

Amgen Response to ICER's Draft Evidence Report and Voting Questions on CAR-T Therapy for B-Cell Cancers

SUMMARY OVERVIEW

Amgen appreciates the opportunity to comment on ICER's draft evidence report and voting questions on Chimeric Antigen Receptor T-Cell (CAR-T) for B-Cell Cancers. ICER compares tisagenlecleucel (Kymriah™ [CTL019]) therapy to clofarabine-based therapy and blinatumomab-based therapy for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (B-ALL) that is refractory or in second or later relapse. This is an intensely critical point in patient treatment: having failed the initial line of therapy, children with relapsed/refractory (R/R) B-ALL face a median overall survival of 3 months.¹ Patient heterogeneity is extensive and its relationship to response is poorly understood.² On top of this, the therapeutic armamentarium of a handful of drugs is too small to address this huge patient and disease variation.³ Moreover, small numbers of patients in this orphan indication mean in the first 2 years after FDA approval, very little is known about new treatments (e.g., type of patients the treatment is best for, mechanism of action). It is at this point in tisagenlecleucel's introduction that clinicians need real world experience and far more data to assess how and in which patients this treatment will save lives. The absence of adequate tisagenlecleucel clinical data negates the budgetary and cost-effectiveness evaluations which hinge on these data.

After a careful review of the draft report and consulting the opinions from practicing oncologists and hematologists, we remain concerned that this assessment is premature. This assessment is based on promising but inconclusive evidence and methodological flaws which may lead to results that are harmful to patients. The difficulty and imprecision in capturing value when there are too few patients alive or progression free is a commonly cited shortfall of value frameworks when applied to oncology.^{4,5} Hence, ICER should delay this assessment until more conclusive evidence is available. In addition, ICER's consideration of blinatumomab and tisagenlecleucel as mutually exclusive therapies is misaligned with real world clinical practice as these drugs are likely to be given sequentially.

*B-ALL is an FDA-defined orphan disease with approximately 620 pediatric and young adult patients who relapse each year in the United States after achieving an initial response.*⁶ This is well under the 10,000-prevalence threshold identified by ICER for its ultra-orphan framework. Assessing tisagenlecleucel as a non-orphan treatment fails to capture the complexities and distinctions faced in orphan drug development and use. Moreover, ICER's decision to assess emicizumab for Hemophilia A under their ultra-orphan framework⁷ sets a strong precedent for ICER to conduct this R/R B-ALL assessment under this same ultra-orphan framework.

Our main recommendations on the draft report are summarized below:

1. The evidence base on tisagenlecleucel at this time is promising but inconclusive: ICER should rate the net health benefit as "I" (insufficient evidence) instead of "B+", and wait for more data to perform a more accurate assessment.
2. Blinatumomab is not an appropriate comparator for tisagenlecleucel therapy in the pediatric R/R B-ALL population: ICER should remove it from the clinical effectiveness question.
3. The clinical effectiveness assessment in the leukemia setting lacks validity as it does not include all relevant studies: ICER should ensure all relevant clinical studies are included in the analysis.
4. The patient heterogeneity between trials is not addressed: ICER should apply well-established methods to assess the comparative effectiveness of treatments.
5. The economic value assessment has methodological flaws, greatly underestimating the uncertainty of results: ICER should reanalyze survival outcomes and cost estimations and perform sensitivity analyses around the survival outcomes.

DETAILED COMMENTS AND RECOMMENDATIONS

1) The evidence base on tisagenlecleucel at this time is promising but inconclusive: ICER should rate the net health benefit as “I” (insufficient evidence) instead of “B+”, and wait for more data to perform a more accurate assessment.

ICER’s draft report points out the limitations in the current evidence base in 5 places: 1) “*there are currently no randomized or observational trials directly comparing tisagenlecleucel therapy to salvage chemotherapy, any comparisons were at substantial risk for selection bias*” (p. 10). 2) “*All of the clinical studies were small (less than 100), single arm designs with limited follow up*” (median follow up less than one year) *and incomplete reporting*” (p.19); 3) “*most of the pivotal trials of CAR-Ts have yet to be published in peer reviewed journals.*” (p. 25); 4) “*Both the benefits and duration of and long-term relapse-free survival is unknown at this point* (p. 40)”; and 5) “*uncertainty around long-term harms of therapy,...which makes the analyses versus standard therapy controversial*”(p. 40). These important flaws and limitations in the evidence base introduce a low certainty in the net health benefit of tisagenlecleucel. This invalidates the draft report’s conclusion: “*there is at least a small net health benefit compared with current salvage chemotherapy although the benefit may be substantial (“B+” rating)*”(p.35).

According to ICER’s framework, an insufficient (I) rating should be granted in any situation in which the level of certainty in the evidence is low. Strictly adhering to ICER’s value framework,⁸ tisagenlecleucel should be rated as insufficient evidence (I) rating. Given this rating, per the United States Preventive Services Task Force guidelines, this makes the answer ‘No’ to ICER’s question, “*Is the evidence adequate to demonstrate a net health benefit for treatment with tisagenlecleucel (Kymriah™, Novartis) versus treatment with clofarabine or comparable chemotherapy (e.g., blinatumomab, multi-agent chemotherapy including clofarabine)?*”. Assuming the panel also recognizes the insufficient evidence and votes ‘No’, then by default, it negates any subsequent votes on the value of tisagenlecleucel, given that the evidence base has been deemed promising but too inconclusive to determine value. The development of questions and the subsequent panel voting process must be designed and navigated carefully to ensure an accurate capture of value in order to best serve patients, their families and providers.

In addition, blinatumomab is not a “chemotherapy” and has demonstrated significant survival benefit over salvage chemotherapy in adult patients with R/R B-ALL in a randomized, controlled study.⁹ Blinatumomab is a first-in-class, bispecific T-cell engager (BiTE®) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin, and to CD3 expressed on the surface of T cells. We ask ICER to correct the terminology throughout the evidence report and the voting questions.

2) Blinatumomab is not an appropriate comparator for tisagenlecleucel therapy in the pediatric R/R B-ALL population: ICER should remove it from the clinical effectiveness question (first voting question for the pediatric B-ALL population, page 1).

Based on feedback from oncologists and hematologists who treat these patients every day, in the real-world setting it is highly likely that tisagenlecleucel therapy and blinatumomab will be used sequentially to produce the deepest remission possible.^{10,11} Moreover, blinatumomab has been used in patients who failed tisagenlecleucel on trial, and it is likely to be used this way in clinical practice. The cornerstone of B-ALL treatment is combination therapy rather than a discrete choice between treatments. Several oncology and hematology practitioners, who are also opinion leaders, have confirmed the sequential use of blinatumomab and tisagenlecleucel therapy in their practice. These insights suggest that ICER’s draft report comparing these treatments is likely irrelevant to real world clinical practice and assesses a scenario that may never exist.

3) The clinical effectiveness assessment in the leukemia setting lacks validity as it does not include all relevant studies: ICER should ensure all relevant clinical studies are included in the analysis.

If ICER proceeds to conduct the assessment with blinatumomab as a comparator, ICER should include all relevant clinical studies (see Appendix A). Amgen agrees with ICER on the need to rely heavily on grey literature given the evolving evidence base. However, the studies included in the draft report for the comparators are not comprehensive. According to ICER's policy on inclusion of grey literature in evidence reviews, grey literature includes conference proceedings and/or abstracts. As mentioned in the two data packages sent by Amgen to ICER, for blinatumomab studies in the pediatric R/R B-ALL population, in addition to the already included MT103-205 study, another expanded access study of blinatumomab in the pediatric R/R B-ALL population (RIALTO, NCT02187354) should have been included. The RIALTO study data sent to ICER was presented at the ASCO 2017 annual conference.¹² RIALTO has many similarities to MT103-205, providing a significant increase in the number of subjects, with almost the same length of follow up as MT103-205 of blinatumomab for pediatric patients with R/R B-ALL. It is worth noting that the baseline inclusion criteria on blast level of RIALTO is identical to that of the ELIANA study, *i.e.*, $\geq 5\%$, whereas MT103-205 required the baseline blast level to be $>25\%$. Therefore, pooling the RIALTO study with MT103-205 data will help to increase the number of patients that share similar characteristics to tisagenlecleucel patients and allow for more precise estimates. Endpoints of RIALTO are consistent with MT103-205 as well, including: complete remission (CR) within the first two cycles; relapse-free survival (RFS); overall survival (OS) and rate of hematopoietic stem cell transplantation (HSCT) after CR.

In assessing the efficacy of tisagenlecleucel, the draft report includes three single-arm studies of tisagenlecleucel in the pediatric R/R B-ALL population (B2101J with split dosing of tisagenlecleucel; standard dose study B2205J; and standard dose pivotal study B2202/ELIANA). At the end of the clinical effectiveness assessment, tisagenlecleucel data are pooled across all three trials to estimate the long-term survival of patients. We disagree with this approach as the B2101J study had a completely different dosing regimen than the other two studies. This severely biases ICER's tisagenlecleucel efficacy estimation.

In contrast to presenting pooled data on three tisagenlecleucel studies in assessing efficacy, only study B2202/ELIANA data is evaluated to assess the harms. This approach is both incomplete and misleading in that the B2101J study was primarily designed to assess the safety, tolerability and engraftment potential of tisagenlecleucel in pediatric R/R B-ALL.

4) The patient heterogeneity between trials is not addressed: ICER should apply well-established methods to assess the comparative effectiveness of treatments.

As stated in ICER's draft report, there are no randomized or observational trials directly comparing tisagenlecleucel therapy to the comparators, making any comparisons subject to major risk for selection bias. The draft report attempts to describe the study sample characteristics, but this fails to address the selection bias problem. Instead, ICER should apply existing methods that have been used extensively in assessing treatment comparative effectiveness.^{13,14,15}

The ELIANA¹⁶ and MT-103-205¹⁷ studies in pediatric R/R B-ALL patients are all small single-arm studies enrolling quite heterogeneous patients:

- 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 bone marrow 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% of patients with refractory disease compared to 56% of patients in MT103-205. ELIANA required patients to have life expectancy longer than 12 weeks, but MT103-205 did not have any such requirements.

In addition, the patient characteristics described in the ICER report do not include all the important potential factors that might determine the outcomes. Using the method applied in Quinn *et al.*,^{18,19} we found that patients in MT103-205 and RIALTO on average had a 29% higher risk of mortality than an average patient in the ELIANA study. This method considered available baseline characteristics from both blinatumomab and tisagenlecleucel trials. Among the prognostic factors explored (age and age squared, gender, race, primary refractory, chemotherapy refractory, prior HSCT, previous lines of therapies), many of these proved to be impactful factors on the risk of mortality. For example, refractory status is an important factor that impacts OS. Of note, 52 (34.2%) patients in MT103-205 and RIALTO were chemotherapy refractory,²⁰ whereas 9 (10%) of ELIANA study enrolled patients were chemotherapy refractory (Appendix A). These results highlight the heterogeneity of patient characteristics between blinatumomab and tisagenlecleucel studies and the critical importance of adjusting for that heterogeneity in comparing these studies.

Given the aforementioned differences in patient characteristics, the indirect treatment comparison needs to adjust for all effect modifiers and prognostic factors: for reference on methods for population-adjusted indirect comparisons, please see NICE's recent technical support document.²¹ Without this analysis, the conclusions on treatment effect and causation may be a function of other unrelated and coincidental variables.

5) The economic value assessment has methodological flaws, greatly underestimating the uncertainty of results: ICER should reanalyze survival outcomes and cost estimations and perform sensitivity analyses around the survival outcomes.

Survival outcomes are the most important model inputs in cost-effectiveness (CE) models in oncology. Therefore, the estimations of OS/event-free survival (EFS) and the sensitivity of the model around OS/EFS should be examined carefully. In the current ICER model, the OS/EFS results of tisagenlecleucel are derived by pooling the three single-arm studies, which is inappropriate; as mentioned above, study B2101J should not be included.

In addition, it appears that the ICER model assumes no further relapse after 13 months and no further B-ALL related death after 30 months, an assumption that is not based on any evidence and further inconsistent with the 4-year cure assumption mentioned in the method section of the report. The current CE model sensitivity analyses (one-way and probabilistic) does not include sensitivity around survival curve parameters. Failure to incorporate uncertainty in the survival distribution estimates renders the sensitivity analyses results virtually meaningless, as the survival distributions represent the main source of uncertainty in the model. Moreover, survival curves for immuno-oncologic agents differ from chemotherapy, cautions need to be taken while selecting the parametric distributions for survival.^{22,23} Therefore, the current conclusion that the CE model results are robust through one-way and probabilistic sensitivity analyses is unfounded.

Two other cost assumptions are also biased in favor of tisagenlecleucel. In the base case, ICER assumes that the cost of tisagenlecleucel is only applicable for responders at one month. Although this might be appropriate for publicly insured patients per the manufacturer's public statement, it is unclear if the payment strategy will be the same for privately insured patients. Also, the markup rate applied in the model is not evidence-based given the high degree of uncertainty both due to marked differences between hospitals and the confidential nature of real mark-up rates. In addition, the cost per day for hospital stay is estimated

based on HCUP estimation for all children, which is an underestimation for the pediatric R/R B-ALL patients. The model also underestimates the cost of B-cell aplasia.

ADDITIONAL COMMENTS/CORRECTIONS

In addition, we have identified a total of 80 areas of concerns and/or errors that we ask ICER to address in their Revised Report; 13 of these are methodological concerns that need to be addressed and 67 are factual errors or inaccuracies that need to be corrected. Please see Appendix B for details, including suggested corrections.

CONCLUSION

The need for continued innovation in R/R B-ALL is reflected in the low number of available treatments. Tisagenlecleucel is a welcomed option desperately important to this extremely vulnerable pediatric patient population. A fundamental tenant in the application of value frameworks is in their timing, and despite ICER taking on this assessment to raise this important dialogue, the timing is premature and the assessment should be reconsidered. If ICER decides to proceed with this assessment, then the draft report needs to address the above noted limitations and concerns, including acknowledging insufficient evidence (I) for tisagenlecleucel and removing blinatumomab as a comparator to better align with real world clinical practice.

Appendix A: Patient characteristics in tisagenlecleucel and blinatumomab clinical studies

Trials	Blinatumomab MT103-205 trial (n=70)	Blinatumomab RIALTO trial (n=82)	Blinatumomab pooled MT103-205 and RIALTO (n=152)	Tisagenlecleucel B2202 ELIANA ITT (n=88)	Tisagenlecleucel B2205J ENSIGN Infused (n=29)
Median age, years (range, SD)	8.0 (0-17, 5.0)	10.0 (1-21, 4.7)	9.0 (0-21, 4.9)	11.5 (3-23, 5.4)	12.0 (3-25, NR)
Gender, n (%)					
Male	47 (67)	47 (57.32)	94 (61.84)	48 (55)	11 (37.9)
Female	23 (33)	35 (42.68)	58 (38.16)	40 (45)	18 (62.1)
Race, n (%)					
White	55 (78.57)	70 (85.37)	125 (82.24)	65(74)	25 (86.2)
Others	15(21.43)	12 (14.63)	27(17.76)	20(26)	4 (13.8)
Prior HSCT, n (%)					
0	30 (42.86)	45 (54.88)	75 (49.34)	36 (41)	12 (41.4)
1+	40 (57.14)	37 (45.12)	77(50.66)	52 (59)	17 (58.6)
Disease status					
Primary refractory, n (%)	2 (2.86)	11 (13.41)	13 (8.55)	8 (9)	2 (6.9)
Chemo-refractory, n (%)	37 (52.86)	15 (18.29)	52 (34.21)	9 (10)	2 (6.9)
Relapse disease, n (%)	31 (44.29)	56 (68.29)	87 (57.24)	71 (81)	25 (86.2)
Previous lines of therapy					
Median	2	2	2	3	3
1 prior line of therapy, %	8 (11.43)	15 (18.29)	23 (15.13)	NA	NA
2 prior line of therapy, %	41 (58.57)	35 (42.68)	76 (50.00)	NA	NA
3+ prior line of therapy, %	21 (30.00)	32 (39.02)	53 (34.87)	53(60.3)	NA
BLAST level	>25%	>=5%	>5%	>=5%	>=5%
Life expectancy	no restriction	no restriction	no restriction	>12 weeks	NR

Appendix B: Other Comments and Corrections

Based on our detailed review, we identified the following methodological flaws or concerns that we ask ICER to address as they incorporate changes for their Revised Report.

