draft scoping document on CAR-T Therapy for B-Cell Cancers. ICER proposes to compare CAR-T therapy to therapies recommended by NCCN guidelines, such as clofarabine, tyrosine kinase inhibitor-based chemotherapy, or blinatumomab in patients ages 3-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-cell ALL).

Pediatric cancer is the number one cause of disease death in U.S. children. An orphan disease, ALL accounts for 75% of all pediatric cancer with the greatest number of cases occurring between 2-5 years of age. Relapsed/refractory patients face a median survival of 3 months with a limited number of treatment options left to save their lives. In this disease, the value of innovative treatments is not so much in question, eclipsed by the far more pressing issue that there are not enough treatments to address the heterogeneity of patient populations. Oncologists do not face an ‘either-or’ decision but increasingly implement combinations that will address unique characteristics of patients and disease aggressiveness such as performance status, prior therapy, chromosomal/molecular abnormalities, and relapse location. No oncologist wants to have a discussion with patients and their families that their cancer is not responding to treatment. No parent or child wants to hear this and make hard decisions from a shrinking set of treatment options.

1) It is too early to do an assessment on CAR-T in R/R B-cell ALL in children and young adults; ICER should delay this assessment. The lack of therapeutic options and mature outcomes data, combined with extraordinary patient heterogeneity indicate that it is too early to perform a meaningful assessment. Amgen supports ICER’s stated goal of creating a “more effective, efficient, and just health care system”.

With an estimated $750 billion in healthcare spend wasted on areas such as unnecessary services and administration costs, ICER has the opportunity to provide insights in areas transformative for US healthcare. It is an unintended but inevitable consequence that a premature ICER assessment could result in more hurdles for this patient population where payers and PBMs introduce barriers to treatment access. This is at an extremely critical time in a young patient’s fight for survival. In this setting, time and an oncologist’s freedom to choose the right drugs is literally a matter of life and death.

When adequate data and treatments are available in pediatric R/R B-cell ALL to conduct this assessment, then ICER should consider orphan assessment issues and technical challenges to the proposed approach as outlined in the following points:

2) ICER should assess CAR-T in pediatric R/R B-cell ALL as an “ultra-orphan” drug: use of ICER’s “non-ultra-orphan” value framework (as applied for common diseases) runs counter to provisions in place to protect these patients. With only 2,870 new cases each year in the US, this rare disease has been externally validated by the FDA’s tisagenlecleucel-t/CTL-019 Orphan Drug and Breakthrough Therapy designation. Classifying R/R B-cell ALL as a common disease runs counter to the Orphan Drug Act, the very law that was put in place to protect these patients. Rather than attempting to extrapolate what the future treatment population might be, ICER should inform its assessment decisions based on data that are currently available.

3) Any trial comparison is fundamentally confounded by severe selection bias, and would lack validity: ICER should remove blinatumomab as a comparator from the CAR-T draft scoping document and compare within the class of CAR-T therapies. An apples-to-oranges comparison of CTL-019 in the ELIANA study vs. blinatumomab in the MT103-205 study will highlight conclusions that are essentially non-existent:

- The unique requirement for patients to wait for manufacturing of the CAR-T after enrolment to the CAR-T studies meant patients were excluded from the reporting of results because they died, were too sick to continue on study or their CAR-T manufacturing process failed. This alone constitutes a major selection bias.

- 85% of CAR-T patients also received an additional line of active “bridging” chemotherapy. How patients respond to this treatment prior to CAR-T infusion introduces definitive patient selection bias that prevents any comparison between the study results of the two treatments.
Beside this definitive selection bias, patient characteristics of both single-arm studies are heterogeneous and cannot be adjusted: indirect treatment comparison using single-arm studies is associated with an unknown amount of bias. The studies used different inclusion / exclusion criteria and baseline patient characteristics are different on several key prognostic factors. Techniques to address this are infeasible due to the paucity of studies and small study sample sizes in pediatric R/R B-cell ALL.

**KEY RECOMMENDATIONS**

1) ICER should wait to assess treatments in pediatric R/R B-cell ALL until Phase III/confirmatory studies and a greater number of treatment options are available.

**It is too early to perform a value assessment in R/R patients: not enough data are available on these treatments at a stage in a patient’s cancer where there is a shrinking set of treatment options.**

- Having failed the initial line of therapy, R/R B-cell ALL patients face a median overall survival of 3 months. Patient heterogeneity is extensive and its relationship to response is poorly understood. Oncologists understand well that a patient’s disease is killing them but they do not have enough information on why. On top of this, the therapeutic armamentarium of a handful of drugs is too small to address this huge patient and disease variation. Moreover small numbers of patients mean in the first 2 years after FDA approval, far too little is known about new treatments (e.g., type of patients the treatment is best for, mechanism of action) to put one-size-fits all value-based guidelines that second-guess a hematologist-oncologist and the very individual n-of-one cancers they treat.

**A premature assessment based on inadequate evidence could result in delayed treatment access**

- As a society, U.S. children with cancer have special protected status and it is unacceptable to impose treatment barriers to childhood patients and their parents. This is particularly important for ALL, a leading disease-related cause of death for children aged 1-19. With few remaining treatment options for R/R B-cell ALL patients, a premature assessment and pricing threshold for a new treatment would not result in lower prices but in delayed access to treatment. This could cause serious harm to the very patients it aims to help. It could lead to stress and additional time for parents, robbing them of valuable time with their sick child. More importantly, with a child’s survival at risk, there is no time to wait for pre-authorizations or step-therapy from insurers, which could likely result from a premature assessment.

**A premature assessment in pediatric B-cell ALL would threaten first-in-child drug development.**

- Few drugs are approved in pediatric cancer due to challenges in drug development. In the 20 years before the enactment of the Creating Hope Act, the FDA approved only two drugs developed expressly to treat a pediatric cancer: Erwinase and Clofarabine. Even with current laws and policies, only 28 formal labeling approvals involved pediatric oncologic indications.

2) ICER should assess CAR-T in R/R B-cell ALL as an “ultra-orphan” drug; use of ICER’s “non-ultra-orphan” value framework (also applied for common diseases) runs counter to societal provisions developed to protect these very patients.

**ICER’s proposed “non-ultra-orphan” designation for CAR-T is in direct conflict with legislation designed to encourage pediatric cancer drug development.**

The FDA has defined R/R B-cell ALL as an orphan disease and CTL019 received Breakthrough Therapy and priority designation for this indication. ICER’s inclusion and exclusion of what is considered “ultra-orphan” conflicts with the Orphan Drug Act, the law developed to protect and ensure these patients have access to therapies.
which treat life-threatening conditions. R/R B-cell ALL treatments should be considered and assessed as “ultra-orphan” drugs whether or not these therapies treat other diseases.

3) Technical assessment issues: ICER should not conduct an assessment of CAR-T therapy in pediatric patients with R/R B-cell ALL with blinatumomab as a comparator.

The CAR-T reinfusion waiting period, unique to CAR-T, in which patients receive an additional line of active chemotherapy, introduces definitive patient selection bias that prevents any comparison between the two study results.

- A major difference between the two trials is that in ELIANA, the majority of patients used active “bridging chemotherapy” prior to CAR-T infusion. Patients who died, were too sick to continue on study or whose CAR-T manufacturing process failed between enrollment and reinfusion were excluded from the analysis. This constitutes a considerable selection bias between the two studies. MT103-205 investigating the “off the shelf” immunotherapy technology, blinatumomab, ensured patients were infused upon enrollment, without “bridging therapy”.
- Moreover, in ELIANA, because of the need for bridging chemotherapy a proportion of patients actually even achieved a treatment response (rendering them MRD+, not R/R) before receiving their CAR-T infusion. This definitive selection bias prevents any comparison between the two study results.

The heterogeneous populations in ELIANA and MT-103-205 make indirect comparisons infeasible. Important prognostic factors (age, previous treatment history, baseline blast levels) differed between the two trials.

- Age differences: ELIANA enrolled older pediatric patients up to 3 to 21 years of age while the MT103-205 enrolled younger patients from 0 to 18 years old.
- Baseline blast level differences: ELIANA required baseline blast levels at enrollment to be greater than or equal to 5%, whereas MT103-205 required baseline blast levels to be greater than 25%.
- Previous treatment history differences: In ELIANA, the median number of previous lines of therapy was 3.0, meaning that at least 50% of patients had 3 or more prior lines of therapy; whereas in MT103-205, 49 patients (70%) had only 1 or 2 prior therapies. ELIANA contained only 21% patients with refractory disease compared to 56% of patients in MT103-205. ELIANA required patients to have life expectancy longer than 12 weeks, MT103-205 did not have any such requirements.

Given the aforementioned imbalances in patient characteristics, the indirect treatment comparison needs to adjust for all effect modifiers and prognostic factors as noted in NICE’s recent technical support document on methods for population-adjusted indirect comparisons. This is extremely challenging given ELIANA and MT103-205 studies are single-armed and of very small sample sizes (68 vs. 70 patients), notwithstanding the need to develop an ‘overlapping’ patient cohort due to different patient characteristics. In addition, the paucity of single-arm trials for blinatumomab makes the inference unstable. In choosing comparators, ICER should only use CAR-T therapies and not include blinatumomab.