1. **On page 7**, the report states “*blinatumomab, which has been used as a bridge to SCT with some success*”. This is not an accurate statement in that blinatumomab has been shown to improve patients’ outcomes independent of SCT²⁴ and should not be presumed to be limited to SCT eligible patients as a bridging therapy.
2. **On page 11, Table 1.1, Key outcomes and harms**, the rationale for selecting this list of outcomes and harms is not provided. The anxiety over the receipt of a novel treatment based on genetically modified cells should be considered as harms. On page 13, “*some of the patients will die and others will become too sick to tolerate treatment with the CAR-T cells*” should be included as a potential harm of treatment.
3. **On page 11**, the evidence on intervention effectiveness and harms is derived from studies with a median duration of at least three months. No rationale is provided for this requirement.
4. **On page 16, Section 3.2, Clinical guidelines**, fails to mention blinatumomab is recommended by NCCN guidelines as a category 1 designated therapy and the fact that blinatumomab is recommended by NICE within its marketing authorization as an option for treating Philadelphia-chromosome-negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia in adults.²⁵
5. **On page 25**, “*it was not possible to estimate the comparative benefits or harms of these novel therapies...using either direct or indirect comparisons*”. This statement is incorrect. It is possible to conduct unanchored indirect comparisons using single-arm studies. As such, on page 27, “*since none of the studies included comparator groups, we were unable to perform any statistical comparisons...*” The absence of a comparator group does not eliminate the possibility of statistical comparisons.
6. **On page 26**, the study selection fails to describe how the comparator studies were identified.
7. **On page 28, Table 4.1, Summary of treatments for relapsed/refractory pediatric B-ALL**, this table presents patient characteristics based on the infused patients. Given that patients assigned to tisagenlecleucel could die/experience manufacture failures and/or AEs waiting for tisagenlecleucel therapy and not all patients were infused, it is more appropriate to compare the characteristics of the enrolled patients. ICER’s report underpins this on page 24 with, “*The reported overall remission rates for tisagenlecleucel in the three trials (from 69% to 95%, Table 4.2) represents an optimistic presentation of the results that violates the intention to treat principle because they are based on patients who received successful infusion of CAR-T cells, thereby excluding patients who did not receive the therapy because of manufacturing failures, death prior to infusion, or AEs.*”
8. **On page 29**, “*thus, patient selection suggested that the patients in the trials of tisagenlecleucel had undergone more prior therapies and, thus, had a worse prognosis at enrollment*”. This statement is unfounded and not evidence based. The precise direction and relative importance of the factors for predicting survival in these patients has not been established. This statement fails to account for other potential differences in patient characteristics between trials including patient age and percent of patients who are relapsed, which were higher in the tisagenlecleucel than blinatumomab trials and which, according to analyses of data from blinatumomab trials, are both favorable prognostic factors.
9. **On page 31, Table 4.4, Estimated event-free survival at six months in therapies for relapsed or refractory childhood B-ALL**, the estimates of EFS at 6 months for tisagenlecleucel reported in Table 4.4 appear to be calculated by multiplying reported estimates of EFS at 6 months among infused patients from Table 1-2 of the Novartis FDA Briefing Document by the ratio of the number of infused vs. enrolled patients in Study 2101J, 2505J, and 2202. This approach yields EFS estimates

for these studies of 58%, 46%, and 53% respectively, which are the same as the estimates reported by ICER.

EFS was not evaluated in the 205 trial of blinatumomab. The value reported (16%) appears to be the product of the % with CR (39%) from Table 4.2 from the ICER report and the estimated RFS at 6 months (42%) reported by Von Stackelberg *et al.* (2016). RFS was not reported for 2101J, 2205J, or 2202 so it is not feasible to replicate this precise calculation for these studies. However, the Kaplan Meier estimate of duration of remission (DOR) may be a reasonable proxy for RFS for these studies. Accordingly, the value for Study 2202 obtained by multiplying the % CR among enrolled patients with ≥ 3 months FU reported by ICER (63%) in Table 4.2 by the Kaplan Meier estimate of DOR at 6 months reported in Table 1-2 the Novartis FDA Briefing Document (75.4%) is 47%. This value, which is arguably more comparable to the 16% reported for blinatumomab, is significantly lower than the 53% reported for Study 2202 by ICER. The corresponding calculated values for Studies 2101J and 2205J are 54% and 38%, respectively, which also are lower than the values of 58% and 46% reported by ICER.

10. **On page 30**, the report says the CR rate for B2101J study enrolled cohort is $52/71=73\%$ (61%-83%) and does not specify the source. This number is incorrect. It is reported in the ODAC briefing document that the number of patients achieving ORR=52; CR=38 (p. 51). Therefore, the CR rate for the enrolled cohort should be $38/71=54\%$ and ORR rate for the enrolled cohort should be $52/71=73\%$.
11. **On page 30**, the report says the CR for B2205J study enrolled cohort is $20/35=57\%$ (39%-74%) and does not specify the source. This number is incorrect. It is reported in the ODAC briefing document that the number of patients achieving ORR is 20, CR is 18 (p. 51). Therefore, the CR rate for the enrolled cohort should be $18/35=51\%$; the ORR for the enrolled cohort should be $20/35=57\%$.
12. **On page 30**, the report says that the CR rate for the B2202 study enrolled cohort should be $52/83=63\%$ (51%-73%) and doesn't specify the source. The number is incorrect. It is reported in the FDA briefing document for the ODAC 2017 Tisagenlecleucel meeting that the number of patients achieving ORR=52, CR=40 (p. 39). In B2202 study, 88 patients are enrolled, it is not 83 (5 patients should NOT be excluded from the enrolled cohort due to lack of follow-up). Therefore, the CR rate for the enrolled cohort should be $40/88=45\%$; the ORR rate for the enrolled cohort should be $52/88=59\%$.
13. **On page 31**, the report states that the ORR in the enrolled population in the B2202 study is 65.8% (95% CI 54%-76%). It is unclear how 65.8% is obtained. There are 52 patients who achieved ORR in B2202. Among all the enrolled patients, the ORR should be $52/88=59.1\%$; among enrolled patients and patients with at least 3 month follow up, the ORR should be $52/83=63\%$.

In addition, we identified these factual errors/inaccuracies in the draft report. We ask that ICER make corresponding corrections and reflect them in the Revised Report.

14. **On page 14**, definition of the complete remission, neutrophils $>1 \times 10^9/L$ should be corrected to $1 \times 10^9/L$, same for platelets.
15. **On page 96, Table C1**, the report says the median follow-up duration for B2202 study is 4.8 months. According to the ODAC briefing document, the median follow-up duration of response = 4.8 months. Median follow-up EFS = 5.6 months. It is unclear why 4.8 months is selected over 5.6 months. Source: Oncologic Drugs Advisory Committee Briefing Document. Tisagenlecleucel (CTL019) for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. 2017
16. **On page 96, Table C1**, the report says the prior lines of chemo for 2205J is 3 and references the Buechner 2017 publication. This is the wrong reference. The number appears in FDA Briefing

Document Oncologic Drugs Advisory Committee Meeting. BLA 125646 Tisagenlecleucel Novartis Pharmaceuticals Corporation.

17. **On page 96, Table C1**, the report says the number of patients enrolled in B2101J is 71 and references the Maude 2015 and Grupp 2013 publications. The references are incorrect. The numbers are presented in the Oncologic Drugs Advisory Committee Briefing Document. Tisagenlecleucel (CTL019) for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. 2017.
18. **On page 96, Table C1**, the report says the number of patients infused in the B2101J study is 55 and references the Maude 2015 paper. The source is incorrect. The number appears in Oncologic Drugs Advisory Committee Briefing Document. Tisagenlecleucel (CTL019) for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. 2017.
19. **On page 96, Table C1**, the report says the median follow-up for the B2101J study is 7 months for the 30 patients and references Maude 2015 and Grupp 2013 publications. The sources are incorrect. The correct source should be Maude SL, Frey N, Shaw PA, *et al.* Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England journal of medicine. 2014;371(16):1507-1517.
20. **On page 96, Table C1**, the report says the age in B2101J study is 11 years and references Maude 2015 and Grupp 2013 publications. The sources are incorrect. The number is presented in Oncologic Drugs Advisory Committee Briefing Document. Tisagenlecleucel (CTL019) for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. 2017.
21. **On page 96, Table C1**, the report says number of prior lines of chemotherapy for B2101J is 4 and references Maude 2015 and Grupp 2013 publications. The sources are incorrect. The number is presented in Oncologic Drugs Advisory Committee Briefing Document. Tisagenlecleucel (CTL019) for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. 2017.
22. **On page 96, Table C1**, the report says the proportion of patients with prior SCT in the 2101J study (n=30) cohort is 72%. The number is incorrect. The 72% is actually among the pediatrics cohort (n=25) as reported in the Maude *et al.*, 2014 NEJM. The correct number should be 63.6% as reported in the Oncologic Drugs Advisory Committee Briefing Document. Tisagenlecleucel (CTL019) for the Treatment of Pediatric and Young Adult Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. 2017.
23. **On page 96, Table C1**, the report says the median follow-up for the MT103-205 study of blinatumomab is >2 years. However, the correct number should be 23.8 months (Von Stackelberg *et al.*, 2016, JCO).
24. **On page 29**, the report says “*There is no accepted definition of a cure, as relapses can rarely occur more than 10 years after remission*” and references the Pui *et al.*, 2003 publication. This is an incorrect interpretation of the publication, where it says “*Our results suggest a new working definition of cure: 10 or more years of continuous complete remission, a standard that could be used to gauge the effectiveness of current and future treatment plans*”.
25. **On page 30, Table 4.2**, the report says the ORR for blinatumomab in the MT103-205 study is 45% and the CR rate is 39%. This is incorrect. The 39% reported in the von Stakelberg 2016 publication is the ORR rate.
26. **On page 31**, the report states that the B2202 study requires patients to have >5% blasts in bone marrow at screening. It should be $\geq 5\%$.
27. **On page 33**, the report says that the incidence of CRS (all grades) in B2202 study (n=68) is 79% and references the Novartis ODAC 2017 document. The correct source should be the KymriahTM FDA package insert, 2017 (p. 7).

28. **On page 33**, the report says that the incidence of CRS, grade ≥ 3 , in the B2202 study (n=68) is 49% and references the Novartis ODAC 2017 document. The correct source should be the KymriahTM FDA package insert, 2017 (p. 7).
29. **On page 33**, the report says the incidence of neurologic toxicities (all grades) in B2202 study (n=68) is 65%, same comment as above.
30. **On page 33**, the report says the incidence of grades ≥ 3 neurologic toxicities in B2202 study (n=68) is 18%, same comment as above.
31. **On page 33**, the report says the incidence of all grades encephalopathy in B2202 study (n=68) is 34%. Same comment as above.
32. **On page 33**, the report says the incidence of grades ≥ 3 encephalopathy in B2202 study (n=68) is 10%, same comment as above.
33. **On page 33**, the report says the incidence of all grades headache in B2202 study (n=68) is 37%, same comment as above.
34. **On page 33**, the report says the incidences of grades ≥ 3 headache in B2202 study (n=68) is 3%, same comment as above.
35. **On page 33**, the report says the incidence of all grades acute kidney injury in B2202 study (n=68) is 22%, same comment as above.
36. **On page 33**, the report says the incidence of grades ≥ 3 acute kidney injury in B2202 study (n=68) is 13%, same comment as above.
37. **On page 33**, the report says the incidence of grades ≥ 3 hypotension in B2202 study (n=68) is 22%, same comment as above.
38. **On page 33**, the report says the incidence of grades ≥ 3 hypoxia in B2202 study (n=68) is 18%, same comment as above.
39. **On page 33**, the report says the incidence of all grades infections with unknown pathogens in B2202 study (n=68) is 41%, same comment as above.
40. **On page 33**, the report says the incidence of grades ≥ 3 infections with unknown pathogens in B2202 study (n=68) is 16%, same comment as above.
41. **On page 33**, the report says the incidence of all grades viral infections in B2202 study (n=68) is 26%, same comment as above.
42. **On page 33**, the report says the incidence of grades ≥ 3 viral in B2202 study (n=68) is 18%, same comment as above.
43. **On page 33**, the report says the incidence of all grades bacterial infections in B2202 study (n=68) is 19%, same comment as above.
44. **On page 33**, the report says the incidence of grades ≥ 3 bacterial in B2202 study (n=68) is 13%, same comment as above.
45. **On page 33**, the report says the incidence of all grades fungal infections in B2202 study (n=68) is 13%, same comment as above.
46. **On page 33**, the report says the incidence of grades ≥ 3 fungal infections in B2202 study (n=68) is 7%, same comment as above.
47. **On page 33**, the report says the incidence of grades ≥ 3 disseminated intravascular coagulation in B2202 study (n=68) is 9%, same comment as above.
48. **On page 33**, the report says the incidence of grades ≥ 3 histiolympocytic hemophagocytosis in B2202 study (n=68) is 7%, same comment as above.
49. **On page 33**, the report says the incidence of grades ≥ 3 heart failure in B2202 study (n=68) is 7%, same comment as above.
50. **On page 33**, the report says the incidence of grades ≥ 3 cardiac arrest in B2202 study (n=68) is 4%, same comment as above.
51. **On page 33**, the report says the incidence of grades ≥ 3 seizures in B2202 study (n=68) is 3%, same comment as above.

52. **On page 33**, the report says the incidence of grades ≥ 3 intracranial hemorrhage in B2202 study (n=68) is 1%, same comment as above.
53. **On page 33**, the report says the incidence of all grades fever in B2202 study (n=68) is 50% and references the Novartis ODAC 2017 document. The number presented in the source document is 40% (p. 65).
54. **On page 33**, the report says the incidence of grades ≥ 3 fever in B2202 study (n=68) is 15% and references the Novartis ODAC 2017 document. The source reports that incidence for serious fever is 7% (p. 66).
55. **On page 97, Table C2**, the report states that the inclusion criteria for B2101J is “*relapsed and refractory CD 19+ cancers B-ALL in 1st to 4th relapse; 3 refractory primary B-ALL*” and references the Maude *et al.*, 2015 Blood publication. This information is not presented in the Maude *et al.*, 2015 publication. Another publication of the study (Maude *et al.*, 2014 NEJM) mentions that “*26 had B-cell ALL in the first to fourth relapse, 3 had primary refractory B-cell ALL*”.
56. **On page 98, Table C2**, the report says that the MT103-205 study of blinatumomab includes patients with $\geq 25\%$ blasts in bone marrow, it should be $>25\%$. The report says the study includes patients refractory or in 1st subsequent relapse, this is incorrect. It should be “*primary refractory, in 1st relapse after full salvage induction regimen, in second or later relapse, or in any relapse after alloHSCT*”. The report says the study includes B-ALL, it should be B-precursor ALL.
57. **On page 99**, the report says that the median weight (kg) in B2202 study is 43 and references the KymriahTM package insert. This number is not reported in the source.
58. **On page 99**, the report says that the baseline performance status for the B2202 is 90 and references the KymriahTM package insert. The number is not reported in that source.
59. **On page 99**, the report says that 12% of the B2202 patients are chemorefractory, 9% are primary refractory, 79% are relapse disease and references the KymriahTM package insert. The numbers are not reported in the source.
60. **On page 99**, the report says that 85% of the B2202 patients receive bridging chemotherapy and references the KymriahTM package insert. The number is not reported in the source.
61. **On page 99**, the report says that 45% of the patients in B2101J are female and references the Maude 2014 NEJM publication. The number reported is incorrect. In the Maude 2014 publication, it reports 44% of the pediatrics cohort are female, whereas 46% is reported in the ODAC 2017 briefing document.
62. **On page 99**, the report says that “*87% in 1st-4th relapse 60%*” in study B2101J and references the Maude 2014 NEJM publication. The numbers reported in the publication are 100% with ≥ 1 relapse and 0% primary refractory for the pediatrics cohort (p. 1509).
63. **On page 99**, the report says that 64% of the B2101J patients have prior SCT and references the Maude 2014 NEJM publication. The number reported in the source is 72% in the pediatric cohort.
64. **On page 101**, the report says the median OS for B2202 study is 16.6 months and references the KymriahTM package insert. The number is not reported in the source.
65. **On page 101**, the report says the rate of PR is 7.0% (87.4-77.4) and references the KymriahTM package insert. The number is not reported in the source. In addition, the number does not make sense as the point estimation is not included in the confidence interval.
66. **On page 101**, the report says the % dead before response assessment in the B2202 study is 7.5% and references the KymriahTM package insert. The number is not reported in the source.
67. **On page 101**, the report says the % of non-responders in the B2202 study is 7.9% (n=8) for N=63 and references the KymriahTM package insert. The numbers are not reported in the source.
68. **On page 101**, the report says the proportion of patients receiving allo-SCT in the B2202 study is 10.5% and references the KymriahTM package insert. The number is not reported in the source, where it states that the “*stem cell transplantation rate among those who achieved CR/CRi is 12% (6/52).*”