CONCLUSION

There is a significant unmet need in the ultra-orphan pediatric R/R B-cell ALL population with median overall survival of only 3 months, which is reflected in the granting of Breakthrough Therapy designation for this indication by the FDA. Moreover, it is important to consider the provisions put in place by the Orphan Drug Legislation to protect treatment access for these patients and ensure future innovation. ICER should consider the above recommendations and delay this assessment until there is adequate data, more treatment options and a deeper understanding of pediatric R/R B-cell ALL in order to inform a meaningful assessment that puts the patient at the center.
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9 Novartis. CTL019 (tisagenleucleucel): In pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia. U.S. Food & Drug Administration, Oncologic Drugs Advisory Committee July 12, 2017. [Internet]. Food and Drug Administration website;[cited 25 Aug 2017]. Link
10 U.S. Food and Drug Administration (FDA). The Orphan Drug Act. Relevant Excerpts (Public Law 97-414, as amended) Last updated August 2013. Link
11 Novartis. CTL019 (tisagenleucleucel): In pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia. U.S. Food & Drug Administration, Oncologic Drugs Advisory Committee July 12, 2017. [Internet]. Food and Drug Administration website;[cited 25 Aug 2017]. Link
14 Patient heterogeneity is too extensive to make any accurate value assessments, echoed by oncologists such as Dr. Richard Gorlick, Division Chief, Pediatric Hematology/Oncology, The Children’s Hospital at Monte ore., “The sample size is too small. We can’t see a pattern with 80 samples because the cancer is too complex, perhaps we could see a pattern if our n was 1,000, but we can’t get there with pediatric cancers,” in Op. Cit. Adamson P. et al.2016. p.13. Link
15 Moreover, understanding of chromosomal and molecular abnormalities determining prognosis is shifting so rapidly that ICER’s assessment will be incomplete and outdated even in the 8 months to finalization. See NCCN Clinical Practice Guidelines in Oncology. Acute Lymphoblastic Leukemia. Version 1.2017. June 2017. p. MS7
18 Challenges include the small size of the population, biological /genetic differences between children and adults and the potential long term health impact due to cancer and therapies.
19 Congress created two programs to promote pediatric research on drugs that are otherwise developed for adults. 1) The Best Pharmaceuticals for Children Act (BPCA) provides incentives for drug sponsors to conduct research using their drugs for childhood diseases. The incentive is in the form of an extra six months of market exclusivity for the drug being tested. 2) Congress passed the Creating Hope Act in 2011 which created a priority review voucher program. The vouchers are awarded to newly formulated drugs that treat any rare disease in children (not just childhood cancers). A priority review voucher entitles a company to obtain a short FDA review time cutting it from 10 months to six months. The Advancing Hope Act replaced the Creating Hope Act when it expired in 2016.
20 FDA approvals from 1953 to 2015.
21 FDA. Search Orphan Drug Designations and Approvals [Internet]. Food and Drug Administration;[cited 25 Aug 2017. Link
22 Novartis. CTL019 (tisagenleucleucel): In pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia. U.S. Food & Drug Administration, Oncologic Drugs Advisory Committee July 12, 2017. [Internet]. Food and Drug Administration website;[cited 25 Aug 2017]. Link
24 Breakthrough designation – Congress directed the FDA to establish another program to expedite the development and review of new drugs under Section 902 of the July 9, 2012 Food and Drug Administration Safety and Innovation Act. Congress passed the Orphan Drug Act (ODA) in 1983 in order to promote the development of drugs for indications like B-ALL and clearly define orphan drugs as drugs that treat conditions that affect 200,000 or fewer people in the US. Priority Review was developed under the 1992 Prescription Drug User Act (PDUFA) to ensure that overall attention and resources be given to treatments which treat serious conditions.
25 The goal of the ODA is to provide incentives for manufacturers to develop drugs in conditions that impact a small number of patients as defined as 200,000 or fewer people in the US. Benefits such a reduced “user fees”, tax deductions for clinical trials, grants and market exclusivity are necessary to encourage research but have not been sufficient to encourage significant growth and development in the pediatric oncology space.
26 The Pediatric Research Equity Act (PREA) was made into law to increase the number of drugs by requiring manufacturers who develop drugs that are made for adults, to test them in children as well. Under the current statute, oncology drugs classified as orphan drugs are exempt from the PREA
requirement. Non-orphan cancers such as lung, breast and prostate afflict adults and not children and PREA only requires pediatric studies of a drug in the same disease, which is being studied. Thus due to the orphan disease and indication-based exemptions, PREA has limited impact on childhood cancer drug development.

August 29, 2017
Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Call for Comments on ICER’s Review of Chimeric Antigen Receptor T-Cell (CAR-T) Therapies for B-Cell Malignancies
Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson,

Celgene appreciates the opportunity to provide comments on the draft scoping document for the Institute for Clinical and Economic Review’s (ICER’s) review of Chimeric Antigen Receptor T-Cell (CAR-T) Therapy for B-Cell Cancers: Effectiveness and Value, including tisagenlecleucel-t (CTL-019) and axicabtagene ciloleucel (Axi-Cel [KTE-C19]). Celgene is a global biopharmaceutical company committed to improving the lives of patients worldwide. We seek to deliver truly innovative and life-changing treatments for the patients we serve. With diverse expertise in hematology, oncology and immunology we have approximately 50 compounds in development, including CAR-T therapies, to address approximately 100 diseases.

People are living longer, healthier lives than ever before, and much of the increase can be attributed to innovative medicines\(^1\). As the population ages, the burden of disease continues to increase and scientific advances allow better targeting of diseases, the need to invest in medical innovation has never been more important.

CAR-Ts are an example of medical innovation that can provide tremendous value to patients, caregivers, and the broader healthcare system. They not only have the potential to be transformative for patients, but they may also revolutionize the treatment paradigm in several cancers. The long time horizon over which a patient may experience both disease related and quality of life benefits and the expedited development timelines require special considerations as the value of specific CAR-Ts are assessed.

Consideration of real world data (RWD) is important in the context of assessing value for CAR-Ts. The RWD generated by the healthcare ecosystem is enabling all stakeholders to make more informed decisions across the continuum of care. RWD is reflective of the clear majority of the population as well as real world outcomes, treatment patterns, patient experience and health related quality of life. The generation and acceptance of RWD will be particularly important to understand and measure the value of CAR-T therapies over time. Celgene is committed to working with healthcare stakeholders to harness

RWD and generate insights which are tailored, relevant and meaningful to the individual payers and stakeholders and thus aiming towards making health care more personalized and effective.

**Considerations for ICER’s CAR-T Evaluation**

There are still several ambiguous areas of the scoping document for which ICER should provide more clarity and transparency in its final scoping document. First, throughout the scoping document ICER refers to evaluating CAR-Ts for B cell malignancies in totality, while at other points it refers to specific populations or specific CARTs. For each CAR-T therapy it intends to review, ICER should provide greater specificity on the population to be evaluated including subtypes, line of and types of prior therapy and should delineate the specific PICOTS (population, intervention, comparators, outcomes, timing and settings) in the table for each. The assessment and discussion should be presented in the context of the specific CAR-T therapy. Also, there is mention of manufacturing failure in the list of potential harms that would be considered. ICER should clarify how this will be defined (e.g., a patient not receiving the targeted dose, a patient receiving a dose out of specification, and/or a patient not being dosed at all) and incorporated into the assessment as well as how any costs incurred by the manufacturer if a patient becomes no longer eligible for treatment will be calculated and incorporated into the framework. Further, ICER notes that it will consider “all relevant settings” including inpatient, clinic, and outpatient setting in each review of each CAR-T therapy. Given the multitude of relevant payment systems across payer type and setting of care in the US, which may also differ by CAR-T, ICER should clarify how that will be assessed.

**ICER’s General Approach to Determining Value**

While we agree that it is imperative to support the achievement of the best patient outcomes in the most efficient way, as we have noted in our feedback in ICER’s previous public comment periods on its general methodology we continue to believe that ICER is utilizing an approach and methodology not designed to achieve this purpose.

The ICER value assessment framework and its one-size-fits-all approach does not allow for the numerous factors that must be considered for optimal patient access in the multi-payer system in the US. Each public and private payer in the United States needs to consider the uniqueness of the population it provides benefits for and those individuals’ circumstances when making formulary decisions. Depending on the stakeholders involved and the specificities of the decision-making context they operate within, the elements of value they must consider and the relative importance they attach to each of them are likely to differ. Therefore, it is neither possible nor desirable to develop a quantitative algorithm that would be universal and applicable across drugs, diseases and payers in the US.

**Continued Emphasis on the Use of Quality-Adjusted Life Years (QALYs) in ICER’s Framework**

Cost effectiveness (cost per QALY) analyses, upon which the ICER value assessment algorithm are founded are not appropriate for assessing the value of innovative medicines. We have previously indicated our significant concerns with ICER’s reliance on the QALY metric. Value is a multi-dimensional concept and, therefore, a flexible multi-criteria method for value assessment is required.

While the attempt to consider additional contextual elements is a step toward acknowledging the multi-dimensional nature of value, the subjective nature of how appraisal committees will be asked to vote regarding these contextual considerations is an arbitrary way to incorporate these factors into the QALY thresholds and highlights the inherent challenges of the QALY metric itself.
**Reliance on the budget threshold/cap**

We also continue to have concerns regarding the arbitrary nature of the budget impact threshold. We have previously indicated our concerns that the structure of the budget impact threshold penalizes innovative therapies that meet unmet need and impact significant patient populations. In addition, we remain concerned that the short-term budget impact threshold fails to account for the value that spending on innovative prescription drugs can provide across the healthcare system. We do not dismiss the importance of budget impact to the healthcare system, but the structure of this measurement within the framework does not view budget impact holistically across the healthcare system. Furthermore, the proposal to create an “affordability and access alert” based upon this artificial budget threshold continues to conflate the notions of budget impact and value.

With significantly more new medicines that meet the needs of patients with serious and debilitating diseases being introduced, near-term pressure on healthcare systems’ pharmacy budgets is increasing. Thus, a public discussion on how to best to assess the value of innovative therapies is an important one. Celgene understands the need to ensure that innovative medicines not only meet important clinical endpoints, but also meet important measures of value – both patient value and economic value. When determining value, Celgene considers the following criteria:

- **Patient Benefit**: How well the therapy treats disease, patients’ quality of life while on treatment, any side effects caused by the medicine, and the convenience of taking the medicine.
- **Benefit to the Healthcare System and Society**: The impact of a therapy on society, such as the benefits to the caregiver and family of the patient; the potential reduction in other healthcare costs; the ability to return patients to work; increases in economic productivity; and the overall positive impact of innovation on social and economic welfare.
- **Benefit of Advancing Medical progress in a Disease**: The impact a new treatment can have to cure or manage the disease, the severity and rarity of the disease and the availability of other treatments.

We urge ICER to factor these considerations into its methodology specifically, for the immediate CAR-T review, but also for its broader methodology in general.

Value evolves over time as more evidence is generated via clinical trials and in the real world. It also varies based on the decision makers’ perspective and from stakeholder to stakeholder. We believe that a collaborative approach to working with payers to meet their needs for predictability and stability while ensuring access for patients to transformative treatments, like CAR-T, demonstrates Celgene’s commitment to value based care.

Thank you for the opportunity to comment.

Sincerely,

Richard H. Bagger
Executive Vice President, Corporate Affairs & Market Access
August 28, 2017

Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Via electronic submission: publiccomments@icer-review.org

Re: GSK recommendations on the proposed scope for ICER’s value assessment of CAR-T therapies for B-Cell hematologic malignancies

Dear Dr. Pearson:

GlaxoSmithKline (GSK) is pleased to submit comments on the proposed scope for ICER’s value assessment of CAR-T therapies for B-cell hematologic malignancies. GSK is a science-led global biopharmaceutical company dedicated to improving the quality of human life by enabling people to do more, feel better and live longer. As an industry leader, GSK develops a broad range of innovative products in Pharmaceuticals, Vaccines and Consumer Healthcare. For ease, we have categorized our comments into four core themes as detailed below.