69. **On page 101**, the report says the median OS for the B2101J study is 32.7 months and references the Maude 2014 NEJM publication. The number is not reported in the source.
70. **On page 101**, the report says the % of CR in the B2101J study is 69% and references the Maude 2014 NEJM publication. Same comment as above.
71. **On page 101**, the report says the % of non-responders in the B2101J study is 5.5% and references the Maude 2014 NEJM publication. Same comment as above.
72. **On page 101**, the report says the % of ORR in the B2101J study is 95% and references the Maude 2014 NEJM publication. Same comment as above.
73. **On page 101**, the report says the % of non-responders of blinatumomab is 55% and references the von Stackelberg JCO 2016 publication. The number should be 30% (p. 4).
74. **On page 102**, the report says the proportion of patients with grade three/four AEs in B2202 study infused cohort is 65% and references the KymriahTM package insert. The number is not reported in the source.
75. **On page 102**, the report says the proportion of patients with treatment-related death in the B2202 study infused cohort is 17% total death and references the KymriahTM package insert. The number is not reported in the source.
76. **On page 102**, the report says the proportion of patients with prolonged B-cell aplasia in B2202 study infused cohort is 84% and references the KymriahTM packager insert. The number is not reported in the source.
77. **On page 102**, the report says the proportion of patients with grade three/four CRS in the B2101J study is 17% and references the Maude 2014 NEJM publication. The number reported in the source is 27% (severe CRS, 8 patients, p. 1507).
78. **On page 102**, the report says the proportion of patients with prolonged B-cell aplasia in the B2101J study is 90% and references the Maude 2014 NEJM publication. The number is not reported in the source.
79. **On page 102**, the report says the proportion of patients with neurotoxicity in the MT103-205 blinatumomab study is not reported and references the von Stackelberg JCO 2016 publication. The number should be 24% (17/70).
80. **On page 102**, the report says the proportion of patients with grade three/four neurotoxicity in the MT103-205 blinatumomab study is not reported and references the von Stackelberg JCO 2016 publication. The number should be 4% (3/70) (p. 4).

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- ² 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 Adamson P. *et al.* Childhood Cancer Research Landscape Report. Translating Discovery into Cures for Children with Cancer. p.66. [Link](#)
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- ²⁵ Note that a further stipulation from NICE is that the company must provide it with the discount agreed in the patient access scheme. *Source:* NICE. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. Technology appraisal guidance [TA450] Published date: 28 June 2017. [Link](#)

January 24, 2018

Institute for Clinical and Economic Review
2 Liberty Square
Boston, MA 02109

RE: Public Comments for CAR-T Therapies Draft Evidence Report

Dear ICER Review Panel:

Genentech, a member of the Roche Group, would like to take the opportunity to provide comments on the draft evidence report of chimeric antigen receptor t-cell (CAR-T) therapies for treatment of B-cell malignancies. Genentech is committed to advancing the science of oncology and pursuing the development of novel therapies to help individuals with unmet medical need. We support value frameworks that account for the needs of individual patients and enable meaningful dialogue between patients and their healthcare providers.

We encourage ICER to consider our comments in the interest of improving value framework assessments for patients that need access to impactful therapies. Relapsed refractory diffuse large B-cell Lymphoma (R/R DLBCL) is an area of high unmet need due to poor prognosis and lack of effective therapeutic options. The comments are focused on the following priorities in R/R DLBCL:

1. Methodological issues and limitations should be clearly and comprehensively communicated in order to ensure appropriate interpretation and application of the value framework assessment.
2. Additional sensitivity analyses and alternative model approaches should be undertaken to increase the robustness of the value framework assessment.
3. Real-world data provides the most current and relevant data to support model assumptions on the cost and clinical outcomes of comparator treatments.

1. Methodological issues and limitations should be clearly and comprehensively communicated to the public

Genentech acknowledges the conduct of single-arm trials to support regulatory approval is appropriate given the urgency for effective therapies and poor prognosis in R/R DLBCL. However, indirect treatment comparisons with single-arm trials are subject to methodological limitations. Genentech encourages ICER to provide detailed considerations on the limitations of indirect treatment comparisons of single-arm trials in the evidence report, facilitate robust discussion around the interpretation of ICER's early assessment with the voting panel, and ensure members of the voting panel possess the appropriate expertise in hematology to evaluate the therapies of interest. These recommendations are made in order to limit risks to patient access and ensure information from ICER's early assessment of recently FDA approved therapies are applied appropriately in healthcare decisions.

Patient populations of the studies of interest are different, rendering the comparison prone to bias and uncertainty. The trials had an imbalance of key prognostic factors between study populations and different definitions of treatment response and remissions.^{1,2} Further, a significant bias in patient selection is introduced due to the manufacturing time of 17 days for axicabtagene ciloleucel treatment.^{2,3} These differences warrant discussion and education on how it limits the ability to make treatment comparisons based on aggregate level data without controlling for differences.

To address selection bias, we recommend that the model be updated with a propensity score analysis of the cross-study comparison of SCHOLAR-1 and ZUMA-1.⁴ This propensity score analysis reported a median overall survival (OS) of 16.4 months (95% CI of 11.5 months - NR) for axicabtagene ciloleucel and 5.4 months (95% CI 5.0 months - 6.4 months) for salvage therapy. A sensitivity analysis using a median OS of 11.5 months for axicabtagene ciloleucel as a lower bound estimate of median OS can be used to test the impact on model outcomes.

2. ICER should conduct additional sensitivity analyses and consider alternative model approaches to increase the robustness of the value framework evaluation.

We recommend that key model outcomes of clinical benefit be further evaluated in sensitivity analyses given that the long-term benefit of axicabtagene ciloleucel is unknown.

Duration of response (DoR)

We recommend that progression-free survival (PFS) data from the most recent ZUMA-1 datacut be used to update the model.² Currently the model assumes DoR from ZUMA-1 as a proxy for PFS for axicabtagene ciloleucel. This raises significant methodological concerns. DoR and PFS are fundamentally different endpoints and results in potential overestimation of clinical benefit. DoR is defined as the time from documentation of tumor response to disease progression or death amongst patients that respond to treatment. PFS is the time from study randomization until disease progression or death for all patients irrespective of their response status. Published literature further corroborates the differences between DoR and PFS in ZUMA-1. First, the mDoR and mPFS values are different based in ZUMA-1 (median DoR of 8.2 months, 1/27/2017 datacut; mPFS 5.8 months from 8/11/2017 datacut).^{2,3} Second, it is clear that DoR and PFS curves are not the same in ZUMA-1. The PFS has a steeper slope than the DoR curve in the first 6 months, illustrating clear differences in clinical outcomes.

Application of the relationship between PFS and OS for rituximab in combination with dexamethasone, high dose cytarabine, and cisplatin (R-DHAP) to salvage chemotherapy

Given the lack of evidence that the relationship between PFS and OS can be applied to all salvage chemotherapy in R/R DLBCL, a sensitivity analysis in which the proportional relationship between PFS and OS is varied can help characterize the impact of this parameter on model results.

We acknowledge that PFS was not reported in the SCHOLAR-1 study.¹ The model estimate of PFS for R-DHAP, based on the proportional relationship between PFS and OS in Schirmbeck et al. 2016, is subject to significant limitations.⁵ There are noted differences in patient characteristics, histologies, treatment exposure and outcomes between Schirmbeck et al. 2016 and SCHOLAR-1.^{1,5} Please consider the following differences in patient populations and clinical outcomes from Schirmbeck et al. 2016 and SCHOLAR-1 that limit the extrapolation of an estimated PFS curve:

- There was a higher proportion of patients in first relapse in Schirmbeck et al. 2016, indicating differences in disease burden between study populations (61% in Schirmbeck et al. 2016 vs. 28% in SCHOLAR-1). Patients in first relapse may have better survival than patients in 2nd + relapse.
- Patients in Schirmbeck et al. 2016 were treated with R-DHAP salvage therapy followed by high dose chemotherapy and stem cell transplantation (SCT), which can impact long-term outcomes, whereas not all patients in SCHOLAR-1 received SCT.
- The magnitude of difference in survival outcomes was high between Schirmbeck et al. 2016 and SCHOLAR-1, raising concern about the comparability of study populations (Schirmbeck et al. 2016: median PFS of 29 months and median OS of 37 months; SCHOLAR-1 median OS of 6.6 months).

Survival assumptions for responders versus non-responders

Genentech recommends a sensitivity analysis be performed on the survival outcomes of the responder and non-responder patients. The model currently assumes that PFS and OS do not depend on response status and is reported as an average between responders and non-responders. This assumption may have a significant impact on the incremental model outcomes because different proportions of responders are observed across treatment arms in the model. This assumption also suggests that the survival of patients who never respond to treatment is equal to the survival of patients who respond and ultimately stop responding to treatment (e.g. survival is not adjusted to response status). The validity of this assumption is questionable because these two patient groups are inherently different such that patients who initially respond may have better outcomes than those patients who never respond. ICER can address this limitation by adjusting the survival curves to reflect the expected difference in survival between these two population groups. This adjustment factor should be informed by expert clinical advisors.

The current model also assumes that patients with complete response (CR) and partial response (PR) have the same survival outcomes. However, the clinical data suggests that outcomes are worse for patients with PR based on the median DoR (1.9 mo PR vs. could not

be estimated CR).² Therefore, the incremental clinical benefit with axicabtagene ciloleucel vs. salvage chemotherapy may be misestimated in the model. We suggest applying an adjustment factor for the survival of patients with CR vs. PR and vary this assumption in sensitivity analysis to understand the impact of changes in the model results. The adjustment factor should be informed by clinical experts.

Cure model to estimate long-term survival outcomes

To increase the rigor and complement the long-term survival estimates of the current analyses, we suggest that ICER use a cure model to estimate the plateauing of the survival curves.⁶ A cure model can be an alternative approach to the Cox proportional hazards model when survival curves are expected to have plateaus at the end of the tails. It can also be used to describe patient populations who are likely to be long-term survivors.

The validity of the current methodological approach to estimate long-term survival is uncertain due to limited follow-up. The current analysis takes a piecewise approach by separating parametric curves at months 0-12 and years 1-5 in order to address the “flattening” of survival curves. It was assumed that the survival curve in years 1-5 was flatter, representing durable response and long-term survival. It is unclear whether 1-year is an appropriate time point to estimate the flattening of the survival curve given the lack of long term data of a new therapeutic class. Furthermore, the appropriate time point for this plateau should be informed by clinicians with established expertise in hematology and use of CAR-T therapies.

3. Real-world data should be used to estimate the cost and clinical outcomes of salvage chemotherapy

We recommend that the costs and outcomes for salvage chemotherapy treatment be based on real-world data such as administrative claims data and medical chart review. ICER has selected R-DHAP to inform the costs and outcomes of salvage chemotherapy (comparator) in the cost-effectiveness model. The rationale for selecting R-DHAP only is unclear given the multitude of treatment regimens used in refractory DLBCL setting. In the NCCN guidelines, 14 combination treatments with or without rituximab are recommended depending on patients' candidacy for high dose therapy.⁷ Furthermore, the use of real-world data to characterize clinical outcomes in a broad salvage chemotherapy population will help address the limitations in deriving a hypothetical PFS curve. If there is a lack of real-world analyses in published literature, ICER should conduct such analyses in order to support their value framework assessment.

4. Additional comments for consideration

Treatment costs for R-DHAP should be based on the regimen and should not include other costs so that patients, physicians, and payers understand the actual treatment regimen costs.

ICER's current estimate of the cost of R-DHAP (\$46,096) should be further clarified as it is unclear whether treatment costs represent R-DHAP only or include additional healthcare costs that are not described in the report. The estimated drug cost of R-DHAP is \$38,311.20 based on the drug acquisition per-unit costs, ICER's hospital mark-up and a BSA assumption of 2.0 m². We suggest that the drug treatment costs alone for R-DHAP be represented separately, and the difference in costs (approximately \$7,784.80) be reported as palliative care.

Please note that we assume treatment administration included 3 cycles of rituximab (375 mg/m²) on day 1 of each cycle with an additional rituximab (375 mg/m²) on day 1 of the first cycle; 3 cycles of dexamethasone 40 mg on days 1-4 + cytarabine 2g/m² every 12 hours for 2 doses on day 2 + cisplatin 100 mg/m² on day 3.

Summary

Given the evidence gaps in clinical data and long-term benefit, we recommend that ICER provide more detailed clinical rationale for their assumptions, conduct additional sensitivity analyses, and communicate the strengths and limitations of the value framework evaluation to the public. Further, it is imperative that ICER inform and educate the voting panel, which is comprised of a diverse set of healthcare decision makers who may not have the oncology expertise to fully appreciate the complexities of treating B-cell malignancies.

In closing, Genentech appreciates the opportunity to provide comments to ICER's ongoing value framework evaluation. We hope these comments will contribute to a more robust assessment.

Sincerely,



Jan Hansen, PhD
Vice President, Evidence for Access
Genentech, U.S. Medical Affairs

Refer to the Rituxan prescribing information for the full FDA-approved indications and safety information, available at: https://www.gene.com/download/pdf/rituxan_prescribing.pdf

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C#18-M0006

January 24, 2018

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Submitted via email: publiccomments@icer-review.org

RE: Juno's Response to the Institute for Clinical and Economic Review (ICER) Draft Report on Chimeric Antigen Receptor T-Cell for B-Cell Cancers: Effectiveness and Value

Juno appreciates the opportunity to comment on the ICER Draft Report "Chimeric Antigen Receptor T-Cell for B-Cell Cancers: Effectiveness and Value." The introduction of CAR-Ts as a new paradigm of oncology therapy addresses a significant unmet need in the treatment of B-cell ALL and aggressive B-cell lymphomas, specifically among patients who have relapsed or are refractory to earlier lines of chemotherapy and stem cell transplantation. These populations represent a group of patients with very poor clinical outcomes and limited treatment options. The introduction of innovative CAR-T therapies can play a meaningful role through value brought to patients, providers, payers, and society, and the conclusions by ICER reflect this value.

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 developing multiple cell-based product candidates to treat a variety of B cell malignancies as well as multiple solid tumors. Although Juno's investigational CAR-T therapy (JCAR017) is not currently evaluated in the draft evidence report, we recognize the importance of the review to CAR-Ts as a therapeutic class and seek to provide comments to improve the robustness of the report.

Juno recognizes the Draft Report includes many comprehensive methods and analyses, but key issues may influence the credibility and interpretation of conclusions. The concerns include:

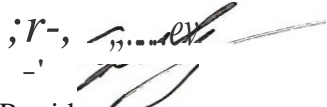
- (1) The comparator selected for aggressive B-cell lymphoma is flawed and results in downstream limitations to the analyses and interpretation of results. The use of the R-DHAP regimen for comparator costs, despite only representing a small fraction of the therapies used in SCHOLAR-1, reflects a lack of alignment across the sections of the report.
 - Recommendations: ICER should (1) conduct a systematic review of literature which includes the comparator regimens that represent a broader sample of commonly utilized salvage chemotherapy regimens; (2) provide clarity as to which comparator(s) are considered salvage chemotherapy by including specific treatment regimens and costs or scenario analyses with higher cost therapies from the SCHOLAR-1 study, such as R-Bendamustine, R-ICE and other forms of salvage chemotherapy and biologics (e.g. ibrutinib); and (3) ensure that all clinically-relevant model inputs are consistent with the results of the systematic literature review.
- (2) Key model inputs, such as the administration and monitoring costs, lack transparency on how they were determined and presented. A lack of scenario analyses around some of these key input hinders the ability to assess the sensitivity of the model outcomes.