A. HTA Approach

We encourage ICER to reconsider its multiple technology appraisal (MTA) approach to the value assessment of CAR-T therapies, tisagenlecleucel-t (CTL-019) and axicabtagene ciloleucel (Axi-Cel [KTE-C19]). Perceived similarities in the target antigen, manufacturing process, and clinical outcomes between these two agents may confer some potential methodologic efficiencies. However, at the core of this value assessment are separate research questions that reflect distinctly different target patient populations for two very different diseases. These differences require significantly different epidemiologic, clinical, and economic inputs and assumptions.

We concur with ICER’s proposal to assess the ALL and DLBCL patient populations separately, as these populations and their respective places in therapy are distinct. However, combining these two assessments within the same MTA may insufficiently counter the tendency of lay audiences to compare these therapies across and within indications. Additionally, less technical audiences may ignore the important drivers of heterogeneity such as age, cytogenetic markers, and study-related differences. Historically, NICE’s use of a MTA approach has been largely contained to class reviews for a specific indication.\(^1\) This is not coincidental, as well-formed health policy questions and significant comparative evidence are compulsory to manage the scope of the MTA. Moreover, simplicity and clarity in the payers’ decision problem can help to ensure the delivery of useful, evidence-based policy recommendations. In the absence of robust comparative evidence for CAR-T therapies, we believe that combining the assessments of ALL and DLBCL into one MTA will create needless complexity. This approach may also contribute to conflation and misunderstanding of the true benefits and harms to patients amongst healthcare decision-makers.

**Recommendation:** We encourage ICER to revise its approach to the value assessment of CAR-T as two separate single technology assessments (STA) for acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL).
B. Impact of Data Immaturity

The current knowledge base and data supporting the efficacy, benefits, costs, and harms for CAR-T therapies across different B-cell malignancies is both thin and immature. Data immaturity in oncology can dramatically impact regulatory review, value assessment outcomes, and policy recommendations. One example from UK’s NICE is olaparib, which recently had a negative appraisal for the maintenance treatment of BRCA-mutated ovarian cancer reversed. The supporting evidence from the manufacturer included follow-up data from Study 19 (ClinicalTrials.gov Identifier: NCT00753545), additional modeling of long-term survival and sensitivity analyses, and a patient access scheme. With oncology value assessment, the consequences of an initial recommendation that is later reversed can directly impact patient survival. We urge ICER to use its influence to shape how US healthcare stakeholders understand and use uncertainties in evidence. We recommend that ICER formally incorporate value of information or real-options analyses that would help to quantify the impact of data gaps and uncertainties for US decision-makers.3-5

**Recommendation:** Alongside the value assessment of ALL and DLBCL, we recommend that ICER formally incorporate value of information or real-options analyses, which would help to quantify the impact of data gaps and uncertainties for US decision-makers. Minimally, we urge ICER to objectively assess the feasibility of conducting a STA, given the immaturity and scarcity of clinical and economic data on the target US ALL and DLBCL populations.

C. Accounting for the Full Costs and Benefits of Innovative Therapies

GSK believes that the value of innovative therapies should be measured and presented using multiple metrics and perspectives. This approach aligns with the 2nd Panel on Cost-Effectiveness, which has recommended that a societal perspective be a standard complement to a healthcare sector perspective in all US cost-effectiveness analyses. GSK recognizes that methods are still being developed to allow for the full consideration of the 2nd Panel’s recommended non-healthcare factors. These non-healthcare factors, and novel value elements such as patient satisfaction and the value of hope, can’t be adequately quantified by QALY’s or current standardized instruments.6

Despite its limitations, the QALY metric represents one of the most researched and documented tools available to facilitate the value assessment of new health technologies.7-11 Thus we encourage ICER to consider a more holistic position, promoting the use of alternative cost-effectiveness outcomes as a compulsory complement to the cost-per-QALY assessment in this value assessment. For both DLBCL and ALL, one alternative approach may be to consider a cost per quality-adjusted time without symptoms and toxicity (Q-TWiST) analysis as commonly reported symptoms amongst relapsed/refractory patients are fatigue and pain.12,13

We call to ICER’s attention the need for robust estimation of healthcare factors specific to CAR-T, as differences in study design and/or center processes could lead to observed differences in direct healthcare costs incurred by patients who underwent different CAR-T therapies, both in the short and long term. Additionally, we urge ICER to explicitly quantify the indirect costs and gains associated with these indications, not only to patients but care-givers alike. Specific economic impacts resulting from lost productivity, increased absenteeism, transportation to and from office visits/procedures, and others costs can be significantly variable.
Recommendation: ICER should estimate and report a non-QALY based cost effectiveness metric as a compulsory complement to the cost-per-QALY assessment. Alternative and complementary endpoint and outcomes selection for cost-effectiveness analyses should be driven by clinicians or health economic modelers who have deep clinical knowledge of the disease area. Finally, ICER should include a societal perspective in the context of oncology value assessment, including indirect costs and benefits for patients and care-givers.

D. Prioritizing Patient and Care-giver Voices

GSK is committed to championing for meaningful patient engagement and inclusion of patient and caregiver perspectives in value assessment. Our position is aligned to key US recommendations on delivery of quality, patient-centered care.14,15 A growing body of research has shown that patients’ perceptions of healthcare value are highly heterogeneous.16,17 For example, a metastatic cancer patient may set a higher value for a treatment that delivers comparable overall survival but less fatigue so that they may return to work, school or play.18 This is especially relevant for diseases like DLBCL where the average age of diagnosis is 64 years of age. Healthcare value also extends beyond the patient, as care-givers of seriously ill patients experience significant financial and psycho-social burden.19-21 Improvements in patients’ health and outcomes resulting from new therapies may substantially offset unpaid care-giving or loss in care-giver productivity.

We contend that any definition and quantification of healthcare value, in the absence of patient and care-giver perspectives, is fundamentally incomplete. We encourage ICER to consider broader contextual considerations as proposed in the draft ICER value framework for treatments for ultra-rare conditions. CAR-T therapies may not explicitly fit ICER’s criteria as a treatment for ultra-rare disease. Nevertheless, characteristics such as seriousness of the condition, unmet need, and vulnerability of the target patient population (pediatric ALL) are sound reasons for a more holistic value assessment of CAR-T therapies. Overall, the perspectives of patients and care-givers on the value of health technologies should be secured during scoping, evidence syntheses, economic analyses, and reporting.

Recommendation: ICER should recommend the engagement and incorporation of patient community (patients, care-givers, patient advocacy) representatives, throughout the value assessment process, including full membership and voting participation on appraisal committees, irrespective of the perspective of the decision context.

GSK appreciates the opportunity to share our recommendations with ICER. These comments are not exhaustive, and please feel free to contact us should you wish to discuss in further detail.

Sincerely,

Martin D. Marciniak, Ph.D.
Vice President, US Medical Affairs, Customer Engagement, Value Evidence and Outcomes
References


9. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Initiative on US Value Assessment Frameworkshttps://www.ispor.org/ValueAssessmentFrameworks/Index


Dear Dr. Pearson,

Juno Therapeutics, Inc. (Juno) appreciates this opportunity to provide comments on the Institute for Clinical and Economic Review’s (ICER) draft scoping document entitled “Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value” focusing on two specific CAR-T therapies, including tisagenlecleucel-t (CTL-019) and axicabtagene ciloleucel (Axi-Cel [KTE-C19]) that was published on August 9, 2017.

At Juno, we have a bold mission - a quest to radically change the course of medicine. We are aligning our investments in scientific research, manufacturing, and most of all, people to change the way cancer and other serious diseases are treated. Juno is building a fully integrated biopharmaceutical company focused on progressing innovative cellular immunotherapies for the treatment of cancer. Juno is developing cell-based cancer immunotherapies based on chimeric antigen receptor and high-affinity T cell receptor technologies to genetically engineer T cells to recognize and kill cancer (CAR-T therapies). More specifically, Juno is developing multiple cell-based product candidates to treat a variety of B cell malignancies as well as multiple solid tumors.

The ICER draft scoping document has several issues that introduce uncertainty into how the evaluation is to be conducted, which may compromise the review and the robustness of the findings. As Juno continues to develop CAR-T therapies to treat various tumor types, manufacturers hold significant responsibility in the establishment of how a CAR-T therapy’s value is evaluated. Summarized below are issues with ICER’s draft scoping document and recommendations on how to address these concerns to align with technology assessment standards and practices.

Issues and Recommendations:

1. **The proposed evaluation is premature.** The current regulatory status and final indications including specificity on the populations, place in therapy (line of therapy, prior failures), efficacy and safety are lacking finalization as well as public sources to assess validity of the ICER evaluation. In addition, the data and evidence of the potential of CAR-T therapies on long-term benefits and durability of outcomes require additional evidence that has yet to be disseminated.

   **Recommendation:** Delaying such an evaluation may allow for greater time to capture more evidence on long-term outcomes, but will also ensure the final efficacy and safety profile is known. Most importantly, the place in therapy and indication will be established and, given the focused and targeted use of CAR-Ts, such a gap in this information may result in misinterpretation of the findings when the review is conducted out of context from the likely real-world place in therapy.

2. **Evaluating Two Different Cancers in One Review.** The structure of the scoping document as one of the first to include two distinct populations lacks clarity on differentiating the scope, methods and analyses for R/R ALL and R/R aggressive lymphoma given key differences in patients, unmet need, prognosis and
treatments. The combination of diseases as stated is not in line with other established value assessments like
the NICE evaluation of CAR-Ts, which focused on ALL1 or past ICER reviews such as the report on
comparative clinical effectiveness and value of poly (ADP-ribose) polymerase (PARP) inhibitors for
treatment of ovarian cancer2, the report on tyrosine kinase inhibitors and immunotherapies (PD-1 or PD-L1)
for the treatment of NSCLC3, and the report on various novel agents for treatment of relapse or refractory
multiple myeloma.4 Traditional value assessments focus on a specific technology and disease state. The
proposed scoping document is significantly broader in reach, introducing challenges to interpretation and
unintended consequences for patient access.

**Recommendation:** It is recommended the scoping document and ultimately the reviews be split into two
mutually exclusive evaluations, which provides more detail and clarity into the assumptions surrounding the
R/R ALL and R/R aggressive lymphoma populations.