- Recommendations: ICER should (1) provide details on all inputs and parameters to allow for validation and improved interpretation; (2) test the impact of the monitoring costs based on length of stay; (3) conduct a scenario analysis with a shorter "time to cure;" (4) where possible, quantify and specify the direct non-medical costs in the societal analysis to capture the travel burden experienced by patients as well as caregivers
- (3) The research protocol and resulting gaps in search terms lead to an imbalance in collection and documentation of short- and long-term adverse events for the comparators and subsequently results in the application of multiple methods to account for treatment-related disutilities.
- Recommendations: ICER should (1) comprehensively capture the rates of all anticipated adverse events for all therapies to accurately compare the potential harms and disutility of treatment; (2) consistent application of disutilities for each treatment arm, utilizing a single method to account for any treatment-related disutilities.
- (4) The implied inclusion of all direct medical costs with a predefined health system perspective is misleading, especially when cost inputs for the healthcare utilization reflect the differing perspectives of hospital costs, private payer's reimbursements, and Centers for Medicare and Medicaid Services (CMS) payments.
- Recommendation: ICER should (1) provide a more precise definition of the health system perspective and ensure that all model inputs are aligned with the intended audience.
- (5) The current clinical and economic evaluation structure and inputs would prevent accurate future comparisons between individual CAR-T products.
- Recommendation: The report should (1) acknowledge that the present analysis is limited to current CAR-Ts compared to a class to salvage chemotherapy; (2) clearly document the limitations of the current model design to inform future evaluations that may be built off of this initial CAR-T evaluation; (3) lower grade AEs, manufacturing differences, and potential clinical outcome differences that result from complete and partial response rates should be included in any future CAR-T to CAR-T analyses.

Details on the above issues are summarized on the subsequent pages along with recommendations on how to address such issues within the Final Version of the ICER CAR-T Report. In addition, ICER should carefully align the draft voting questions with the design and results of the report. The lack of consistency between the report and questions may lead the audience to overgeneralize the results and draw unwarranted conclusions. For example, question 10 references long-term value relative to regimens within SCHOLAR-I, but the economic evaluation only includes one regimen for costing. Generalizing the voting questions may misrepresent the conclusion of the Draft Report.

Conclusions:

Juno recommends ICER address the above-noted issues in the CAR-T Draft Report. Addressing such issues will produce a more balanced and methodologically sound value assessment that aligns its methods, inputs, and assumptions with health economics good research practices, clinical guidelines, and real-world clinical practice.

Sincerely, / 
 Robert Azelby
 Executive Vice President
 Chief Commercial Officer

Details of each issue are summarized below:

(1) The comparator selected for aggressive B-cell lymphoma is flawed and results in downstream limitations to the analyses and interpretation of results. The use of the R-DHAP regimen for comparator costs, despite only representing a small fraction of the therapies used in SCHOLAR-1, reflects a lack of alignment across the sections of the report.

ICER compares CAR-T therapies to a non-specific class of "salvage chemotherapy." The resulting generalization of the comparator limits the value of the systematic review due to the limited search strategy selected and applied. This further results in a heavy reliance on the single SCHOLAR-I study¹ as it relates to the efficacy and safety of the clinical and economic comparator. ICER cites SCHOLAR-I as the source for the model inputs within the "salvage chemotherapy" arm for the lymphoma population. SCHOLAR-I presents a pooled analysis of four studies²³⁴⁵⁶⁷ with multiple therapy options including HyperCVAD, R-Bendamustine, R-ICE, R-DHAP, ESHAP, Gem-OX, R-GDP, and others.

The reference to SCHOLAR-I for salvage chemotherapy would thereby be expected to translate into a weighted cost input from multiple regimens in the economic model; however, ICER represents the cost of these pooled treatments with the R-DHAP regimen only. Among the array of treatment options reported within SCHOLAR-I, R-DHAP is the least costly regimen. The use of the R-DHAP regimen to represent the cost of the comparator is misleading as R-DHAP is reported to account for only 14% of the treatments in the MDACC study² and 50% of the treatments in the LY12.³ Thus, the use of the lowest cost chemotherapy option is not supported by the source documents reporting on the use of the therapy within the pooled analysis and represents biased cost inputs for the comparator.

(2) Key model inputs, such as the administration and monitoring costs, lack transparency on how they were determined and presented. A lack of scenario analyses around some of these key inputs hinders the ability to assess the sensitivity of the model outcomes.

Cost Inputs

ICER does not itemize or cite the administration and monitoring resources used for the CAR-T therapies. Administration and monitoring costs are likely to vary considerably based on the assumed length of stay assumptions for CAR-T. In addition, the application of a single hour for administration per salvage chemotherapy cycle is not accurate based on recommended dosing regimens. At a minimum, current NCCN guidelines report R-DHAP (the regimen used for costing) requires 3 days of administration per cycle.⁸

Improved transparency is also needed on the 31- and 15-inpatient hospital days of therapy for KYMRIATM and YESCARTATM that are used in costing the monitoring costs for CAR-Ts. These numbers are not supported by references to the literature or trials and do not match our understanding of the administrative burden for the CAR-T therapies. YESCARTATM patients are expected to have an inpatient stay of between 7 and 10 days.⁹ The modeled length of hospitalization for any therapy will have a substantial impact on the total costs and should be described in detail with supporting citations.

Lastly, ICER's calculated future healthcare costs are substantially lower for chemotherapy patients than for YESCARTATM patients (\$36,286 vs \$99,293) without supporting detail on the inputs used to arrive at these figures. It is logical that increased survival with CAR-Ts will result in greater future healthcare costs, but the lack of detail on the inputs used to arrive at these figures and sensitivity analyses evaluating the impact on results should be addressed.

5-year Event-free Survival Assumption

The model operates under an assumption that patients with event-free survival for five-years are effectively cured. Any patient who is alive but not responding to therapy enters the death state by the end of year five. While the assumption of a prognostic value of a five-year cure is similar to a previous NICE evaluation specific to ALL,¹⁰ it is not aligned with the literature findings ICER cites in their report. For the lymphoma population, ICER discusses a 2014 publication¹¹ which suggests that event-free survival of two-years is a reasonable surrogate outcome for a cure, while also citing an additional publication¹², that states children with ALL in remission for four-years could be considered cured. Within the lymphoma population, the survival curves for SCHOLAR-1 also suggest that 2-years of event free survival are prognostic of long-term outcomes. Despite published findings suggesting shorter durations as adequate markers for returning to normal health, sensitivity analyses do not directly test this assumption.

Societal Perspective

The scenario analysis that takes a societal perspective lacks key elements such as potential long-term productivity. The scenario analysis results in an increase in the baseline cost-effectiveness by \$1,196 per life year for KYMRJAHTM and \$1,171 per life year for YESCARTATM.¹⁴ These uncharacteristic decreases in value when assessed from a societal perspective are due to an incomplete analysis of costs and outcomes. The model omits the long-term productivity benefits for those patients who survive, thereby discounting the value of the potential durable benefits of CAR-Ts. The durability gain may be a key benefit, particularly for the ALL population, where the patients have the potential for many years of productivity if they age into the workforce. In addition, to more accurately capture the societal costs, ICER should accurately capture the costs of travel multiplied by the number of visits required for therapy. While only certain facilities are currently administering CAR-T therapies, it is reasonable to anticipate that the delivery will expand to more centers -including outpatient centers -in the near future.

(3) The research protocol and resulting gaps in search terms lead to an imbalance in collection and documentation of short- and long-term adverse event for the comparators and subsequently results in the application of multiple methods to account for treatment-related disutilities.

The lack of inclusion of the comparator therapies in the search strategy resulted in the absence of a description of the adverse events rates and severity within the clinical comparativeness section. This omission of detail is a fundamental flaw of the report as it defeats the purpose of a 'clinical comparativeness' section; which is to have the model inputs be informed by the findings within the clinical comparativeness section. As a consequence, ICER applies a generalization of the adverse events associated with the chemotherapy regimens by applying a global disutility to account for the reduction in quality of life while receiving each treatment, as well as with stem-cell transplantation. In contrast, disutilities are assigned for individual adverse events associated with the CAR-T therapies, such as cytokine release syndrome. ICER claims that the important harms commonly associated with CAR-T therapy are arguably no worse than the serious adverse events associated with chemotherapy.¹⁴ Thus, the application of multiple methods to account for treatment-related disutilities is unwarranted and can have a potential negative impact on the model results for the CAR-T therapies.

(4) The implied inclusion of all direct medical costs with a predefined health system perspective is misleading, especially when cost inputs for the healthcare utilization reflect the differing perspectives of hospital costs, private payers reimbursements, and Centers for Medicare and Medicaid Services (CMS) payments.

ICER's use of an equivocal "health system" perspective does not clearly define the intended audience for the report, which impairs the interpretation of the results. Table D10¹⁴ in the report appendix provides detail on the inputs for unit costs of healthcare utilization, however, the referenced sources are not

unanimously applicable to all perspectives. For example, the HCUP statistical briefs^{15, 16} provide cost data for adult and pediatric hospital day utilization and reflect the costs of operation within a hospital setting. Yet the Physicians' Fee and Coding Guide¹⁷ represents bundled payments from CMS for an event associated with treatment. Having multiple perspectives of costs makes the interpretation of the results difficult, because the hospital costs and subsequent payments are usually not perfectly aligned, and can essentially offer multiple definitions of costs for the same event. These costs represent multiple perspectives of the same healthcare utilization event resulting in an unclear perspective.

(5) The current clinical and economic evaluation structure and inputs would prevent accurate future comparisons between CAR-Ts.

The current Draft Report compares CAR-Ts to salvage chemotherapy. Any future evaluation that may compare CAR-Ts to other CAR-Ts must address the significant shortcomings in the current model design.

The inclusion of lower grade adverse events becomes especially relevant for CAR-T to CAR-T analyses. The economic model assumes that only adverse events of grade 3 or 4 are clinically relevant. While Juno agrees that grade 3 and 4 adverse events are likely to have the most significant impact on the costs and patient health utility, grade 1 and 2 adverse events can significantly impact patient health outcomes and utility. The ambiguity in disutility by grade is especially true for cytokine release syndrome (CRS), for which multiple grading systems exist. Each system defines the grading criterion differently and allows for varying interpretations of what is considered to be a grade 3 or 4 event. Both grading scales recognize that grade 2 CRS may be accompanied by moderate organ toxicity/dysfunction, requiring intravenous drug administration and potentially requiring hospitalization for management and continued monitoring.^{18, 19} When considering that rates of grade 1-2 CRS are 35% for Kymriah^{TM20} and 81% for Yescarta^{TM21}, the cost of care for such an event is likely to be substantial and impact the patient's health and quality of life. The inclusion of the lower grade events is supported by a recent study assessing the impact of chemotherapy-related adverse events on the health utility and patient-reported outcomes, which found that some grade 1 and 2 adverse events are significantly associated with disutility, as measured by the EQ-5D-3L scale, and should be incorporated into economic models.²²

Additionally, ICER's use of an overall response rate to determine long-term survival rates may bias future CAR-T analyses. Under this current framework, ICER will not be able to comprehensively compare CAR-T therapies against each other. Survival curves stratified by complete and partial response in DLBCL have been shown to be statistically different and suggest that complete response may result in improved survival over partial response.²³ While the current model framework adequately captures the relative benefit of CAR-Ts compared to chemotherapy, a more granular estimation of survival, using stratified responses, is necessary for any future comparisons between CAR-T therapies.

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Kite, a Gilead company, is pleased that ICER's analysis confirms Yescarta's cost-effectiveness and clinical benefits in terms of gains in quality-adjusted and overall survival compared to chemotherapy for the adult relapsed/refractory B-cell lymphoma population. However, Kite believes further changes can be made to ICER's analysis to reflect clinical realities and best practices for the assessment of health technologies.

GENERAL RECOMMENDATIONS: Reorganize presentation for clarity

The presentation of results for pALL vs. NHL is misleading. Parallel presentation of results implies cross-disease comparison. Kymriah is only evaluated for pediatric relapsed/refractory B-ALL and Yescarta only for adult relapsed/refractory aggressive B-cell lymphoma.

Recommendation: Present reviews of leukemia results and lymphoma results separately. Clearly specify population ("pediatric relapsed/refractory B-ALL" or "adult relapsed/refractory aggressive B-cell lymphoma" as opposed to "Population 1/2") for all analyses and results.

THERAPEUTIC SUMMARY AND COMPARATIVE CLINICAL EFFECTIVENESS

Kite is encouraged that ICER has recognized the clinical effectiveness of Yescarta, whose response rates for adult patients with large B-cell lymphoma continue to be supported by longer term evidence. The follow-up for Yescarta is longer than any of the other CAR-T therapies included in ICER's review.

On p. 7, the report notes that "Some data suggest that CD28-based CAR-T cells have a more rapid initial proliferative response, while the 4-1BB-based CAR-T cells may drive more progressive T cell accumulation, which serves as a counterbalance to their lower immediate potency." These two CAR-T therapies are in different diseases, making comparisons related to efficacy inappropriate. As a result, these therapies have not been studied head-to-head in a prospective randomized trial, and therefore the clinical significance of these mechanistic differences are not fully understood.

Recommendation: Remove cross-study/disease comparisons and specifically the sentence "Some data suggest that CD28-based CAR-T cells have a more rapid initial proliferative response, while the 4-1BB-based CAR-T cells may drive more progressive T cell accumulation, which serves as a counterbalance to their lower immediate potency" (p. 7).

HOSPITAL MARK-UP: Follow established practices and ensure real-world consistency

ICER has added a substantial hospital mark-up to the cost of Yescarta (\$100,000 or 27%), despite the fact that no mark-ups are included in the reimbursement mechanisms that are used in practice and likely to be applied to Yescarta.

Medicare reimbursement for inpatient services are based on Medicare Severity (MS) Diagnosis Related Groups (DRGs), where costs for all inpatient services and drugs associated with CAR-T treatment, including the therapy itself, would be rolled up into one payment. Similarly, for commercial coverage, CAR-T inpatient administration could be reimbursed using several methods, none of which have incorporated a mark-up to date: as part of a DRG, under a case rate, or at a *per diem* cost. In any of these methods, the cost of Yescarta would most likely be covered as a pass-through payment (at WAC). Therapies reimbursed through pass-through payment do not include a mark-up. For example, for allogeneic stem cell transplant, the cost is often a pass-through and, based on early market research, Kite expects that a number of payers will employ similar pass-through pricing for Yescarta (0% mark-up).

The decision to implement a mark-up appears to be *ad hoc*, may be subject to bias, and interferes with pricing and reimbursement agreements between hospitals and payers, in which Kite has no involvement. ICER does not provide a reference case from the cost-effectiveness literature indicating what an appropriate mark-up should be. Further, the analysis lacks a clear and validated framework on how to apply mark-ups, and the methodology used has led to an unrealistically high estimate. For example, ICER cites a mark-up of ASP+152% for treatment obtained under commercial insurance based on an editorial that lacks any description of how this figure was estimated (e.g., which oncology treatments, populations, time frame, and care settings). ICER then used a mark-up cap of \$100,000. Kite disagrees that a cap is necessary and further feels it should NOT be employed at all given concerns with ICER's estimated mark-up. Further, ICER derives this cap based on discussions with stakeholders without describing the formal scientific process used for estimation. Finally, the mark-up leads to confusing policy, as the current report holds Kite responsible for costs negotiated between hospitals and payers. While payers reimburse hospitals, the policy implications of such mark-ups are distinct from manufacturer drug costs.

Recommendation: Align with real-world pass-through pricing and follow established practices by NOT applying a hospital mark-up to Yescarta in base case.

HEALTHCARE COSTS AND UTILIZATION: Align with real-world clinical practice

Several of ICER's estimates of healthcare use and costs do not capture real-world clinical practice. ICER's application of *per diem* costs for hospital stays overestimates the actual costs of procedures, which instead follow pricing by DRG as discussed above.

Specifically, to estimate the cost of the hospitalization for CAR-T administration, ICER applies a 15-day hospital stay (Table D11) at a rate of \$4,075 per day (Table D10), for total over \$60K. This total cost is well-above the cost for DRGs comparable to those that would be employed to cover hospitalization for Yescarta administration. The reference ICER cited for this cost (HCUP Statistical Brief #125) provides a *per diem* hospital cost of \$2,400 for Non-Hodgkin's lymphoma. We were unable to find reference to the \$4,075 cost per day used by ICER in this brief. ICER previously used 2016 Kaiser State Health Facts for a cost per hospital day of \$2,357.

ICER also applies a *per diem* add-on for ICU stay, thus overestimating this cost. DRGs (or case rates, for commercial payers) are a lump sum by design and include all inpatient services and drugs under the bundle. Hospitals cannot add DRGs for AEs while hospitalized, but instead use the DRG with (major) complication/comorbidity ((M)CC). The cost for DRGs with (M)CC would be greater than the original DRG, but would not amount to an incremental ICU stay.