3. **Populations Lack Specificity Introducing Uncertainty in the PICOTS Framework.** The proposed
populations lack specificity as it relates to the R/R aggressive lymphoma subtypes to ensure the evaluation
aligns with the trial populations, intended indications and use in the real world. Specifically, the focus
among R/R aggressive lymphoma as it relates to subtypes such as Diffuse Large B-cell Lymphoma, is
unknown. Additionally, the line and types of prior therapies to be evaluated are unclear.

**Recommendation:** The scoping document requires additional detail to better understand the specific R/R
aggressive lymphoma subtypes to be evaluated and the planned clinical and economic comparisons that will
be undertaken. Previous ICER reviews like multiple myeloma used a focused approach by line of therapy.4
This detail should be considered within the CAR-T scoping document as the population drives the selection
of comparators.

4. **Comparators are Limited and Lack Alignment to Line of Treatment.** The comparators proposed for
both R/R ALL and R/R aggressive lymphoma cross multiple lines of therapy. For R/R ALL, a therapy like
Blincyto® may be considered 3rd line while others are 2nd line.5 Clarity is needed on whether the evaluation
will be specific to line of therapy when selecting efficacy data and comparators. For R/R aggressive
lymphoma, the SCHOLAR-1 study is a mix of 2nd and 3rd line patients and includes patients who failed
transplant.6 NCCN therapies mentioned may not be most common 2nd or 3rd line therapies, which may
include R-ICE and R-DHAP.7-9

**Recommendation:** The comparators for both R/R ALL and R/R aggressive lymphoma require expansion to
other regimens as well as alignment to the line of therapy to be evaluated. Value assessments should compare
closer therapies to a standard of care for a given population. To date, R/R aggressive lymphoma treatments
vary by line and subtype and the outcomes vary as well. To provide the appropriate comparators, the scoping
document requires further feedback upon finalizing the exact types of R/R aggressive lymphoma to be
evaluated.

5. **Clinical Comparison Methods May Not Be Viable.** The suggestion to identify head-to-head studies
requires reevaluation given the known evidence is premature and are single-arm in origin. The use of
historical controls from the SCHOLAR-1 study may not be appropriate and representative of the R/R
aggressive lymphoma populations evaluated for treatment with KTE-C19 or CTL-019.6

**Recommendation:** The scoping document and potential evaluations should clearly lay out the methods and
variables for making indirect comparisons to comparator therapies. The methods must clearly establish how
such studies will addresses differences in patient populations. Transparency and assumptions surrounding
such comparisons should be clearly laid out in the scoping document to allow feedback prior to evaluation
and the draft report.
6. **The Economic Comparisons Are Not Optimal as They are Generalized Across Indications.** The proposed models based on the NICE ALL evaluation\(^1\) may not reflect the actual indication for CTL-019\(^10\). The NICE model was a hypothetical mock assessment with a focus on R/R ALL, not R/R aggressive lymphoma. Such a model structure may not be optimal for R/R aggressive lymphoma given differences in patient types and prognosis. The inputs, benefits, and risks cannot be generalized across disease states as proposed.

**Recommendation:** It is recommended the scoping document provide further clarity on the modeling approaches with a clear distinction by disease state. It would be optimal to see the proposed economic comparative analyses presented as separate sections by disease state or the evaluation of CAR-T be conducted by disease states, which is in line with most value assessments methods and practices used by ICER in the past.\(^3-5\)

7. **The Economic Model Inputs Are Disconnected from Other Sections.** The focus of the models solely on direct medical costs does not reflect the patient input on the value of reducing toxic side effects that impact quality of life and other indirect non-health related outcomes. The setting of use is also not discussed and needs careful consideration given the health-system perspective will vary by site of care with a combination of different payment mechanisms. Lastly, the mention of manufacturing failures as a key harm lacks connection to other relevant sections within the scoping document, specifically the economic modeling.

**Recommendation:** The stakeholder rationale such as adverse event avoidance and the indirect benefits to patients should be included. The value of manufacturing should also be considered in the economic comparisons and not only focus on the risk of failures, but also consider the benefit of efficient production. The benefits of optimal manufacturing may result in reductions in mortality, reduced hospitalizations and utilization of chemotherapy.

**Conclusion**
Juno urges ICER to address the above-noted issues that may compromise the entire evaluation. Ensuring such an evaluation is not completed until more evidence is available represents the most scientifically sound approach by ensuring an understanding of the evidence package and final regulatory standing is known. In addition, focusing the evaluations to unique disease states, one for R/R ALL and a separate evaluation for R/R aggressive lymphoma is warranted. This will capture the differences that exist in the patient populations, burden of disease and unmet need prior to assessing the value of a specific CAR-T is a necessity. Population specificity is a common characteristic of any value assessment that focuses on a technology of interest. The combination of diseases within a single review and premature nature of the evaluation introduces the potential for unintended consequences that may put patients at the greatest risk due to conclusions being taken out of context. A more disease-specific value assessment that is conducted with a more complete evidence package including real world use will improve the alignment of the rationale to the scope and proposed methods.

Sincerely,

Robert Azelby
Executive Vice President
Chief Commercial Officer
References


August 29, 2017

Kite Pharma thanks ICER and CTAF for the opportunity to comment on the scoping document for the review of CAR T therapies for B-cell cancers. Current treatment practices for patients with refractory aggressive non-Hodgkin Lymphoma (NHL) produce consistently poor outcomes, indicating considerable unmet need for this population.¹,²

Axicabtagene ciloleucel (axi-cel) is currently being reviewed by the FDA for the treatment of aggressive NHL. While the indication is still pending, axi-cel is currently expected to treat a very small population of lymphoma patients (approximately 7400 patients¹). The pivotal trial for axi-cel, ZUMA-1, remains unique in its target population for CAR T, specifically patients with refractory aggressive NHL, which includes (diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), or transformed follicular lymphoma (TFL)).³ In clinical trials, axi-cel has demonstrated rapid and durable responses at unprecedented rates (82% overall response rate; 39% ongoing complete response) for this population. The therapy is delivered in a single infusion, and demonstrated a 99% manufacturing success rate in the pivotal trial, with an industry-leading 17-day median turnaround time between apheresis and delivery back to clinical site.³

Below we provide suggestions for the analysis of CAR T treatments, based on ICER’s scoping document. Kite looks forward to working with ICER to further clarify details of the scope and analysis, to ensure appropriate evaluation of axi-cel.

**VALUE FRAMEWORK: Apply ultra-orphan framework to axi-cel**

Axi-cel should be assessed under ICER’s ultra-orphan framework, as we expect axi-cel will treat approximately 7400 patients¹ given 1) the target population from ZUMA-1; and 2) outcomes in ZUMA-1 suggest the potential for major life-years gained relative to the SCHOLAR-1, the historical benchmark for this population.

**Recommendation**: Apply ICER ultra-orphan framework to axi-cel.

**POPULATION: Alignment with axi-cel target population**

Adequate evaluation of axi-cel requires the therapy be assessed in the appropriate population, the ZUMA-1 clinical trial. To align with the trial, ICER should evaluate axi-cel in the following population only: adult patients with DLBCL, PMBCL, or TFL who are refractory as defined by either refractory to their last line of chemotherapy as defined as progressive disease (PD) or stable disease (SD) as best response to chemotherapy, OR relapse within 12 months of receiving autologous stem cell transplant (ASCT). This definition aligns with ZUMA-1 and the SCHOLAR-1 study, a key source of outcomes evidence for the axi-cel target population.¹,³

**Recommen**dation:

1. The relevant target population for the evaluation of axi-cel aligns with the study population in ZUMA-1 and SCHOLAR-1: Adult patients with DLBCL, PMBCL, or TFL who are
refractory as defined by either refractory to their last line of chemotherapy as defined as PD or SD as best response to chemotherapy OR relapse within 12 months of receiving ASCT.

2. Remove the criterion “ineligible for ASCT” for the evaluation in lymphoma

**INTERVENTION: Treatment intent of axi-cel**

ICER indicates that interventions will be evaluated as (1) treatment with curative intent and (2) as a bridge to ASCT (page 6). This framework is adopted from Hettle et al. (2017), which was focused on evaluation of CAR T in pediatric acute lymphoblastic leukemia (ALL). However, CAR T treatment intent differs between NHL and ALL, as demonstrated by the different clinical trial constructs between the disease areas. Only 3% of ZUMA-1 subjects underwent allogeneic SCT (2 in partial remission; 1 in complete remission). No subjects underwent autologous SCT after responding to initial axi-cel infusion. Bridge to SCT is not representative of the clinical course of the ZUMA-1 population, and should not be a focus of the evaluation of axi-cel. Given the differences between the two CAR T therapies and their likely use, we request ICER clearly separate the analyses of the interventions in the Evidence Report, to clarify that axi-cel and CTL-019 are currently being reviewed for distinct populations.

**Recommendation:**
1. Evaluate axi-cel as treatment with stand alone therapy, not as a bridge to SCT.
2. Clearly separate axi-cel and CTL-019 in text on research question, results, and interpretation

**INTERVENTION: Axi-cel has demonstrated a durable response**

Page 2 of the scoping document notes “…questions remain regarding the durability of their [CAR T] effects.” Two studies have demonstrated the durability of response to axi-cel. Follow-up from two Phase 1 studies found durable CR as far out as 22+ and 56+ months, respectively.4,5

**Recommendation:** Remove statement “questions remain regarding the durability of their effects.”

**INTERVENTION: Long-term data for axi-cel**

Long-term data are currently being generated for axi-cel. One-year follow-up data is planned to be presented at a medical congress in Q4 2017.

**Recommendation:** Use results from one-year follow-up data after the presentation in Q4 2017.

**COMPARATORS: Use SCHOLAR-1 to capture comparators**

Assessment of axi-cel requires the use of comparators representative of current practice in refractory lymphoma. As demonstrated by the SCHOLAR-1 study, there currently exists no standard of care for patients with refractory lymphoma.1 These patients undergo a multitude of therapies – for example, 69% of ZUMA-1 patients underwent 3+ prior therapies and 53% were refractory to 2 or more consecutive lines of therapy.3 The treatment regimens vary widely among patients and represent a compilation of NCCN salvage therapies. Despite this diversity, the limited efficacy of existing treatments is well-demonstrated in SCHOLAR-1. We therefore suggest that SCHOLAR-1 be used as the sole reliable source for efficacy of the relevant comparators for axi-cel.