Similarly, under the DRG-based billing practice, the cost of tocilizumab should not be an add-on cost but instead covered under the DRG for the initial hospitalization. For example, the CMS summaries of the 2015 national and state inpatient charge data for "lymphoma and non-acute leukemia" DRGs (842 without CC/MCC, 841 with CC, and 840 with MCC) list average total payments to all providers as \$8,977.53, \$13,247.50, and \$26,147.32, respectively.¹ These costs are well below the \$60K hospitalization cost plus add-on costs of AEs employed by ICER.

¹ 2015 are the most recent data. Data are available for download: <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Inpatient2015.html>

The report also contains errors regarding healthcare utilization. First, as in Crump et al. (2004), a small fraction of patients (7%) under chemotherapy obtain later rounds on an inpatient basis, yet ICER's chemotherapy regimen (Table D11) assumes all treatment is conducted on an outpatient basis. ICER should therefore add charges for inpatient stay to a fraction of patients under chemotherapy. Second, for patients experiencing cytokine release syndrome (CRS), ICER assumes an ICU stay of 8 days, which overestimates the stay for grade 3/4 CRS. In practice, the stay for grade 4 CRS is approximately 7 days, and based on the ZUMA-1 trial, occurred in only 5/108 (< 5%) of patients, and is included in the 15-day median stay for CAR-T administration. Further, as stated above, CRS-subsequent ICU stay or tocilizumab use should be collectively charged as a DRG with complication rather than costed as add-ons to the initial hospitalization.

Recommendation: Correct cost of hospitalization for CAR-T administration to \$2,357 per day. Account for ICU admission due to grade 4 CRS by replacing 7 days of initial hospitalization with 7 days of ICU stay (ICU stay should not be an add-on to the hospitalization for CAR-T administration). Incorporate inpatient treatment for chemotherapy patients (7%). Remove tocilizumab add-on cost to reflect DRG pricing practices.

ADVERSE EVENT RATES: Align with clinical trial evidence

ICER overestimated the rate of IVIG therapy utilization for those treated with Yescarta. Approximately 15% of ZUMA-1 patients experienced hypogammaglobulinemia, and a further subset (8% of those treated with Yescarta) received IVIG treatment. These treatment practices are consistent with NCCN and other guidelines, which specify IVIG treatment only if patients have "recurrent infections" due to hypogammaglobulinemia (Baden et al, 2018, Sullivan et al, 2001, Compagno et al, 2012). ICER's description of B-cell aplasia (p. 8) indicates all patients experiencing hypogammaglobulinemia are treated with IVIG, which is incorrect. Further, B-cell aplasia is also a chemotherapy outcome, but omitted by ICER (Casulo et al 2013 and Makatsori et al 2014). For example, one study found that 6.6% of lymphoma patients treated with rituximab were treated with IVIG (Casulo et al, 2013). Further, ICER applied a febrile neutropenia rate of 93% subsequent to Yescarta use, whereas the rate should be 36% as per the label.

Recommendation: Revise text on p. 8 to "This can cause long lasting hypogammaglobulinemia. In patients with severe or recurrent infections, intravenous immunoglobulin replacement is given until the B-cell aplasia resolves." Table D7: add hypogammaglobulinemia grade 3+ rate at 0% (of note, only 15% experienced any grade) and remove B-cell aplasia. Apply IVIG to 8% of patients treated with Yescarta as in ZUMA-1. Apply IVIG treatment to 6.6% of chemotherapy patients as in the literature. Correct febrile neutropenia rate to 36% as per Yescarta label.

FUTURE MEDICAL COSTS: Adhere to established best practices

ICER has estimated large future healthcare costs associated with increased longevity due to treatment from Yescarta. The implementation is concerning because ICER has not issued guidance on a reference case, thus the inclusion of future costs in ICER evaluations is subject to inconsistency and the methods used are not standardized (Sanders et al, 2016). Without a reference case, ICER modeling teams have flexibility on whether or how to include future costs, and these costs and methods may be incorporated in an *ad hoc* fashion. For example, ICER has included future unrelated medical costs in their evaluation of CAR-T, but did not do so in their recent evaluation of treatments for ovarian cancer. Such heterogeneity across evaluations is inherently unfair to the technologies being evaluated and the patients who may benefit from these advances. If ICER chooses to include future medical costs, it should first issue a reference

case for its CEAs. Further, best practices suggest that only direct medical costs are included and that results are presented side-by-side with and without future costs (Olchenski et al 2015).

Additionally, in ICER's analysis that incorporates a societal perspective, productivity impacts are only included as costs due to treatment administration and ignore the likely substantial benefits to productivity through increased longevity due to therapy use. It is inconsistent to incorporate productivity costs but not benefits in the analysis, particularly given the inclusion of future medical costs in ICER's base case analysis. ICER should either include both productivity costs and benefits over the entire horizon, or exclude considerations of productivity impacts entirely. Simple assumptions could be used to incorporate future productivity impacts such as estimating extended life-years and applying the hourly wage or annual income.

Relatedly, ICER has not detailed the calculation of future healthcare costs or the included health services. This omission precludes confirmation that the components of future healthcare costs align with clinical practice and are accurately priced.

Recommendations: Issue and follow a validated reference case for future healthcare costs specific to lymphoma. If future healthcare costs are included, only include direct costs and provide side-by-side results with and without future medical costs, in alignment with best practices. Include productivity benefits through increased longevity OR remove analysis of productivity impacts altogether. Provide the breakdown of future medical costs by the health services utilized, for transparency and validation.

POTENTIAL BUDGET IMPACT: Remove mark-up and arbitrary threshold

Kite believes that the eligibility and uptake of Yescarta will not lead to a substantial budget impact. ICER's estimate of the eligible population for Yescarta likely overestimates the actual number of patients who will receive treatment. For example, comorbidities would reduce utilization relative to ICER's estimate. Prior literature on ASCT suggests about 10% of patients considered for Yescarta may have comorbidities precluding treatment (Sorrer et al., 2007).

ICER's estimated budget impact at WAC also includes the hospital mark-up, which obfuscates potential health-care savings solutions. As noted above, the hospital mark-up applied by ICER substantially overestimates actual reimbursement as many payers are likely to cover Yescarta as a pass-through (0% mark-up) and should therefore be removed.

Finally, Kite is concerned with ICER's use of an arbitrary budget impact threshold. This threshold is uniform across products in a given year and does not account for the literature demonstrating longstanding societal preferences to treat those affected by severe or life-threatening illness, such as in the case of Yescarta (Dolan et al, 2005; Shah, 2009; Ubel, 1999).

Recommendation: Remove mark-up from base case budget impact. Do not use arbitrary budget impact threshold.

OUTCOMES-BASED CONTRACT: Reflect real-world status of agreement

ICER has applied an outcomes-based contract (OBC) in the leukemia base case and in scenario analyses for lymphoma. OBCs remain hypothetical, the data continues to mature, and details of any such agreements remain to be set.

Recommendation: Note that OBCs for either leukemia or lymphoma have not been published at this time.

SOCIETAL PERSPECTIVE: Apply societal preferences

As noted above, an extensive literature demonstrates societal preferences to treat the severely ill (Dolan et al, 2005; Shah, 2009; Ubel, 1999). Relatedly, ICER's ultra-rare value framework recommends a willingness-to-pay threshold of \$500,000 per QALY for therapies that treat 10,000 individuals or fewer, based on societal preferences to treat patients suffering from rare or severe disease. As such, Kite recommends that ICER's societal perspective should employ higher willingness-to-pay thresholds to accommodate such preferences for potentially life-saving treatments such as Yescarta. This aligns with ICER's eligible population for Yescarta being within the ultra-rare category and with the FDA designation of Yescarta as an orphan drug².

Recommendation: Consider willingness-to-pay thresholds that align with the rationale behind ICER's ultra-rare disease value framework, given societal preferences to treat those with severe disease and the eligible population size for Yescarta.

HORIZONS SCENARIO: Remove irrelevant short-term horizons

ICER has included results for a variety of shorter-term time horizons. The purpose of including time horizons at 1, 5 and 10 years is unclear, given the established practice of using a lifetime horizon. In particular, a time horizon of 1 year for lymphoma treatment almost entirely precludes incorporation of the health benefits of the therapy.

Recommendation: Remove scenario analysis with shorter time horizons.

MISCELLANEOUS CORRECTIONS

The population description "Adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who are ineligible for auto-SCT" (p. 43) does not align with ZUMA-1.

Recommendation: Remove "ineligible for auto-SCT."

The report incorrectly notes that the NCCN guidelines have not been updated to incorporate axi-cel for DLBCL, FL, and PMBCL (p. 16-17). The current NCCN guidelines recommend axi-cel in adult patients with ≥ 2 relapses or inadequate response to second-line therapy (PR as best response) for DLBCL/PMBCL, and ≥ 2 chemoimmunotherapies or inadequate response (PR as best response) to first-line anthracycline-containing chemoimmunotherapy for TFL.

Recommendation: Update text to reflect new NCCN guidelines incorporating axicabtagene ciloleucel in lymphomas.

Table 4.3 states that 52/83 patients experienced CR in B2202/ELIANA. However, the text on p. 25 notes that 88 participants enrolled in the trial. The CR rate is also higher in the intention to treat estimate for B2101J in Table 4.3 than the modified intention to treat estimate in Table 4.2. Please confirm the accuracy of these numbers.

Recommendation: Confirm accuracy of values in Table 4.3 and ensure analysis is correct.

P. 28 and 30 of the report incorrectly note that the ZUMA-1 trial had median follow-up of less than one year. Median follow-up for the ZUMA-1 data in the report is 15.4 mos.

Recommendation. Correct ZUMA-1 trial follow-up (15.4 mos.).

² <http://ir.kitepharma.com/releasedetail.cfm?releaseid=968528>

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Comments on ICER's Draft Evidence Report of Chimeric Antigen Receptor T-Cell Therapy

Executive summary

Novartis appreciates the opportunity to submit comments on the Draft Evidence Report "Chimeric Antigen Receptor T-Cell Therapy (CAR-T) for B-cell Cancers: Effectiveness and Value." Novartis is committed to a comprehensive and evidence-driven approach to value its compounds. We appreciate ICER's efforts towards this evaluation and ICER's willingness to engage various stakeholders during the review process. Meanwhile, we believe the following approaches should be revised in the evaluation:

1. Intent to treat analysis: Novartis suggests that the revised report evaluate CAR-T therapies' efficacy from the time of infusion instead of from leukapheresis.
2. Clinical efficacy assessment: although the criteria used for assessing quality of evidence are well established, this method underestimates the quality of clinical trials for rare and life-threatening diseases.
3. Approach to estimating mark-up rates in the draft report: Novartis suggests that the revised report incorporates appropriate mark-up rates considering the treatment settings (e.g., outpatient vs. inpatient).
4. Approach to estimate potential budget impact: Novartis suggests that the budget impact analysis (BIA) framework in the draft report be revised to incorporate realistic market uptake of the new intervention.

Our detailed comments are below:

Comments applicable to both the acute lymphoblastic leukemia (ALL) and lymphoma evaluations

Approach to evaluate efficacy of CAR-T starting from leukapheresis:

- Novartis suggests that the analytical framework be revised to include patients without CAR-T infusion in the clinical and cost effectiveness assessments. The reasons are specified below:
 - This approach is not standard for analyzing efficacy data for comparable technology. For example, allogeneic stem cell transplantation (alloSCT) is the only curative option for pediatric patients with relapse or refractory ALL and evaluations of alloSCT always focus on the patients who received SCT.^{1,2} Even though a large percentage of patients who cannot proceed to alloSCT due to patient health status (such as the lack of remission before transplantation) or a lack of a matched donor, clinical assessments (i.e., survival data) are always reported for patients who received alloSCT in the literature. There are no studies reporting efficacy in patients who have not received alloSCT.
 - It is important to note that the wait time and dropout rate between leukapheresis and infusion observed in tisagenlecleucel clinical trials was not due to the drug's intrinsic efficacy, nor a manufacturing failure, but rather a logistical situation only applicable in early trials. At the start of these early clinical trials, demand from enrolled patients outweighed manufacturing capacity; therefore, patients had to wait for an available manufacturing slot. This contributed to the observed wait time and dropout rate in the trials. As manufacturing capacity increased, the wait time and dropout rate (currently 7%³) declined.
 - Leukapheresis can be done even before consideration of CAR-T treatment in clinical practice.
- Based on the comments above, Novartis recommends that the analytical approach is reconsidered, starting the evaluation from the time of infusion for CAR-T therapies.

Rating of tisagenlecleucel's clinical benefits:

- The draft report assigned a B+ rating for the clinical benefits of tisagenlecleucel in both pediatric ALL and adult lymphoma. This was based on the consideration that, despite the substantial estimated net health benefit, the level of certainty is low because there are no comparative trials and the existing single-arm trials of tisagenlecleucel have small sample sizes with relatively short follow-up times (pgs 35-36).
- We acknowledge that the existing clinical trials of tisagenlecleucel are single arm trials with relatively small sample sizes. However, 3 clinical trials have been conducted in pediatric ALL and 2 clinical trials have been conducted in adult lymphoma. The median follow-up times were 18.6 months in the B2101J trial in pediatric ALL⁴ and 28.6 months in the NCT02030834 trial in adult lymphoma.⁵ Across all trials, the efficacy of tisagenlecleucel remained consistent. Furthermore, the trade-offs between waiting for long-

term follow-up data vs. efforts to make the drug available earlier to the patients in need should be carefully considered, especially in regards to life-threatening rare diseases. Waiting for long-term follow-up data in such situations could be impractical and may raise ethical concerns.⁶

- Fundamentally, Novartis questions the suitability of the criteria used in the draft report to evaluate the level of certainties for rare disease like relapsed/refractory (R/R) pediatric ALL and R/R adult lymphoma. The assessment matrices used in the draft report consider whether the trials are double-blinded with a control group, and the comparative evidence observed in trials. While these criteria are suitable in diseases with high prevalence, this methodology is not applicable for rare and life-threatening disease with no effective standard of care. In fact, randomizing terminally ill patients to the control arm of a potentially life-saving therapy raises ethical concerns.^{7,8} This is the case for both R/R pediatric ALL and R/R adult lymphoma, which have estimated affected populations (617 and 6,223 in the draft report, respectively) well below the threshold (200,000) used by the FDA to classify a rare disease, and below the ICER ultra-rare disease threshold (10,000).^{9,10} The FDA guideline for rare diseases states that controls may be concurrent or historical in these situations.⁹
- Thus, Novartis recommends that the clinical evidence rating for tisagenlecleucel be reconsidered in both indications and revised from B+ to A. Novartis also suggests that the trial quality Tables C4 and C10 be updated from "lower quality" to "good or fair quality." This rating was assigned in the draft report due to lack of comparators in the clinical trials, but as these diseases are rare and without effective standards of care, it would be unethical to have a control arm in these trials. In these situations, the clinical evidence must rely on single-arm trials.⁸ Novartis would welcome an opportunity to develop a different quality assessment methodology for rare and life-threatening diseases with no effective standard of care.

Approach to estimate the potential budget impact:

- Novartis understands that the purpose of the BIA is to generate an "access and affordability alert" if the budget impact for the indication under consideration exceeds a pre-defined threshold. Novartis has concerns regarding the current approach, as it assumes that all eligible patients would be treated with new interventions without considering anticipated market uptake. This approach may cause a false affordability alert, and is inconsistent with the best practice recommended for BIA in the ISPOR guideline.¹¹
- The draft report noted that the current axicabtagene ciloleucel manufacturing capacity is only 4,000-5,000 per year, while the budget impact was estimated assuming that 6,223 would be treated (all potentially eligible patients). Real world evidence demonstrates that uptake is generally limited at first, and might increase over time. Based on estimation from an analyst report, only 600 and 1,200 patients are predicted to receive axicabtagene ciloleucel in 2018 and 2019, respectively.¹² Therefore, assuming all patients would be treated with a new intervention, without considering realistic market uptake and the entry of other interventions, is not reasonable, especially in the situation of cell therapies where the uptake is uncertain.
- Novartis suggests that the current BIA framework be revised to estimate the total budget impact incorporating realistic market uptake of the new intervention.