**Recommendation:** Use SCHOLAR-1 as the source for the efficacy of axi-cel’s relevant comparators.

**OUTCOMES: Incorporate outcomes suitable for analysis of lymphoma**
The scoping document omitted duration of response (available from ZUMA-1) as an outcome (outcomes table, p. 5), which may be considered for ICER’s evaluation of axi-cel’s comparative clinical effectiveness. Complete response with incomplete blood count recovery is not relevant for lymphoma.

**Recommendation:** Consider including duration of response, and excluding complete response with incomplete blood count recovery, in comparative clinical effectiveness analysis for axi-cel.

**OUTCOMES: Improve accuracy and representativeness of adverse events (AEs)**

Cost and utilities of adverse events (“Key Harms”) vary substantially depending on the severity of the event. Also, not all cases of cytokine release syndrome (CRS) require intensive care unit admission, a major component of cost. Thus, grade 3 and 4 CRS and neurotoxicity should be accounted for separately from less severe cases. Further, valid evaluation of axi-cel requires inclusion of major AEs associated with comparators, particularly those that are less likely under treatment with axi-cel. Examples include Graft-versus-host Disease subsequent to allo-SCT or neuropathy subsequent to cisplatin.

**Recommendation:** Separate grade 3 and 4 CRS and neurotoxicity from less severe cases, separate AEs by need for ICU admission, and include additional AEs specific to lymphoma treatments.

**COST-EFFECTIVENESS MODEL: Base model on OS and PFS**

To assess good value for money in oncology, OS and PFS are appropriate endpoints in a cost-effectiveness model. If a comparison is made in terms of response, ICER should utilize the available trial data as per the clinical trial design and disease indication. Therefore, axi-cel should be evaluated for best-overall response post-infusion as per the trial protocol, as opposed to 3 months post-infusion (page 6).

**Recommendation:** CE model should be based on OS and PFS, which are required for the partition survival modeling proposed.

**COST-EFFECTIVENESS MODEL: Ensure clinical validity of long-term extrapolation**

ICER notes that “Parametric survival modeling will inform the five-year post-infusion survival estimates” (page 6). Hettle et al 2017 have suggested that conventional parametric modeling using certain distributions such as exponential, Weibull, or log-normal may not adequately capture the hazard function for treatments with curative intent, or regenerative treatments. We want to emphasize that clinical validity should be the guiding principle for the extrapolation of long-term survival outcomes and caution against over-reliance upon model-fit statistics.

**Recommendation:** Ensure clinical validity when selecting a method used for the long-term extrapolation of survival beyond the available empirical evidence in ZUMA-1 and SCHOLAR-1.

**COST-EFFECTIVENESS MODEL: Cure rate for lymphoma occurs before 5 years**

We do not agree with the 5-year cure assumption. As shown in SCHOLAR-1, the Kaplan-Meier curve for overall survival in the axi-cel target population starts to stabilize much earlier – closer to 2 years (Figure 3). Although for a slightly different population, Maurer et al. also published a pivotal paper in JCO in 2015 reporting that first-line DLBCL patients achieving 24-month event-free survival have long-term life expectancy comparable to the age-adjusted general population.

**Recommendation:** Infer cure rate from SCHOLAR-1, with death hazard stabilizing near 2 years.
REFERENCES


Response to ICER’s Draft Scoping Document regarding Chimeric Antigen Receptor T-Cell Therapy for B-cell Cancers

Novartis appreciates the opportunity to provide comments on the Chimeric Antigen Receptor T-Cell Therapy (CAR-T) scoping document, and recommends the following considerations to be taken into account when finalizing the scoping document.

Comments: In the scoping document, ICER states “There will be two separate populations of interest, including: 1) pediatric and young adult patients with relapsed/refractory B-ALL (CTL019, Novartis), and 2) adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma (KTE-C19, Kite Pharma).”

We agree with ICER’s approach that CTL019 will be evaluated in B-cell acute lymphoblastic leukemia (B-ALL), and that KTE-C19 will be evaluated in aggressive B-cell non-Hodgkin's lymphoma (NHL).

Model approaches: When developing the analysis plan and models for evaluation, ICER should:
(i) only consider “the curative intent” model structure for B-ALL evaluation, (ii) replace the incremental cost per responder by an outcome reflecting durability of response, and (iii) clarify how efficacy extrapolation will be conducted and specify the exact inputs that will be used in the model.

Cost effectiveness model structure:
In the scoping document, ICER references the mock health technology assessment published by the National Institute for Health and Care Excellence (NICE)¹ and proposes to model CAR-T using two approaches: “treatment with curative intent”, and “as a bridge to stem cell transplantation (SCT)”. We agree with the approach of referencing the NICE model and recommend only using “the curative intent” model structure for the following reasons.

- First, the curative intent structure includes the patient subgroup that receives subsequent SCT. This approach incorporates efficacy, cost, and disutility associated with subsequent SCT. The effect of subsequent SCT is captured in the overall survival (OS) estimates within this model. The cost and disutility of subsequent SCT can be incorporated to the model separately for the patient subgroup who received SCT.
- Second, the mock assessment was published in 2015 when long-term data on CAR-T was still limited, however, the long-term data are now available for CTL019 in the B-ALL population which including OS data beyond 3 years and proportion of patients receiving subsequent SCT.² These data will allow ICER to model the long-term OS and the impact of subsequent SCT on efficacy and cost using data directly from clinical trials.
- Third, the proportion of patients receiving subsequent SCT is low (<15%) in CTL019 trials, and therefore a model focused on bridge to SCT is not consistent with the current clinical trial experience.³

Incremental cost by outcome:
In the scoping document, ICER states, "Each intervention will be evaluated in terms of the proportion of responders through three months post infusion... Results will be expressed in terms of the incremental cost per responder." We recommend replacing incremental cost per responder by an outcome incorporating durability of response for the following reasons.

- First, majority of CAR-T cost occurs in the first month due to one-time administration whereas the costs for comparators incur over time, especially regarding the cost of subsequent SCT.
Thus, the cost per responder outcome would not fully capture downstream costs of comparators.

- Second, the proposed responder rate measured through 3 months post-infusion would not capture the durability of response, and would not reflect long-term treatment benefits. Therefore, the incremental cost per responder is not a metric that can effectively be used to assess the value of CAR-T versus its comparators in B-ALL.

We would suggest ICER consider alternative measures that can effectively address the durability of response.

**Long-term OS modeling:**

In the scoping document, ICER states "Parametric survival modeling will inform the five-year post-transfusion survival estimates. Mortality after five years for the alive and event-free health states will be based on general population age- and sex-adjusted all-cause risks of mortality." We agree with the proposed approach in general. The morality risk after five years should be modelled based on the mortality of the general population, adjusting for excess mortality of long-term survivors of ALL using the standardized mortality ratio (SMR) approach. The same adjustment approach was explored by the mock health assessment published by the NICE.\(^1\) We recommend that ICER considers Armstrong et al. (2016) to inform the SMR of long-term survivors of ALL patients (15.2 for ALL patients, per the publication's Appendix).\(^4\) Armstrong et al. is a recent US-based study that evaluated late mortality of 5-year survivors of childhood cancer, including ALL, and the SMR reported in the study was age- and sex-adjusted against the general US population.\(^4\)

**Utility:**

The mock health assessment published by the NICE also provided valuable inputs for utilities of health states that were identified via a systematic literature review study and other relevant inputs.\(^1,5\) Thus, we would suggest that ICER leverage these utility inputs from the NICE model.

**Comparators in B-ALL population: Novartis recommends removing tyrosine kinase inhibitor (TKI)-based chemotherapy as a comparator.** In the scoping document, ICER states that the relevant comparators for R/R B-ALL include "clofarabine, tyrosine kinase inhibitor-based chemotherapy, or blinatumomab as a bridge to stem cell transplant." We agree that clofarabine and blinatumomab are relevant comparators. However, per the 2017 NCCN guideline for ALL, TKI plus chemotherapy is recommended as frontline or second-line treatment for the Philadelphia chromosome-positive (Ph+) subtype of ALL.\(^6\) Ph+ ALL is rare among pediatric patients, with a frequency of <5%.\(^7\) In the CTL019 registration trial (ELIANA), only 2 of 68 infused patients had Ph+ ALL.\(^3\) Therefore, we propose not to use TKI-based chemotherapy as a comparator in this population.

**Comparators in aggressive NHL population: Novartis recommends not considering second-line therapies as comparators.** In the scoping document, ICER states that the relevant comparators for the R/R aggressive NHL population include "salvage chemotherapy regimens such as those used in the SCHOLAR-1 study or second-line therapies recommended by NCCN guidelines such as gemcitabine, dexamethasone, and cisplatin (GDP) as a bridge to stem cell transplant." We agreed that salvage chemotherapy specified in the SCHOLAR-1 study is an appropriate comparator. However, relevant comparators such as GDP should be compared at third-line or later in this assessment. In the Phase II trial ZUMA-1, KTE-C19 was evaluated in R/R aggressive NHL patients who did not respond to last chemotherapy or relapsed within 12 months of autologous SCT.\(^8\) Over 77% of enrolled patients had failed ≥2 lines of treatment, and 69% had ≥3 prior lines of therapy before KTE-C19 infusion.\(^8\)
conclusion, the efficacy of comparators should be evaluated in a population that is comparable to that of KTE-C19.

**Clarification on CTL019 distribution, cost and adverse events:** For CTL019 therapy, Novartis will cover costs of apheresis, cryopreservation, and transportation of the cells, and will not charge for manufacture failures. Therefore in the economic model, there will be no CTL019 charges to healthcare system or patients for manufacture failures. Additionally, with continuous process improvements, manufacturing success rate improved to 97% in recent batches (as of July 2017). ICER considers "discontinuation due to adverse events" as a key harm to be evaluated. Because CTL019 is intended as a one-time administration, discontinuation due to adverse events is not relevant. We would appreciate if ICER can clarify that this metric will only be considered for comparator treatments.

**Ultra-rare condition:** ICER should apply "ultra-rare condition" criteria when evaluating CAR-T in B-cell cancers. In the scoping document, ICER states that the "ultra-rare condition" criteria will not be employed for CAR-T review, due to the expectation that the target populations for CAR-T will expand beyond the relapsed and/or refractory subsets. We request that ICER reconsider this position. Three criteria are provided by ICER for an "ultra-rare condition": (1) the treatment is envisaged for a patient population ≤10,000, (2) there is little chance of future expansion that would extend the size of treatment population >20,000, and (3) the treatment offers a major gain in the length and/or quality of life. We believe CTL019 meets all the above criteria. CTL019 is currently under evaluation by the FDA for the treatment of pediatric and young adult R/R B-ALL patients. Using an incidence estimate of 0.003% for ALL and a rate of 82.5% for B-cell, an estimated 2,691 patients between the ages of 3-25 years have newly diagnosed B-ALL in the US. Of these, an estimated 551 patients (20.5% of B-ALL patients) will ever become R/R after initial treatment. CTL019 will likely be reserved for those who are refractory or who have failed two lines of treatments in the initial indication, thus, the estimated treated population would be well beneath 10,000 threshold. The precise CTL019 label indication is under FDA review. Novartis will share the label when finalized.

In addition, at the time of approval for future indications, there will be additional pricing considerations and the assessment should incorporate the latest efficacy, safety, and indication data. Any future indications will also be assessed at the relevant prevalence and incidence rate of the indication approved. Given that the likelihood of future indications and the related pricing strategy is unknown, pricing evaluation based on the demonstrated data for the current indication only is warranted. Lastly, CTL019 has demonstrated promising efficacy results for B-ALL patients in its Phase I/II trials, and has offered major survival and quality of life benefits for the indicated population.

**Recommendation:** Novartis recommends that ICER involves clinical experts who have experience with CAR-T therapies in both the clinical and economic evaluations. Novartis will, to the extent feasible, provides ICER with information related to the efficacy, safety, and resource use of CTL019. However, the input from clinical experts with CAR-T expertise would be valuable for the current evaluation given the novel mechanism of action of CAR-Therapies. We are happy to provide recommendations on CAR-T experts if needed.

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References


August 27, 2017

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The American Society for Blood and Marrow Transplantation (ASBMT) is an international professional membership association of more than 2,200 physicians, scientists and other healthcare professionals promoting blood and marrow transplantation and cellular therapy research, education, scholarly publication and clinical standards. ASBMT is dedicated to improving the application and success of blood and marrow transplantation and ensuring access to all patients who need hematopoietic cell transplants and other cellular therapies, such as Chimeric Antigen Receptor T Cell (CAR T) therapies. ASBMT members will be the primary group of clinicians initially administering CAR T therapy to patients in the clinical setting and have been heavily involved in the design and administration of the clinical trials associated with these products.

**ICER Request for Public Comment:**
**CAR T for B-Cell Cancers: Effectiveness and Value Scoping Document**

ASBMT appreciates the opportunity to comment as an identified stakeholder on ICER’s planned process for evaluating the value and effectiveness of CAR T in the context of the initial anticipated approvals for treatment of B cell cancers.

**Overall, ASBMT feels that an assessment of the economic value of CAR T is premature.** ICER states in the scoping document that it will “evaluate the health and economic outcomes of CAR-T therapy for B-cell cancers” (p. 3). While ASBMT agrees that a technological advance such as CAR T, in combination with the expected high prices of the products, seems well suited for health economics evaluations, we do not feel that this evaluation should take place until at least one full year after FDA approval. Waiting until at least one year of post-approval data is available, and ideally for at least two separate CAR T products, will allow for much more robust cost and utilization data to be analyzed alongside a clearer non-trial patient population. This delayed timeframe will allow for the integration of CAR T into clinical pathway structures in a way that creates a more accurate set of comparators to be used within an evaluation. Finally, this temporary delay allows for the potential that efficiencies in the manufacturing and delivery process may be found that will reduce costs or health care interactions. Manufacturers will likely find improvements within the manufacturing and delivery processes and clinicians will become more proficient at the therapeutic process, reducing unnecessary costs that may be inflated during the immediate post-approval timeframe. More accurate cost and utilization data
for complications – such as the use of post-infusion immunosuppression or long-term supportive intravenous immunoglobulin (IVIG) – will be available after the initial learning curve of all involved parties. Particularly because of the focus on cost effectiveness and economic value in ICER’s analysis, allowing for costs and utilization across the treatment continuum to “settle” is crucial. It would be unfortunate for an assessment to be conducted at this early point in the lifecycle of CAR T as an intervention; due to the reality of basing evaluations on limited clinical trial information, both clinical and cost data will be incomplete and, subsequently, inaccurate. We ask that ICER suspend the evaluation of CAR T until at least one year after FDA approval of a CAR T product, when more extensive data will be available.

Additional Technical Notes on the Scoping Document

Identification of Low-Value Services: For those patients that experience remission or a complete response, “low-value” service elimination includes of repeated visits for administration of palliative-intent chemotherapy, as well as care services associated with ameliorating the complications and side effects of the chemotherapy.

Populations: The two populations being addressed by the respective products are extremely different and will need to be evaluated completely separately. The scoping document implies that CAR T therapies are relatively uniform products with different disease targets, yet it is becoming increasingly clear through study updates and reports that the manufacturing processes have significant differences that are resulting in both product differences and corresponding variances in outcomes, toxicities and duration. These manufacturing processes influence the timelines for when a patient can have their T cells collected and subsequently infused, which impacts the eligibility of certain patient subpopulations. Additionally, the high likelihood that the B-cell lymphoma population will be skewed towards older adults implies an elevated rate of current comorbidities and past history of disease that could complicate predictions of long-term outcomes.

Comparators: It should be noted that for the pediatric ALL population, autologous HCT is rarely utilized; the analysis should focus on Allogeneic HCT as a comparator.

Outcomes: Novartis’ CTL019 patient population will be largely pediatric and a gain of high quality years of life will be extremely important to all stakeholders. The target population for AxiCel is significantly older, with many patients in the Medicare population, and these adults could be assessed for return to work or return to usual activities in addition to the proposed clinical outcomes. Finally, the subtypes of diseases being targeted by the individual products may mean that certain types of complications or side effects may be more or less common; the analyses should call these out and address them separately while incorporating this information.
**Timing:** ASBMT feels that economic value analyses should be based on studies or clinical data with a longer median duration than 3 months. A significant aspect of the importance of CAR T is the potential for long-term remission (multiple years) and, possibly, long-term complications.

**Settings:** We agree that all settings should be considered but note that the first two products will likely be significantly limited to 20 or fewer facilities and the vast majority (95%+) of therapeutic administrations will be performed in the inpatient setting. Patients will need to be economically secure enough to travel to these locations for care, incurring significant out-of-pocket cost, or their insurance providers will be responsible for these costs in addition to the costs of inpatient treatment. Within the next 1-3 years, CAR T is expected to at least partially transition to the outpatient and/or observational inpatient setting. Cost analyses performed at this point in time will reflect an almost exclusively inpatient care experience and the corresponding cost burden.

**Comparative Value:** We do not dispute the modeling structures being proposed but reiterate that the early clinical and cost/utilization data that could be extrapolated into the described models will not reflect the real-world experience of these products until at least 1 year after FDA approval.

**Summary**

The ASBMT greatly appreciates the opportunity to provide input to ICER’s proposed evaluation of CAR T. ASBMT peer-elected leaders, member clinicians and policy staff are available as a resource when HCT and other cellular therapies are being discussed. Please do not hesitate to reach out whenever we may be of assistance.

Krishna Komanduri, MD  
ASBMT President, 2017-2018

Health Policy Staff Contact:  
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August 28, 2017

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RE: Draft Background and Scope Document—Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value

Dear Dr. Pearson,

On behalf of the Cancer Support Community (CSC), we appreciate the opportunity to provide the following comments regarding the Institute for Clinical and Economic Review’s Background and Scope Document on Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value:

Relevance and Timeliness of Evaluation
The FDA Oncologic Drugs Advisory Committee (ODAC) recommended FDA approval for the first CAR-T therapy (Novartis’ CTL019) on July 12, 2017. The FDA is expected to render a final approval decision around October of this year. CAR-T therapies have only been studied in clinical trials and while they do potentially hold promise for patients, ICER is prematurely evaluating value based on the endpoints of overall survival, relapse-free survival, complete response, overall remission rate, event-free survival, and quality of life. Further, as scientific evidence evolves and new treatments and devices are introduced, it is incumbent that any value assessment be updated to reflect the most up-to-date evidence. With cutting edge technology, we can only expect the administration of CAR-T therapies to be reduced over time. CSC recommends the following:

1. Allow sufficient time for new therapies to be studied in both clinical and real-world populations before rendering a value assessment.
2. Revise assessments on a regular basis when new evidence becomes available and previous information becomes outdated.
3. Provide transparent and specific guidance for assessment updates to reflect the evolution of scientific evidence and introduction of new treatments and devices.

Process for Patient Representation
ICER states that this background and scope document was developed with input from key stakeholders and CSC appreciated the opportunity to engage with ICER via a conference call on July 26, 2017 whereupon CSC repeatedly stated that this analysis was premature, as noted above. Additionally, CSC offered ICER the expertise of a patient panel which the organization has not
utilized. While we do have “hope that CAR-T therapy would offer improved survival” there is currently not enough information to determine the impact of these therapies on quality of life as stated on page 2 of the scoping document. Although ICER did engage our organization prior to development of this document, we do not feel that our comments were meaningfully incorporated. CSC recommends the following:

1. Include a sufficient number of diverse patient representatives (throughout the entire value assessment process) who have experience and knowledge of that specific disease state.
2. Provide patient representatives with information in a transparent, timely, and understandable manner. CSC would be pleased to work with ICER to pilot such information.
3. Allow patients and patient advocacy organizations ample time and opportunity to present the results of their evidence generation and ensure that this happens before the first draft document is released. If their feedback is not incorporated in a meaningful way, note the reasons why.

Concept of Value
It is critical to clearly delineate the differences between the concept of “value” as it pertains to medical treatments and devices, and assessment based primarily on the financial implications of those treatments and devices. ICER identifies the “primary anchor” of the value framework, which is “long-term value for money.” This is bolstered by the complementary perspective of “short-term affordability.” Although cost-effectiveness is a reasonable endpoint in the value discussion, the use of budget impact is inappropriate.

While the short- and long-term financial impacts of drugs and devices are clearly important to consider, there are other aspects of value that are critical to include in any comprehensive “value assessment.” Meaningful patient and stakeholder representation is vital to all institutions determining value, including ICER. Any value framework cannot be a one-size-fits-all approach and the concept of value must be broader than budget impact and cost containment. Patients make different determinations regarding what they value most throughout their illness and service journeys. This is evident in incremental gains for patients who are coping with particularly deadly diseases. CSC recommends the following:

1. Limit inclusion of budget impact in the final value assessment, but rather report it as one endpoint.
2. Recognize value beyond 5-year timeline including late and long-term benefits and effects.
3. Include and apply weights to user preferences. Ensure that user preferences are appropriately reflected in final assessment.
4. Include value endpoints that are important to patients.