Mark-up rates:

- A mark-up of 76% for CAR-T therapies, and capped it at \$100,000 (pgs 44-45) was applied in the draft report. However, we believe these mark-up values do not reflect the actual mark-ups for CAR-T therapies applied in the real world. We respectfully recommend that several points be considered when updating the model:
 - Approximately 25% of patients received tisagenlecleucel in an outpatient setting based on the ELIANA (B2202) trial. Therefore, hospital mark-up should not apply for these patients.
 - Most academic centers and teaching hospitals in the provider network for tisagenlecleucel have 340B Drug Pricing Program certification,² allowing providers to obtain discounted prices on "covered outpatient drugs" (prescription drugs and biologics other than vaccines) from drug manufacturers. When tisagenlecleucel is administered in an outpatient setting under 340B program, CMS will only

pay the average sales price (ASP) minus 22.5%. Otherwise, the mark-up rate would be limited to 6% of the ASP based on the Outpatient Prospective Payment System billing instructions for Medicare.³

- In addition, the draft report noted that "Some facilities that may not negotiate a mark-up (i.e., they will manage CAR-T as a pass-through) while other facilities may charge a mark-up."
- Considering the above, we believe the \$100,000 mark-up rate is too high for CAR-T therapies.

Scenario analyses:

- We suggest updating the societal perspective analysis in the draft report to consider long-term societal benefits. The current societal perspective only considered productivity losses to patients and caregivers during the time of treatment (pgs 46, 53). This presents an imbalanced view of the impact of therapies, especially in pediatric ALL. Pediatric ALL patients receiving tisagenlecleucel can receive substantial health benefit, and both patients and caregivers can have subsequent work gain. Therefore, both short-term work loss and long-term work gain should be considered.
- Novartis recommends removing the scenario analysis of no active treatment therapy as a comparator (pgs 53-54), as the draft reports notes that this comparison may not be pragmatic, especially in pediatric ALL. The scenario analysis currently assumed there were minimal costs when patients received no active treatment (estimated at \$2,528 per data presented). Given that these are terminally ill patients, they are likely to incur significant expenses even if they do not receive active treatment.

Comment on cost per hospital day:

- The reference used by in the draft report for the cost per hospital day reported the daily cost as \$3,200 for pediatric ALL and \$2,400 for adult non-Hodgkin's lymphoma (NHL) in 2009 USD.^{13,14} After inflation to 2016 USD, the costs should be \$3,950 and \$2,962, respectively. We request that these values be updated accordingly, consistent with the inflation adjustment for other costs in the model.

Specific comments on the pediatric ALL evaluation

Hospital length of stay (LOS) assumption for clofarabine:

- Hospitalization was not considered for clofarabine-treated patients (pg 116). We respectfully believe this is not a reasonable assumption. Based on Locatelli et al. 2009, all patients treated with clofarabine combination therapy were hospitalized for the duration of treatment.¹⁵ The UK mock technology appraisal also considered that all patients treated with clofarabine monotherapy would have one episode of non-elective hospitalization for treatment.¹⁶
- We recommend using the same assumption as the UK mock technology appraisal (one episode of hospital stay).¹⁶ The average LOS per inpatient episode for relapsed pediatric ALL is 22.5 days.¹⁷

Size of potential candidate population for tisagenlecleucel:

- The draft report estimated the annual potential eligible pediatric ALL patients for tisagenlecleucel at 617, assuming 20.5% are refractory or in second or later relapse (pgs 58-59). Based on the reference cited by in the draft report (Nguyen et al. 2008)¹⁸, this rate actually reflects the proportion of patients in first relapse after initial diagnosis and is inconsistent with tisagenlecleucel's indication.
- We recommend that the following inputs are considered to estimate the eligible population:
 - Ceppi et al. 2016 reported that 2-3% of patients will become refractory following initial therapy.¹⁹
 - Cooper et al. 2015 reported that 15%-20% of patients with newly diagnosed (ND) ALL will experience first relapse;²⁰ among those, 51.7% of patients will be refractory to 2nd-line treatment (n=31 of 203) or suffer a second relapse (n=74 of 203) per Reismuller et al. 2009.²¹
 - Per the above, 9.8%-13.3% of ND patients would qualify as refractory or in second or later relapse.
- Based on these inputs, the annual eligible population for tisagenlecleucel is estimated to be 294-402.

Comment on SCT costs and others:

- Considering that 14.8% of clofarabine-treated patients received alloSCT (Table 5.4) at an estimated cost of \$560,000 (pg 45), the estimated cost of SCT for the clofarabine arm should be \$82,880. The reported cost was \$64,648 (Table 5.7). Please kindly update this value.
- Please change progression-free survival to event-free survival in the context of ALL (Table D4-5).

- The draft report commented that the follow-up time of the clinical trials of tisagenlecleucel in pediatric ALL was less than one year (pgs 26, 34-35). This statement should be revised, as the median follow-up time of the B2101J trial of tisagenlecleucel was 18.6 months.⁴

Specific comments on the lymphoma evaluation:

Review for tisagenlecleucel in aggressive B-cell lymphoma indication:

- The draft report did not include a cost-effectiveness analysis of tisagenlecleucel in adult lymphoma given that the key efficacy results based on the JULIET trial are not yet available. Novartis is currently in discussions with the FDA regarding this indication. Once the discussion is finalized and the data becomes publically available, Novartis is happy to assist ICER with the evaluation. We also agree with the position in the draft report that tisagenlecleucel and axicabtagene ciloleucel should not be directly compared given the differences in trial population and design, as listed below:
 - **Trial population:** The JULIET trial primarily enrolled DLBCL patients including transformed follicular lymphoma (TFL), whereas the ZUMA-1 trial enrolled patients with aggressive B-cell NHL including DLBCL, TFL, and primary mediastinal B-cell lymphoma (PMBCL). Patients with DLBCL tend to have a worse prognosis than those with PMBCL. In addition, the proportion of patients with prior SCT differed in these two trials (47% in JULIET vs. 21% in ZUMA-1).
 - **Participating centers:** JULIET was conducted in 10 countries, while ZUMA-1 was a US study. Worldwide shipments to and from trial sites increased the logistic complexity and wait time.
 - **Grading system for cytokine release syndrome:** As summarized on pgs 9-10, different grading systems were used in the JULIET (i.e. UPENN scale) and ZUMA-1 (i.e. Lee scale) trials.

Hospital LOS assumption for chemotherapy:

- Hospitalization was not considered for salvage chemotherapy (Table D11). Respectfully, Novartis does not believe this is a reasonable assumption. Huntington et al. 2017 reported that 60.7% of relapsed DLBCL patients were hospitalized. The average LOS per hospitalization for DLBCL was 11.6 days.²² Therefore, conservatively, relapsed patients would have a 7-day stay.

Size of potential candidate population for CAR-T therapies:

- When estimating the eligible population of axicabtagene ciloleucel in adult lymphoma, the draft report assumed that 60% of patients who responded to salvage chemotherapy and received an autoSCT were not cured (pg 59), based on Freidberg et al. 2010 who cited CORAL.²³ Based on CORAL, the proportion of patients who relapsed or died at year 3 should be 47% (i.e., 1- 53% PFS rate at 3 years).²³

SCT rate, costs and others:

- Considering a 29.9% subsequent autoSCT rate among patients receiving salvage chemotherapy, and an autoSCT procedure cost of \$187,145, the estimated autoSCT cost for the chemotherapy comparator should be \$55,956. The reported cost was \$13,771 (Table 5.7). Please kindly update.
- Only subsequent autologous SCT (autoSCT) was considered in the lymphoma evaluation (pgs 42 and 45). However, the evaluation should consider both subsequent autoSCT and allogenic SCT:
 - According to the NCCN guideline, both autoSCT and alloSCT are relevant in lymphoma. AlloSCT is an important treatment option, particularly for relapsed patients after prior autoSCT.²⁴
 - Patients enrolled in the ZUMA-1 trial received subsequent alloSCT.²⁵
 - The subsequent alloSCT rate was not reported in SCHOLAR-1, but it can be inferred from the CORAL publications. The CORAL study, included in SCHOLAR-1, reported that 17.6% of patients received alloSCT after an initial autoSCT (Van Den Neste et al. 2017)²⁶ and 3.9% of those without initial autoSCT received alloSCT (Van Den Neste et al. 2016).²⁷ Novartis requests that these rates and the prior autoSCT rate (22%) in SCHOLAR-1 be used to estimate the alloSCT rate (7%).
- The average alloSCT cost during the first year after procedure was \$473,005 (2016 USD).²⁸
- Novartis recommends that the knot used to model the overall survival (OS) of salvage chemotherapy be re-evaluated. Table D5 specified that after 14 months, there is only death due to all-cause mortality. This, however, is not supported by the OS curve in Crump et al. 2017.²⁹

Comments on the voting questions:

- **Question 7:** Novartis recommends removing this voting question as there are no head-to-head trials nor indirect comparisons between these products. In addition, there are significant differences in the pivotal trials for these therapies in terms of study populations, design, and the criteria for key adverse events.

Suggested corrections, organized by Table or Figure numbers

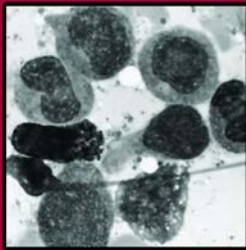
Item	Current Values	Corrected Values; References and Notes
Table 4.2 Clofarabine CR	20%	11%; Jeha et al. 2006. Table 2. ³⁰
Table 4.2 Clofarabine OR	30%	20%; Jeha et al. 2006. Table 2. ³⁰ Partial remission should NOT be included per pg 11 of the draft report.
Table 4.2 Clofarabine combination CR	44%	28%; Hijiya 2011, Table 2. ³¹
Table 4.2 Clofarabine combination OR	56%	44%; Hijiya 2011, Table 2. ³¹ Partial remission should NOT be included per pg 11 of the draft report.
Table 4.2 Blinatumomab CR	39%	17%; Von Stackelberg 2016, supplementary Table S6. ³²
Table 4.2 Blinatumomab OR	45%	39%; Von Stackelberg 2016, supplementary Table S6. ³²
Figure 4.2 Clofarabine alive, responding to treatments		Please update this figure after correcting the overall remission rate for clofarabine based on comments on Table 4.2
Table 4.3 CR		Please use CR or OR rates consistently for all treatments
Table 4.3 B2202 CR	63%	66% for OR [52/(83-4)] and 51% for CR [40/(83-4)]; 4 patients with infusion pending and 5 not evaluated for response should be removed from the denominator. ³
Table 4.4 B2202 EFS	53%	57% [70.2%*68/(88-4)]; 4 patients with infusion pending should not be removed from the denominator. ³
Table 4.7 Axicabtagene ciloleucel objective response rate	82%	72% per USPI, based on an evaluation provided by an independent review committee (IRC). ⁴ The response rate for tisagenlecleucel is based on evaluation by an IRC.
Table 4.7 Axicabtagene ciloleucel CR	54%	51% per USPI. ⁴
Table C1 median follow-up	Table C1 for detail	8.8 months for B2202, 6.4 months for B2205J, and 18.6 months for B2101J; ODAC, pgs 65-66. ⁴
Table C3 B2101J refractory category	Table C3 for detail	94.5% as relapsed disease and 5.5% as primary refractory disease; ODAC, pg 50. ⁴
Table C5 B2101J. EFS and OS at 6 months	Table C5 for detail	EFS at 6 months is 74.6%, OS at 6 months is 85.1%; ODAC, pg 51. ⁴
Table C6 B2101J. CRS	100%	89.1%; ODAC, pg 89. ⁴
Table C6 B2101J. Grade 3/4 CRS	17%	47.3%; ODAC, pg 89. ⁴
Pgs 16, 17. NCCN NHL guideline		Guideline updated on 12/2017. Please update.

CR: complete remission rate; EFS: event-free survival; OR: overall remission rate; OS: overall survival; CRS: cytokine release syndrome

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Institute for Clinical and Economic Review
Steven D. Pearson, MD, MSc, President
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January 23, 2018

Dr. Pearson:

The American Society for Blood and Marrow Transplantation (ASBMT) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's draft evidence report on Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. The ASBMT is a professional membership association of more than 2,200 physicians, scientists and other healthcare professionals promoting blood and marrow transplantation and cellular therapy through research, education, scholarly publication and clinical standards. The ASBMT is dedicated to improving the application and success of hematopoietic cell transplants and other cellular therapies, such as CAR-T.

Hematopoietic cell transplantation (HCT), also known as stem cell transplantation (SCT), is a medical sub-specialty comprised of physicians with Board Certifications in Internal Medicine, Medical Oncology, Pediatrics, Hematology and/or Immunology. Due to their unique clinical expertise and training, ASBMT member clinicians and cellular therapy programs will be the primary individuals and teams initially providing CAR-T to patients in need of treatment. We anticipate that CAR-T is the first of many engineered cellular therapies to be approved in the coming decade.

In our prior comments to ICER regarding the Draft Scoping Document, we noted that both the clinical and financial data are immature for this type of analysis. **We maintain the position that an evaluation of CAR-T is premature at this time.** As both approved products have only been indicated for use by the U.S. Food and Drug Administration for less than six months, our knowledge of the patients receiving CAR-T is largely limited to the small population treated while on clinical trial. We expect that the populations receiving treatment from this point forward will be more clinically heterogeneous than while on the trial. The clinical heterogeneity of the new treatment population will be dwarfed by the financial heterogeneity associated with their treatment, as cell therapy programs are still learning how to integrate the cost of the product into the financial process and how to track the costs of care. Currently, there are not accurate,

consistent and comprehensive diagnosis or procedure codes available between care settings, thus it is not yet possible to conduct multi-center, multi-payer assessments of the average costs of care.

Given that we understand ICER's intention is to move forward with the analysis, we offer the following specific comments on the draft evidence report.

- 1) We acknowledge and support ICER's inclusion of patient and family perspectives in the report. The physical, emotional and financial burden on the patients and families of those being treated for these disease should continue to be a focal point in these types of analyses.
- 2) **The assumed \$100,000 mark-ups on CAR-T products is not a well-substantiated number and should be removed from the analysis or decreased substantially.** There are numerous issues associated with the estimated mark-ups being utilized for either product in the report. First, we note that the term 'mark-up' in the ICER report appears to represent a realized (i.e. reimbursed) margin paid to the provider at the time of claim adjudication. Mark-up generally refers to practice of adding overhead facility costs to the acquisition cost of a product to create the amount placed on a claim, known as the charge, which is then sent to a payer. Claims are then adjusted based on contracts and negotiated rates and a payment is sent to the provider. Thus, the initially filed mark-up is often vastly different than the payment received by the facility. For purposes of this comment, we will interpret ICER's references to mark-up as representing a *paid mark-up* to the provider, vs. what the provider may have filed as a charge on a claim.

On page 45, the authors note that "Most stakeholders with hospital billing expertise agreed that CAR-T mark-ups will be varied and may not follow the relative multiplier norms for other hospital administered therapies." *This sentiment cannot be overstated; CAR-T does not follow the typical mark-up practices due to the high price of acquisition and its use in both the outpatient and inpatient settings.* CMS has assigned a Q code to the Kymriah product and a fee schedule equating to ASP+6%. This payment is specific to the outpatient Medicare setting, though it may be adopted as a benchmark by certain Medicaid programs for their pediatric patients in various care settings. The ASBMT established a Cell Therapy Coding & Reimbursement Task Force in early 2017, which is a group comprised of financial representatives from cell therapy programs administering CAR-T in various locations around the country. Task Force members were surveyed about the mark-up issue and reported that there is very limited ability to secure a mark-up on the product. Responses were between 0-4% mark-up above acquisition cost, depending on payer and center. A few programs were conducting detailed analyses of their costs in the preparation and handling of the product, including cell laboratory resources, specialized personnel and reporting requirements in the hopes of establishing a

mark-up that would account for costs outside of direct acquisition/purchase, but there has been limited success to this point.

On page 45, the authors note that a “bundled payment for CAR-T hospital admission is unknown at this time.” As it pertains to Medicare admissions, there is not a specifically assigned Pre-MDC MS-DRG for CAR-T admissions. However, utilizing public information regarding CMS assignment of MS-DRGs based on principal diagnosis demonstrates that the most likely MS-DRG assignments will be MS-DRGs 840-842, with base payment amounts between \$6,110-\$16,736. Even if facilities utilize the maximum mark-up substantiated by public Medicare guidance for the product, no real dollar gains will be realized upon submission of these claims due to Medicare payment methodology. More detail on these issues are outlined in the [ASBMT letter to CMS](#) dated September 7, 2017, and additional letters to CMS/CMMI which can be found at www.asbmt.org/news-publications/advocacy. **Overall, the assumption of a \$100,000 paid mark-up does not reflect actual practice and is not useful for purposes of this analysis.**

Finally, as ICER is employing a healthcare sector perspective for this analysis, we note that the use of mark-ups should actually be removed from the calculations entirely, as it is a transfer from one part of the healthcare sector (payer) to another (hospital). The case of integrated systems, such as Kaiser Permanente demonstrate the rationale for removing this from the analysis; the only markups that should matter are those from the manufacturer, as the manufacturer is outside of the healthcare sector.