Evidence, Outcomes, and Quality of Life
Patient-definitions of value must be included in any assessment. Outcomes should be important to patients and capture their experiences. While we appreciate ICER’s use of health-related quality of life, we ask that additional patient-defined outcomes be included in the assessment. These should be aligned with the list of “other benefits and disadvantages” and “other contextual considerations” that were included in the 2017-2018 ICER Value Framework update. Infections,
secondary cancers, and failed CAR-T therapy manufacturing process are by no means the only quality of life key outcomes. CSC recommends the following:

1. Ensure transparency at each point of the methodological process including not only the specifics of the method but also the rationale behind the choice and literature to support those decisions.
2. Include a balance of data derived from controlled clinical trials (including observational trials) and real world evidence including data and information from patient and patient advocacy groups.
3. Create principles to ensure that the use of data meets a high level of scientific credibility.
4. Provide a transparent a priori statement of key assumptions.
5. Include weights to accommodate varying user preferences.
6. Incorporate a timeframe that is sufficient to reflect the full range of immediate and late-and long-term treatment benefits and effects.
7. Ensure that outcomes reflect patient experiences and preferences.
8. Utilize patient registries and survey databases to explore and incorporate patient experience data.
9. Incorporate review and approval from multidisciplinary, disease-specific experts.
10. In addition to the ICER-defined “other benefits and disadvantages” and “other contextual considerations” the concepts of “financial toxicity” and “costs associated with late and long-term side effects” should be included in outcomes.

Unrealistic Timeframe to Respond
The timeframe to read, consider, and respond to ICER documents continues to pose a challenge to many organizations and individuals who wish to respond. As noted in previous comment letters to ICER, CSC recommends the following:

1. Provide ample time (at minimum 60 days) to respond to any document included in the value assessment process.
2. Allow stakeholders to submit comments in PDF form.
3. Post all stakeholder comments to all documents on ICER’s website in perpetuity.
4. Allow for comment documents of any length.
5. Incorporate comments from stakeholders into documents or provide rationale why feedback was not incorporated into final documents.

Conclusion
We appreciate the opportunity to provide feedback on ICER’s Draft Background and Scope Document. Please feel free to contact me at 202.650.5382 or linda@cancersupportcommunity.org if you have questions or if we can serve as a resource.

Sincerely,

Linda House
President
Friends of Cancer Research appreciates the opportunity to comment on ICER’s scoping document for the assessment of two CAR-T therapies tisagenlecleucel-t (CTL019, Novartis) and axicabtagene ciloleucel (Axi-Cel, Kite Pharmaceuticals). We believe that CAR-T therapies are truly innovative treatments that have the potential to provide significant benefits to cancer patients and transform the field of oncology. As ICER refines its methodology to assess these therapies, Friends would like to offer a few considerations which we believe will be informative to the proposed methodology.

1. **Level of certainty in available data.** Both CAR-T therapies benefitted from expedited approval due to breakthrough therapy designation (BTD) and are expected to receive FDA approval based upon demonstration of significant response rates. At the point of market approval, assessment of the full clinical endpoints will not have been completed for either therapy and any concurring analysis will include only data based upon a surrogate efficacy endpoint. In its scoping document, ICER acknowledged the outstanding questions regarding management of adverse events, long-term toxicity, and cost compared to other approaches. Without this information, the level of clinical certainty will be insufficient and a more robust assessment will not be possible. While the impetuous for evaluating a therapy prior to market access is understandable, the value of an expedited therapy cannot be adequately assessed based upon the limited information available at the point of market approval. Further, it is important to note that both sponsors have agreed to commitments for extensive post-market surveillance to better understand the long-term benefits and toxicities. A more robust and applicable assessment of the value of these therapies can be conducted once this information is known.

2. **Rapid pace of medicine.** The field of oncology has benefited recently from a fast pace of development as many innovative and transformative new therapies become available to patients. This has led to rapid progression in standard of care for some types of cancer, however significant areas of unmet medical need still exist. As science continues to push the boundaries of new technologies, we must balance the level of available evidence from traditional clinical endpoints with access based on preliminary evidence of benefit. The goal of breakthrough therapy designation (BTD) was to expedite the development of therapies for unmet needs and serious or life-threatening illnesses that demonstrate substantial improvement in preliminary clinical activity. Given the transformative potential of these products, a concurrent goal to expediting development is to minimize patient exposure to a less efficacious treatment. Recognizing these goals, this
designation warrants different approaches to demonstrating efficacy. For example, the traditional methods for assessing the exact magnitude of clinical benefit of a drug, which depends upon the use of pre-market data, will compromise the inherent goal and value of innovative regulatory pathways such as BTD and potentially delay patient access to beneficial therapies. Indeed, it has recently been demonstrated that expedited pathways provide therapies that have greater value than traditional therapies. More flexible assessment models and follow-up studies should be employed to ensure robust assessments of benefit over time that balance patient access to transformative products for unmet needs.

3. **Extrapolation of data for a novel technology.** ICER intends to use overall survival as the endpoint for its CAR-T study based upon evidence generated by clinical trials with a mean duration of 3 months. This methodology is problematic for two reasons. First, CAR-T therapies are innovative technologies for which the long-term durability of response and adverse events are unknown. ICER will have to rely on extrapolation of the available data to estimate long-term value of these therapies. However, as was seen with checkpoint inhibitors, novel therapies can skew the response curve compared to standard of care therapies and reduce the robustness of an efficacy assessment based on extrapolation. Second, CAR-T therapies have an expectation to provide curative benefits to patients. In oncology, “cure” is often measured by overall survival, a particularly difficult endpoint to assess when existing therapies already extend overall survival by a matter of years. For example, the 5-year survival rate in pediatric B-cell acute lymphoblastic leukemia has risen to 85% with available therapies. The current data on CAR-T therapy is insufficient to accurately assess overall survival rates at 5 years, a timepoint well beyond the normal scope of a clinical trial, or to estimate the value of the therapy. Any value assessment for CAR-T will need to incorporate post-market data or commit to ongoing evaluation to adequately incorporate all relevant data.

4. **Population size.** In the field of oncology, therapeutic candidates are targeted increasingly to patients with specific gene alterations and indicated for use only in small subpopulations. In these circumstances, robust analysis, as may be possible for larger patient populations, is not feasible and similar methodologies to assess value are not appropriate. The two CAR-T therapies under review are expected to receive FDA approval for orphan designations. However, because the CAR-T technology is likely to yield therapies for non-rare indications as well, ICER has proposed to evaluate both therapies using methodologies for non-rare populations. This approach is inappropriate

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1. [http://library.vu.edu.pk/cgi-bin/nph-proxy.cgi/000100A/http/content.healthaffairs.org/content/36/8/1408.abstract=3f=3dright](http://library.vu.edu.pk/cgi-bin/nph-proxy.cgi/000100A/http/content.healthaffairs.org/content/36/8/1408.abstract=3f=3dright)
as it will not address the question posed in ICER’s scoping document, which is to assess the value of the therapy in its intended population. Further, this methodology differs from assessments of previous therapies in which ICER’s evaluation was limited to the approved indication. Both therapies should be assessed according their indication, as are other therapies, until sufficient data for additional uses becomes available.

5. **Patient-reported outcomes.** Incorporating patient reported outcomes (PROs) in value assessments is an important step to increasing the accuracy and relevance of evaluations. This is particularly true for therapies with ultra-rare indications where robust clinical trial data is difficult to obtain and patient centricity is vitally important to development and value assessments. However, there currently exists wide variability in the quality and sources available for PROs which impede informative use of PROs in assessments of value. Before PROs can be integrated into value assessment frameworks, it will be necessary to develop standards for collection of and quality of PRO data. Further, models should be developed to appropriately incorporate PRO data into value frameworks to best inform an assessment of value. Once quality standards and innovative PRO integration models have been developed, PROs can be appropriately used to inform more accurate and relevant value assessments. Similarly, disease modeling using quality of life (QoL) metrics and values risk inaccuracy without the ability to include long term toxicity and QoL data. This information is currently not available for these new technologies. Designing an approach for incorporating emerging data over time would help ensure a more accurate assessment of the effectiveness and value of CAR-T therapies.
August 25, 2017

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

Dear Dr. Pearson:

We are writing on behalf of the Lymphoma Research Foundation (LRF) and the people with lymphoma whom we exist to serve. We are pleased that you and your colleagues at the Institute for Clinical and Economic Review (ICER) have included representatives of LRF in discussions regarding the ICER review of chimeric antigen receptor T-cell therapy (CAR-T therapy) for B-cell cancers.

As the ICER scoping document for the CAR-T therapy review indicates, patient advocates have keen interest in CAR-T therapies that are being developed and their potential as treatments for certain B-cell cancer patients who may have few other options. As you also know from our conversations related to the CAR-T therapy review, LRF is dedicated to providing lymphoma patients the best available information about their treatment options and about the sequencing of possible treatment options, so that patients are equipped to make informed decisions about their treatment.

It is precisely this commitment that prompts us to voice reservations about the CAR-T therapy review you are undertaking, or more precisely, the timing of this review. The integration of CAR-T therapy into lymphoma treatment will pose challenges to patients, their care teams, and institutions at which the treatments will be administered. We anticipate a measured and deliberate incorporation of CAR-T therapy into lymphoma treatment, as lymphoma experts confront questions about the proper targeting of the treatments, the management of side effects, and other treatment issues. We at LRF are evaluating how we can best serve lymphoma patients during this period, as we anticipate that we may find ourselves in the position of tempering expectations about access to the CAR-T therapies, costs, their impact on the lymphoma treatment landscape, and implications on patient quality of life.

We are concerned that the data related to CAR-T therapy utilization will not be adequate to support the modeling that ICER identifies in the scoping document. We look forward to an ICER review of the CAR-T therapies in the future, but we think that the current ICER schedule for this work is an aggressive one considering the data available. We carefully reviewed the potential engagement of LRF with ICER and how we could best represent people with lymphoma in this review. Our leadership team has concluded that this ICER evaluation is premature, and that we cannot provide added value to this endeavor at this time. We do believe that we can participate constructively in a review of the CAR-T therapies in the future.

We urge ICER to reconsider its plan for CAR-T therapy review. LRF will not be able to participate in the current review process, but we would be receptive to participating in the future.

Sincerely,

Thomas Habermann, MD
Chair, Scientific Advisory Board

Meghan Gutierrez
Chief Executive Officer

Thomas Habermann, MD

Meghan Gutierrez

National Headquarters
Wall Street Plaza • 88 Pine Street • Suite 2400 • New York, NY 10005
Tel: 212 349 2910 • Fax: 212 349 2886 • Email: LRF@lymphoma.org
August 29, 2017

ICER
CAR-T Therapy for B-Cell Cancers - Comments on Draft Scoping Document

To Whom It May Concern:

As a patient advocate and CLL patient myself, I am pleased to provide the following comments to the Draft Scoping Document for the CAR-T Therapy for B-Cell Cancers. I am hopeful the comments I am providing are useful in the Draft Evidence Report on this very important breakthrough treatment.

- How is cytokine release syndrome treated?
- Will the treatment of CRS affect the CAR-T outcome?
- Is there any way to measure or predict (and be proactive) for CRS since research shows it is related to the volume of cancer cells at time of treatment?
- Will insurance cover this treatment? If not, any other financial help available?
- Will this be available only at select facilities or be a standard of care and widely available?
- Would like to see more information on relapse after CAR-T. Can it be repeated, and if so, how many times? Will insurance cover repeated therapy?
- If CAR-T is repeated, are the side effects different or worse? Is the CRS risk higher with repeated treatment?
- What are the long term “late stage” effects of CAR-T and CRS?
- What are the risks of CAR-T-vs-standard protocol chemotherapy?
- If CAR-T doesn’t work, are there other chemotherapy options that can be revisited or is CAR-T only a last resort?
- What is the projected follow up on patients who receive CAR-T?

Regards,

Lisa Beckendorf
August 29, 2017

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

Re: Potential Topics for Review in 2018

Dear Dr. Pearson:

The Academy of Managed Care Pharmacy (AMCP) thanks the Institute of Clinical and Economic Review (ICER) for the opportunity to provide comments on the “Potential Topics for Review in 2018” released on July 26, 2017. AMCP applauds ICER for considering new and emerging therapies, as well as incorporating public feedback, into the development of a robust review agenda for 2018. AMCP believes the topics proposed are timely and will be impactful in helping pharmacists, physicians, and nurses in managed care organizations and other health care decision makers critically evaluate these novel therapies. As highlighted in previous comments to ICER, AMCP continues to advocate for the development of value assessment frameworks that are transparent, adaptable, and updated as new evidence becomes available.

AMCP is the nation’s leading professional association dedicated to increasing patient access to affordable medicines, improving health outcomes and ensuring the wise use of health care dollars. Through evidence- and value-based strategies and practices, the Academy’s 8,000 pharmacists, physicians, nurses and other practitioners manage medication therapies for the 270 million Americans served by health plans, pharmacy benefit management firms, emerging care models and government.

AMCP supports the use of value frameworks as a resource for determining the value of pharmaceuticals and other health technologies when the frameworks are based on sound methods using good scientific evidence and economic models. However, for value frameworks to be meaningful they must be used in conjunction with other tools and resources, such as formulary review by pharmacists, physicians, nurses, and other health care professionals who make population health decisions. AMCP believes that value frameworks should adhere to the following principles:1

- Developers should consider key stakeholder perspectives from across the healthcare continuum, including patients, providers, payers and other health care decision makers, and pharmaceutical manufacturers.
- Analytic methodology, and economic models used in the development of a value framework should be validated and made publicly available.

• Value frameworks should incorporate scientifically valid evidence from a variety of sources, including real-world evidence and patient-reported outcomes, as part of the evaluation of a medication or other health technology, a process fully described in the AMCP Format, v. 4.0.
• Value frameworks should provide interpretable outputs that allow health care decisions makers and health care providers to conduct assessments of medications and health technologies in order to make value-based policy and treatment decisions for patients.
• Value frameworks intended for patient audiences should provide sufficient information in formats that can be understood by patients.
• The identities, credentials, qualifications and/or conflicts of interest of those involved in the development or approval of value frameworks should be publicly available.
• Value frameworks should be updated with the most current product evaluation techniques and should continue to provide accessible information to stakeholders.

ICER’s value assessment framework is one of the many tools utilized by managed care pharmacists and other health care providers in their comprehensive and holistic approach to evaluating the totality of evidence in determining whether medications and other health services are appropriate for the patient populations they serve. While AMCP appreciates the recent updates to the ICER value assessment framework and believes they are a step in the right direction to align with the principles outlined above, additional areas should be re-examined, specifically transparency of the economic models and evidence inclusion, to further enhance the utility and relevance of the value assessment framework.

The Economic Models Used Should be Made Available to Managed Care Pharmacists and Other Health Care Providers

While AMCP appreciates that the general components considered in the ICER value assessment framework are transparent, the economic models used to evaluate treatments are currently not made publicly available. AMCP supports economic models that when appropriately used, should be transparent, disclosed, reproducible, accurate, and valid. Furthermore, AMCP believes economic models should be made available to managed care pharmacists and other health care providers to download, audit, and test the model by modifying the assumptions of the model based on their perspectives and their covered populations. Specifically, the availability of the economic models would, at minimum, allow for the following:

• Realistic adoption rates that accurately reflect the anticipated uptake of a medication based upon utilization management programs and/or the relevance to the population served;
• Consideration of an appropriate quality-adjusted life year (QALY) threshold after consultation with available literature or an organization’s bioethics committee;
• Adjustment of the cost of a medication to more accurately represent the actual acquisition cost;
• Flexibility to extrapolate the data for a short-term (one year) versus long-term (five years) forecast to better understand the immediate budget impact versus overall value of the medication;
• Adaptability for rare diseases or precision medications; and
• Validation that the economic model is applicable to the relevant patient population.

In addition, AMCP urges ICER to consider a process by which stakeholders could be given an opportunity to test and validate the economic models when in draft format and provide feedback on how they can be improved prior to finalization. With this approach, the economic models are more likely to reflect current real-world conditions.

In supporting the need for transparent economic models, AMCP also recognizes the importance of ensuring that individuals who have access to the models have the appropriate training and qualifications to properly evaluate and modify the model. Therefore, AMCP recommends that ICER consider a free licensing process that would allow ICER to evaluate the qualifications of the requestor prior to releasing the economic model, similar to the approach used by the National Institute for Health and Care Excellence (NICE). Many managed care pharmacists have considerable expertise in pharmacoeconomics and therefore, ICER should work with AMCP and other stakeholders to develop the list of criteria to use in selecting eligible recipients of the economic models and the creation of a process to minimize barriers to access.

The Evidence Reports Should be Updated to Incorporate New Evidence as it Becomes Available

AMCP commends ICER for reviewing and incorporating a diverse catalog of studies in its evaluation and development of value assessment frameworks, and for being transparent with the current limitations to the methodology used. However, AMCP urges ICER to develop a process for incorporating real-world evidence (RWE), patient reported outcomes, and other forms of new evidence as they become available into the catalog of evidence that informs the economic models and then updating the evidence reports accordingly. This will become increasingly important as several of the therapies included in the review agenda for 2018 are likely to be approved by the FDA under the breakthrough therapy designation pathway with limited clinical information publicly available at the same of product approval. Therefore, continued evaluation of RWE will be critical for these therapies to truly understand their utility and value.

AMCP appreciates your consideration of the concerns outlined above and looks forward to continuing work on these issues with ICER. Furthermore, AMCP encourages ICER to use AMCP and its members as a resource as AMCP members have a wealth of knowledge and experience in evaluating RWE and pharmacoeconomic information for credibility and relevance. If you have any questions regarding AMCP’s comments or would like further information, please contact me at 703-683-8416 or scantrell@amcp.org.

Sincerely,

Susan A. Cantrell, RPh, CAE
Chief Executive Officer
August 28, 2017

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

To Whom It May Concern:

On behalf of Prime Therapeutics, LLC (Prime), we thank the Institute for Clinical and Economic Review (ICER) for choosing to review the novel therapy chimeric antigen receptor T-cell (CAR-T) for B-cell cancers. We appreciate the opportunity to provide comments. Prime supports safe and effective cancer therapies. However, we are concerned about CAR-T therapy safety and cost-effectiveness. We believe therapies need to be safe and affordable. There are a few issues we suggest ICER evaluate as extensively as possible in their review.

Safety

1. CAR-T therapies to date have been shown to cause potentially life threatening cytokine release syndrome (CRS) in a substantial number of individuals during clinical trials. We encourage ICER to qualify CSR likelihood, harm, and cost.

2. CAR-T therapies long-term safety is unknown. In particular, B-cell aplasia was common in pediatric responders. It is our understanding that lifetime immunoglobulin replacement therapy may be required post CAR-T therapy. We encourage ICER to assess the impact B-cell aplasia may have on future adverse events (e.g., infections, death) and costs. Immunoglobulin replacement therapy can have a cost approaching $100,000 per year.

3. CAR-T therapies long-term safety is unknown. For example, the B-cell aplasia may lead to long-term adverse events and potentially mortality. We encourage ICER to cost model various long-term safety outcomes at 5 years, 10 years, and a lifetime.

Effectiveness

4. CAR-T therapies long-term effectiveness durability is unknown. We encourage ICER to cost model various long-term effectiveness outcomes at 5 years, 10 years, and a lifetime.

5. Manufacturing failure has been reported. Evaluating issues associated with manufacturing failure would be appreciated.

6. The tisagenlecleucel-t product has some data for the treatment of relapsed/refractory B-cell NHL please consider comparing the r/r B-cell NHL data between tisagenlecleucel-t product and the axicabtagene ciloleucel product.

Cost

7. As the CAR-T therapy cost is unknown, please consider modeling $500,000, $750,000 and $1,000,000 for the CAR-T product actual, after discount, cost.

8. Please assess costs for the entire treatment regimen associated with CAR-T therapy including but not limited to:
   a. leukapheresis
   b. pretreatment care
   c. pretreatment chemotherapy
   d. CAR-T infusion and care associated with infusion
e. post CAR-T immediate care, including observation care
f. CAR-T short known adverse events
g. potential long-term adverse events
h. potential long-term therapy failure
i. CAR-T retreatment

Thank you for evaluating this important new treatment modality.

If you have any questions about what we have written here, please feel free to contact me.

Most Cordially Submitted,

Patrick Gleason, PharmD, FCCP, FAMCP, BCPS
Senior Director, Health Outcomes
Prime Therapeutics
1305 Corporate Center Drive
Eagan, MN 55121
pleason@primetherapeutics.com