- 3) The analysis of sequential treatment timelines or pathways is problematic based on the limited evidence available currently. The citation used to establish the expected time frame for receiving HCT after CAR-T was based on a limited number of pediatric patients with B-cell acute lymphoblastic leukemia (B-ALL) in a Phase I study. It does not include data on the adult diffuse large B-cell lymphoma (DLBCL) population. ICER should pursue another source of data for the time estimate and individualize by disease. The [Center for International Blood and Marrow Transplant Research](#) may have additional data available on this issue. In general, as numerous permutations of therapeutic pathways currently exist, and these will multiply further in the next few years, we need maturity of data before attempting to assess the financial impact and economic valuations of these therapies.
- 4) There are more recent analyses of the costs of HCT that may be useful. Additional sources are suggested below.
 - a. Majhail NS, Mau LW, Denzen EM, Arneson TJ. Costs of autologous and allogeneic hematopoietic cell transplantation in the United States: a study using a large National Private Claims Database. Bone Marrow Transplant. 2013;48:294–300. [\[PMC free article\]](#) [\[PubMed\]](#)

- b. Preussler JM, Denzen EM, Majhail NS. Costs and cost-effectiveness of hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2012;18:1620–1628. [[PMC free article](#)] [[PubMed](#)]
 - c. Khera N, Emmert A, Storer BE, et al. Costs of allogeneic hematopoietic cell transplantation using reduced intensity conditioning regimens. *Oncologist.* 2014;19:639–644. [[PMC free article](#)] [[PubMed](#)]
- 5) On page 13, the authors note that they are unable to locate any publicly available coverage policies regarding tisagenlecleucel. Health Net Community Solutions, which provides managed Medicaid benefits to certain counties in California, does have a publicly available [clinical policy](#) on this topic: Policy reference code CP.HNMC.XX, effective September 26, 2017.
- 6) On page 15, the authors note that non-Hodgkin lymphoma (NHL) is not specifically addressed in the CMS National Coverage Determination for Stem Cell Transplantation (110.8.1). This is correct – NHL is a “silent” indication and payment is determined by the MACs on a case-by-case basis. However, National Government Services (NGS), a MAC for regions J-06 and J-K, does provide a Local Coverage Article (A52879, Effective Date 10/01/2017) that includes coverage for allogeneic and autologous transplantation for the following types of lymphoma:
- a. Allogeneic:
 - i. Primary refractory Hodgkin and non-Hodgkin lymphoma;
 - b. Autologous:
 - i. Anaplastic large cell lymphoma
 - ii. Large cell lymphoma/B-cell lymphoma
 - iii. Peripheral T-cell lymphoma
 - iv. Primary central nervous system lymphoma

This policy is not nationally representative, but may be a useful benchmark.

- 7) The ASBMT Value and Health Economics Steering Committee provided additional commentary on the methodology applied in the analysis:
- a. The modified societal perspective included caregiver costs, but did not include long-term productivity. Inclusion of this perspective is important in the B-ALL population.
 - b. ICER should consider running a threshold analysis to find out what annual probability of relapse after 5 years would cause the cost effectiveness thresholds to be crossed.

- c. ICER uses incremental comparison to no active treatment. If the report authors include no active treatment as an option, it should be compared to chemo, not CAR-T. A legitimate analysis should not skip the next-least-effective non-dominated treatment.

The ASBMT welcomes the opportunity to provide input to the ICER process for evaluating CAR-T therapy. ASBMT peer-elected leaders, member clinicians and policy staff are available as a resource for issues associated with HCT, CAR-T and other cellular therapies. Please do not hesitate to reach out whenever we may be of assistance.



Krishna Komanduri, MD

ASBMT President, 2017-2018

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Hematology/Oncology Pharmacy Association

January 24, 2018

Steven D. Pearson, MD, MSc
President
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Two Liberty Square, Ninth Floor
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Re: Call for Public Comments on Draft Evidence Report: *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value*

Dear Dr. Pearson:

On behalf of the Hematology/Oncology Pharmacy Association (HOPA), I would like to thank you for the opportunity to submit comments on ICER's Draft Evidence Report: *Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value*. HOPA is a nonprofit professional organization launched in 2004 to help hematology and oncology pharmacy practitioners and their associates provide the best possible cancer care. HOPA's membership includes not just oncology pharmacists, but also pharmacy interns, residents, technicians, researchers, administrators and industry professionals specializing in hematology/oncology practice. The roles of our membership span from direct patient care, to education, to research and to advocacy. HOPA represents more than 2,700 members working in hundreds of hospitals, clinics, physician offices, community pharmacies, home health practices, and other healthcare settings.

Hematology/oncology pharmacists play an important role in the delivery of care for individuals living with cancer. They are involved with the care of cancer patients at all phases of their treatment: from assessment and diagnosis; to treatment decisions, medication management, symptom management and supportive care; and finally with survivorship programs at the completion of treatment. Additionally, oncology pharmacists work closely with patients and their families to ensure access to the medications that are part of a patient's treatment plan. As part of this work, oncology pharmacists are often faced with the challenge of helping patients overcome the high cost of many cancer therapies and other medications that are needed for quality cancer care.

This draft evidence report on CAR T-cell therapy for B-cell cancers is an important and needed first step in considering the balance of clinical benefit and financial toxicity when making treatment decisions. HOPA supports the need for improved transparency and consistency of

value determinations in order to improve patient care and control costs. We would like to offer the following comments and recommendations to this ICER report:

Section 1. Background

- On page 4, it is listed that tisagenlecleucel is approved for both indications. The authors may want to clarify that the company is working toward the indication for aggressive B-cell lymphomas.
- On page 7, there is no mention of respiratory distress as related to CRS (only high fever and hypotension are mentioned).

Section 3. Summary of Coverage Policies and Clinical Guidelines

- Section 3.2: NCCN guidelines have now been updated to include recommendations for the use of axicabtagene ciloleucel
- On page 16, there is an error - ibrutinib is included in the CML active TKI list and imatinib is excluded.

Section 4. Comparative Clinical Effectiveness

- The model and evaluations performed are somewhat confounded, where it is unlikely to be valid in its assumed outcomes beyond a year and its comparisons are of groups that are not truly representative of the CAR T-cell therapy study populations.
- Comments regarding comparative studies
 - We applaud the authors for noting that some results may be overestimated since none of the data presented is from ITT studies.
 - Data for analysis is derived from clinical studies of patients with limited comorbidities and good performance status. The patients receiving CAR T-cell therapy on a clinical trial may not be representative of the population that will receive the commercial product. Patients receiving the commercial product are not required to meet these study criteria and may be sicker than the population studied on clinical trial. These sicker patients require longer inpatient hospital stays and greater supportive care measures leading to increased costs associated with the overall therapy.
 - Comparators of older trials (e.g., Jeha 2006, Hijiya 2011) may increase bias due to changes in supportive care practices over time; thus, the toxicity and survival data are likely overstated, if anything.
 - SCHOLAR-01: this was an international observational cohort of patients with significant heterogeneity in level of refractoriness being bridged to auto-SCT with multiple estimations in endpoints and only a 2-year follow up. Its use is flawed for any kind of 5-year analysis and is not the same study population as CAR T-cell 19 therapy. A recent editorial¹ illustrates how the retrospective nature of this trial/paper results in it not being a realistic trial to compare a prospective cohort (like these trials) against. And now that these therapies are available to everyone, this will become increasingly more important.

- ZUMA-1 adverse events: toxicities (neurotoxicity for certain) are subsets of each other or if not, the definition of neurotoxicity is unclear. So true adverse event profiles for this set is unclear. Additionally, the grading scales and management of toxicities are different for each CAR T-cell product. This makes it difficult to accurately evaluate QOL values and other endpoints.
- There are no comparative demographics for CAR T-cell therapy patients to tell if the populations are similar versus comparators. We need more complete data on the study subjects.
- There is much speculation about the specific place in therapy for CAR T-cells. Is it needed after failing one-line of therapy, 2-lines of therapy, before SCT, or in the place of SCT? Salvage therapies are not the most appropriate comparator because the efficacy of CAR T-cell therapies is “clinically significantly” superior (SCHOLAR-1 trial). It may in fact replace SCT. There is also speculation that an allo-SCT after CAR T-cell therapy would deactivate the CAR T-cells. This adds another twist to the place in therapy for CAR T-cells. There are also early data showing that CAR T-cell therapy may be superior to SCT in double and triple hit lymphoma.
- Suggest including some comparison to data of both efficacy and pharmacoeconomics for these CAR T-cell therapies compared to SCT.
- The ALL cohort should really have been compared with SCT for outcomes as the comparative trials were never expected to cure these patients; rather therapy was used to bridge them to SCT. As such, it is likely that CAR T-cell therapy would look less toxic and more cost effective, but may not have as good overall and long term response rates as we still are unclear if it is a cure or not.
- There have been no projections for repeat CAR T-cell infusions provided.
- The number for transplants post CAR T-cells in DLBCL may be underestimated.
- On page 27, with respect to B-cell aplasia, there is no mention of steroids or specific guidelines in avoiding the use of steroids in this patient population.

Section 5. Comparative Value

- Comments regarding comparative studies
 - ~15% of the ALL patients went on to SCT. This is not included in cost-effectiveness analysis and really should be incorporated into the QAYLS in some fashion.
 - It is unclear how long CAR T-cell toxicities continue (e.g. neurotoxicities). Thus we do not really know the long-term QOL values, such as the ability to return to work. This is all supposition.
 - Although bridging chemotherapy was not permitted on ZUMA-1, the majority of lymphoma patients now are receiving bridging between apheresis and lymphodepleting chemotherapy. This increases the costs as well.
- ALL outpatient administration and monitoring: due to the toxicities and their management, this seems difficult and potentially unsafe. However, this may be necessary for reimbursement for certain insurance companies. At the present time, traditional MEDICARE does not have an appropriate DRG to bill for CAR T-cell therapy in the

inpatient setting; therefore, infusions may occur in the outpatient setting. This is a concern because many patients will be on MEDICARE based on the indication. Based on the experience of some, the logistics have been complex and significant resources have been used for education and training to ensure safety for outpatient administration.

- When looking at cost, some products purport that the entire cell infusion and monitoring can be done in the outpatient setting with admission only if CRS occurs. This needs to be reviewed more extensively. What would the cost difference be if this were done exclusively on an outpatient basis with admission only if CRS at around the median time of CRS onset (2-3 days post infusion)? One would need to take into account frequent clinic visits and possibly ways to monitor vital signs remotely through newer technology that is available (this would cost money to rent equipment and have a call center monitor and notify a provider).
- On page 42, the study population was supposed to be transplant ineligible yet 3% of NHL went on to transplant compared to 30% of SCHOLAR-1. As noted earlier these are not comparable populations. The ALL cohort could be transplanted and 10.5% actually were, which makes this a less effective bridge regimen than clofarabine it seems.
- On page 44, regarding chemotherapy:
 - As discussed in several places, the authors mention the mark-up of these products by facilities. Some institutions are not marking-up the product up due to the potential “back-lash” from the public and media if it is discovered that there was a high mark-up on an already expensive agent.
 - Drug acquisition costs appear a little misleading and make it seem other drugs are pennies in comparison to the CAR T-cell products. Recommend adding a column to provide cost of therapy for a patient (both pediatric and adult) with a reference height, weight and BSA. Of note there is no cost for blinatumomab in tables 5.5 and 5.6.
 - Were the drug doses in the model representative of the current US population (e.g. degree of obesity, not as many elderly patients, etc.)? Were patients like these allowed in the studies (again, need better patient demographic information)?
- On page 48 (Table 5.7), it is stated the adverse event cost of axicabtagene ciloleucel is \$15,112. This seems low considering the costs for managing CRS (multiple doses of tocilizumab) and neurotoxicity (numerous MRIs, EEGs). This is especially true for \geq grade 3 neurotoxicity, which occurred in 28% of ZUMA-1 patients. Adverse effects may be higher in the patients receiving the commercial product as they are not as healthy as patients on clinical trials.
- On page 53, the number of missed days of work associated with time spent in the hospital is not typical for these patients – very few patients have worked at all through treatment when not hospitalized.
- On page 55, is there any real estimate of what people do post-therapy? The follow-up at this point is too short except for patient vignettes at this point. Do we assume employed for life and at what average earnings/year?
- On page 68, there are bold statements made about long-term outcomes. If patients are already over the age of 65, is it realistic that they would return to work again versus enter into retirement? This should be addressed since this is an economic model and it would

want to point out that Medicare will be funding some of the costs vs. the private insurances reviewed.

- IVIG utilization: there is a lack of concrete evidence (even in the SCT community) that routine use of prophylactic IVIG post SCT regardless of IgG levels offers any advantage over infection prevention or overall survival²⁻⁴. Where is the evidence that these patients need IVIG monthly and that there is a clear benefit that outweighs the risk of giving IVIG just to treat a low number (risk of thrombosis)? Yes, they have B-cell aplasia and arguably longer than SCT patients, but again, what is the benefit versus risk? For the axicabtagene ciloleucel clinical trials, the use was based upon each institution's guidelines, therefore these clinical trials cannot sufficiently provide a solution on its use for these agents.
- Costs associated with travel to centers for treatment, housing and caregiving were not mentioned.
- There appears no accounting for the use of blood products or colony stimulating factors.
- It may be too early to have real estimates on the impact of services utilized throughout treatments (e.g., ICU admission, clinic chair time, imaging, supportive care for toxicity management, long-term follow-up management, etc.) by this patient population compared to other patient groups.

We hope that the recommendations above will improve the utility of the report in improving patient outcomes and controlling costs. We truly support the initiative by ICER to begin this important conversation to improve cancer patient care. Thank you very much for your consideration of our comments. If HOPA can be of any assistance to you, please do not hesitate to contact me or HOPA's Health Policy Associate, Jeremy Scott (202/230-5197, jeremy.scott@dbr.com).

Sincerely,



Susannah E. Koontz, PharmD, BCOP, FHOPA
2017-2018 HOPA President

HOPA Member Reviewers: Christina Bachmeier, Sally Barbour, Joseph Bubalo, Alex Ganetsky, Katie Gatwood, Alison Gulbis, Zahra Mahmoudjafari, Helen Marshall and Julianna Roddy

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January 24, 2018

Steven Pearson, MD
Institute for Clinical and Economic Review
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Dear Dr. Pearson:

The Alliance for the Adoption of Innovations in Medicine (Aimed Alliance) is a tax-exempt, not-for-profit organization that works to improve access to health care. On behalf of Aimed Alliance, I respectfully submit the following comment in response to the Draft Evidence Report, entitled “Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value” (“Draft Report”) published by the Institute for Clinical and Economic Review (“ICER”).

1. **Background**

Acute lymphoblastic leukemia (ALL) is a type of childhood cancer that most often occurs in children ages one to eleven.¹ Each year, approximately 3,000 children under the age of 20 receive an ALL diagnosis, making it an ultra-rare disease.² While 98 percent of children with ALL go into remission within weeks after starting treatment and are cured (*i.e.*, 10 years of remission),³ children with refractory or relapsed ALL have a prognosis of 5 percent long-term survival when treated with chemotherapy or stem cell transplantation.⁴ In comparison, new chimeric antigen receptor T-cell (“CAR-T”) therapy has been shown to significantly increase survival and decrease both short- and long-term adverse events, yielding 82 percent complete remission.⁵

Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is an aggressive form of cancer most commonly found in patients over the age of 60.⁶ It has a poor prognosis, with a median overall survival rate of 4.4 months. Yet, with CAR-T, the rate of relapse-free survival at 6 months was 79 percent.⁷ Given the overall effectiveness of CAR-T treatments patients for whom such treatments are clinically indicated must have access to them. Therefore, we recommend caution when conducting a health technology assessment of CAR-T treatments.

¹ <https://www.stjude.org/disease/acute-lymphoblastic-leukemia-all.html>

² <https://www.stjude.org/disease/acute-lymphoblastic-leukemia-all.html>

³ <https://www.stjude.org/disease/acute-lymphoblastic-leukemia-all.html>

⁴ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5530848/>; <https://www.stjude.org/disease/acute-lymphoblastic-leukemia-all.html>

⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755474/>; <https://www.curetoday.com/articles/cart-cell-therapy-highly-effective-in-acute-lymphoblastic-leukemia>

⁶ <http://www.lymphoma.org/site/pp.asp?c=bkLTkaOQLmK8E&b=6300153>

⁷ <https://www.medscape.com/viewarticle/882163>

2. Limitations of Using QALYs To Evaluate CAR-T Therapy

Aimed Alliance continues to recommend against relying on quality-adjusted life year (“QALY”) measures to evaluate CAR-T therapy. Using QALY measures to evaluate children with refractory or relapsed B-cell ALL and seniors with refractory or relapsed DLBCL raises significant ethical concerns. The price tag QALY measures put on the value of a human life merely reflects the individual’s diagnosis, and deems those with chronic, debilitating, and rare conditions as being worth less than those with common diseases. QALY measures view individuals’ lives and health as commodities, and do not adequately quantify how patients and practitioners ascribe the value of life-saving treatments. QALYs are particularly discriminatory against elderly populations, such as those with refractory or relapsed DLBCL and those with rare forms of cancer. Relying on QALYs to evaluate children with B-cell ALL also represents a potentially discriminatory practice.

As ICER highlights, insurers are already placing stringent prior authorization requirements on CAR-T for children with B-cell ALL that go beyond the FDA indication for the therapy (*e.g.*, Aetna and Health Net require that (1) patients’ disease be Philadelphia chromosome positive (Ph+); and (2) patients fail on two tyrosine kinase inhibitors (TKIs)).⁸ Yet, only 3 to 5 percent of children with ALL are Ph+.⁹ Therefore, very few children with B-cell ALL qualify to receive CAR-T treatment under current health insurance policies. Yet, QALYs are used to justify coverage limitations that prevent individuals from obtaining treatments most appropriate to their individualized needs. As a result, coverage could become even more restrictive.

Moreover, given that B-cell ALL is an ultra-rare disease affecting 3,000 children per year, ICER should look to its rare disease guidelines, which considers alternative methods for determining the value of a treatment. For these reasons, we recommend against using the QALY for evaluating CAR-T therapy for children with B-cell ALL. Instead, outcomes-based pricing arrangements may be more appropriate.

3. A Value Assessment Is Premature

While clinical trials have provided evidence of the safety, effectiveness, and value of CAR-T treatments to children with B-cell ALL and seniors with DLBCL, these treatments are still in their infancy. One CAR-T treatment received approval from the U.S. Food and Drug Administration in August 2017 and the other received approval in October 2017. As such, the treatments have been on the market for less than a year. Moreover, only 33 treatment centers currently offer CAR-T treatment with tisagenlecleucel and 16 offer treatment with axicabtagene ciloleucel in the U.S., meaning the availability of such treatment is significantly limited at this time.

Over time, valuable data will fully emerge in clinical practice, including information on long-term remission and survival rates. However, if CAR-T treatments are deemed inadequately cost-effective now, then the likelihood of third-party payers covering these treatments without imposing significant benefit utilization management policies increases, creating barriers to

⁸ https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Draft_Evidence_Report_121917.pdf

⁹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4349266/>

access for children and seniors who need them. Without market uptake, data cannot be collected and analyzed. Therefore, we recommend that ICER refrain from making a determination on the value of treatments until mature data emerges.

In conclusion, we offer our assistance in working closely with ICER to address our shared goals of access to high quality health care at a price that accurately reflects public and personal benefits.

Respectfully submitted,

Nellie Wild
Executive Director



January 23, 2018

Institute for Clinical and Economic Review
Steven D. Pearson, MD, MSc, President
Two Liberty Square
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Submitted Electronically: publiccomments@icer-review.org

RE: Draft Evidence Report for CAR-T Therapies

Dear Dr. Pearson,

The Haystack Project is an unincorporated coalition of patient and caregiver advocates with a shared commitment to developing and ensuring access to treatments for the subset of rare disorders that impact extremely small patient populations. We commented previously on ICER's adapted framework for assessing products developed for ultra-rare disorders because we believe ICER's initiative will have a bottom-line impact on whether or not some patients with ultra-rare diseases will have access to a treatment option. Our community remains concerned about ICER's process, framework, and resources committed to stakeholder engagement, and we reiterate our recommendations that:

- ICER should incorporate long-term patient benefit into its assessment to accurately capture the value to patients and their families, particularly when the patient is impacted by an ultra-rare disorder;
- ICER's grafting of Quality Adjusted Life Year (QALY) metrics and a willingness to pay threshold onto evaluations of ultra-rare disease treatments will complicate research and development, and encourage payer denial of necessary medical care; and
- ICER should proactively and exponentially increase its engagement with the patient and caregiver community throughout its process.

ICER's recent assessment activities related to both Voretigene and CAR-T therapies has also increased our concern about both the wisdom and utility of rushing to judgment on the "value" of, or even the benefit conferred by, an ultra-rare disorder treatment innovation.

As patients and caregivers potentially impacted by ICER's activities, we urge you to use your absolute best efforts to avoid driving innovators to delay commercialization of new therapies beyond the point where safety and efficacy have been demonstrated. When a treatment is developed as a potential "one-and-done" curative or disease/symptom modifying agent, patients

cannot afford to wait until clinical trials complete the 5 or 10 year, or even multi-decade data collection ICER appears to need to justify pricing that reflects anticipated life-long benefit.

Haystack understands that ICER has developed a process for stakeholder engagement, however collecting information from patients is of far less value if the end product does not reflect patient input other than as “contextual” information that may justify diverging from the an ICER determination of product value. We strongly encourage ICER to withhold analysis of new products for ultra-rare indications until it can either accurately incorporate “contextual” patient information into the QALY mathematical equation or the data is sufficient to perform a more accurate value assessment.

We also urge ICER to place patient and caregiver engagement at the center of each assessment. Whether in the context of QALYs or other measures, ICER should aim to gain a better understanding of the outcomes that are relevant and meaningful to patients and capture that information in assessing value. In addition, meaningful endpoints specific to patients and their disease state, such as alleviation of symptoms or the ability to be productive in work or home settings, may not be reflected by global or specific clinical measures that feed into a QALY – this reduces the validity of the framework in assessing value on patient-centric outcomes. The Haystack Project also believes that patients and their caregivers need more time than ICER has allocated at each stage, and all parties would benefit from an engagement process that allows for more interactive communication, including patient panels.

Once again, we appreciate the opportunity to comment. As the voice of ultra-rare disease stakeholders, we look forward to working with you in the future to facilitate patient and caregiver engagement, and to further inform your ultra-rare disease policies, proposals, evaluations, and frameworks. If you have any questions or would like to discuss our comments and recommendations, please contact Saira Sultan at 202-360-9985.

**PAUL KLEUTGHEN
3404 TORCA COURT
SOUTHPORT, NC 28461**

January 17, 2018

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
2 Liberty Square – 9th floor
Boston, MA 02109

Dear Dr. Pearson,

With this letter I submit my comments to the draft evidence report ‘Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value’, published on the ICER website on December 19, 2017. As a patient, I consider myself a stakeholder in the debate about the pricing of CAR-T therapies. CAR-T therapy may provide me with a lifeline in the future to help me in my quest against the effects of my primary plasma cell leukemia (pPCL) – the rarest and most aggressive form of multiple myeloma (MM) – plus a recently diagnosed case of acute myeloid leukemia (AML). I am writing to you not only on my own behalf but also on behalf of my fellow MM and AML patients, and hope you will treat my letter as such. I fully acknowledge that the report does not cover prospective CAR-T therapies for either MM or AML, but kindly ask you to bear with me for a few minutes.

Let me first commend the ICER staff on the very rigorous analysis that is presented in a very clear form. I have no issues with the approach taken, quite to the contrary, but would like to raise a few points. I have grouped my comments into six major categories.

1. Patient population

I disagree with the decision to limit the Kymriah patient population to just pediatric and young adult RR ALL. Novartis announced several months ago that the company had filed for approval of a sBLA to expand the label claims for Kymriah to several NHL's, including the largest portion of the NHL population : DLBCL. This supplemental submission was given ‘Priority Review’ by FDA¹ and it is expected that approval will be granted before the end of April 2018. In addition, Novartis has been conducting later phase clinical trials in several B-cell malignancies, most of them with near term filing timelines. I am providing a summary list of these studies in the Workbook labeled “Clinical Studies with CTL019 12-10-2017” as a separate file in the email addressed to you. I have taken the information gathered from the clinical trials data base and summarized it into patient pool estimates using the methodology outlined in Appendix 1 of this

¹ <https://www.novartis.com/news/media-releases/novartis-granted-us-fda-priority-review-kymriahtm-tisagenlecleucel-formerly-ctl019-adults-rr-dlbcl>

letter.² Appendix 2 provides you with the projections for Kymriah for current and expected indications. I come up with the following total patient pool estimates for Kymriah for the period 2017-2022.

Kymriah patient pool estimates	2017	2018	2019	2020	2021	2022
US	50	2,435	7,170	7,791	9,535	9,746

In an article published online, MIT Technology review, indicates “Yescarta treats large B-cell lymphoma in adults, and Gilead estimates it could help around 7,500 people a year.”³ This number is somewhat larger than both the ICER and our estimates. Gilead is, undoubtedly, aware of Novartis’ regulatory submission for DLBCL and its projections must reflect that reality, especially since Novartis has been more aggressive in activating treatment sites than Gilead has (see reference 1 provided below).

I would like to make the point that ICER’s analysis of the economic impact of Kymriah (or Yescarta) on the total healthcare system should not be limited to just the currently approved indicated for a small patient population, especially since Kymriah’s indication for DLBCL will most likely be approved around the time that ICER will hold its public hearing on CAR-T therapies. ICER should look forward and include the product approvals that are expected to be granted over the next few years in its overall analysis.

2. Kaplan-Meier curves

I was surprised that in the case of Kymriah, the ICER team used clofarabine as a comparator instead of blinatumomab, as blinatumomab has a superior efficacy profile. Please refer to the Kaplan-Meier curves provided in Appendix 3.

I feel that, by choosing clofarabine as an outcomes comparator, ICER is giving Kymriah an (unfair) advantage that it has not yet earned since there are few patients for whom 2-year EFS, PFS and OS data are available. Comparing tisagenlecleucel against blinatumomab will decrease the incremental LYs and QALYs compared to what is reported in table 5.9 of the ICER draft report.

At the very least, I hope that, in the interest of completeness and full disclosure, the final issue of the ‘draft report’ ICER will provide the analysis of Kymriah vs. blinatumomab. That will allow us, the patient stakeholders, to better understand the economic impact against the currently available superior treatment for pediatric RR ALL.

3. Simulation concerns

I was pleased to see that 5,000 simulations were run by the ICER team. Still, I would like to raise several concerns.

² Compilation of these data were done by Paul Kleutghen and David Mitchell, President of Patients for affordable drugs. Mitchell and Kleutghen gratefully acknowledge the review of this information by Aaron Kesselheim, MD, Ph.D (Harvard University), Ameet Sarpatwari, Ph.D. J.D., (Harvard University) and Mehdi Najafzadeh, Ph. D. (Harvard University). Their many comments and suggestions have all been incorporated in the final product.

³ “Gene Therapy Could Make Cancer Care More Unequal, and This Map Shows Why”, Emily Mullins, January 12, 2018, MIT Technology Review. <https://www.technologyreview.com/s/609890/gene-therapy-could-make-cancer-care-more-unequal-and-this-map-shows-why/>

- a. Simulation runs typically tend to use normal distributions around a mean/point estimate, using standard deviations that have been observed around the means. I was happy to see that means and standard deviations for the Adverse Event Unit Costs in Table D.12 of the ICER draft report. In looking through the data in this table I noted that in every adverse event line in this table the standard deviation is larger than the mean. This, by itself, is not necessarily a problem and is most likely due to the small number of data points the ICER team had available. The problem, however, comes in when one uses normal distributions that are characterized by the reported means and standard deviations. I estimate that, on average, the reported standard deviations are about 125 % of the mean which results in situation where one has a 40 % chance that negative values for adverse event costs may have crept into the analysis. This would have the net effect of lowering the overall costs of treatment, with the larger impact affecting the CAR-T products.

I would like to kindly request that you validate with your technical team that this did not occur, and that appropriate care has been given to make sure that adverse event costs are positive and well above ZERO in all simulation runs. Will you please be so kind to confirm back to me that an appropriate statistical distribution has been used that precluded negative, or close to zero, numbers for cost factors.

- b. Table D.6 includes the proportion of the cohort that is in each health state at one year, two years, and five years after treatment completion, stratified by treatment and population. This table shows that the probability to be 'dead' at 1 year of Kymriah treatment is 22.7 % or, that therefore the probability to be alive at 12 months is 77.3 %. That, however, is at variance with table 4.4 (page 31) where the average OS at month 12 for the 3 Novartis studies is 74 %. Will you please be so kind to look into this and, if needed, to re-run the simulation to reflect a correction with lower OS.
- c. The three Novartis studies submitted with the Kymriah provide OS data for up to 15 months. There are quite considerable differences in the Kaplan-Meier curves between the studies. See for example the comparison curves between study B2101J and B2105J, provided in Appendix 4. You will note that there is a 20-percentage point difference in OS at month 15. In reading and rereading the draft report I have not been able to find how variability in the OS curves for either Kymriah or Yescarta was established and how it may have been used in the simulation runs.

I would like to suggest that ICER use the spread between these two curves as a measure of the variability of outcomes. One suggestion is to use the Kaplan-Meier curve, pooled from the three Novartis studies, as an upper bound and use the spread of OS between studies B2101J and B2205J to set a lower bound of outcomes. I will be perfectly happy to see the spread at month 15 extended to the five-year point, even though there seems to be a growing divergence in the spread from month 0 to month 15. An even likelihood of occurrence over the range of the spread in the simulation will work just fine. At least we will all have a more accurate reading of LYs and QALYs that reflects the probabilistic nature of OS compared to the point estimates of the pooled Kaplan-Meier curve that has been used in the current draft analysis.

- d. I understand that upper and lower bounds have been set using seasoned expert judgement. The difference between the upper and lower bounds then seems to be equaled to 4 standard deviations providing a mean and standard deviation used for a normal distribution for each model factor to be varied in the 5,000 simulation runs. I

would like to make the following comments regarding the upper and lower bounds used for the sensitivity analysis (ICER draft tables 5.10 and 5.11) :

- I cannot understand why the technical staff used an upper bound of 45 % over the \$ 100,000 drug cost mark-up for Kymriah (Table 5.10), but 50 % was used for Yescarta.
- There is inconsistency in the mark-up percentages used for comparator treatments. Clofarabine (Kymriah comparator) has a mark-up range of 46 to 108 %, whereas rituximab (Yescarta comparator) has a mark-up range of 23 to 75 %. No reason is given for this difference.
- The upper and lower bounds for the treatment of CRS are \$ 1,285 to \$ 187,362 respectively. This lower bound is just plain ridiculous. I would like to request that these bounds be revisited.

4. Base case discounted Lifetime costs

Table 5.7 in the ICER draft presents the discounted lifetime costs for Kymriah and Yescarta. In essence, ICER estimates that the full treatment costs add up to about \$ 650,000 for each. This is quite at variance with the \$ 1.0-1.5 million costs that have been reported recently (see Appendix 5 for examples).

I respectfully submit to you that the discounted lifetime costs for both Kymriah and Yescarta have been underestimated by, possibly, as much as 50 %. I admire and respect the detail the research team used in the analysis but it seems to be substantially at variance with what is being reported in actual practice. I would like to suggest to you two key areas that may need to be revisited : the mark-up amount and the cost to treat CRS. I was surprised that the institutional mark-ups for both Kymriah and Yescarta were capped at \$ 100,000 per infusion [tables 5.5 and 5.6], especially since the treatments are expected to be administered in academic/tertiary treatment centers that allow for mark-ups of up to 152 % of ASP. Either way, it seems that a round number for the CAR-T treatment costs is most likely closer to \$ 1 million per patient, which will have a dramatic impact on the economics of this breakthrough therapy.

At treatment costs of \$ 1.0 million, table 5.9 “Base Case Incremental results” will look very different. For completeness sake I have provided summary of the impact of a \$ 1.0 million cost in Appendix 6.

Please note that at the \$ 1.0 million treatment cost and the inclusion of part of the DLBCL patient pool for Novartis we are now looking at CE ratios per LY and per QALY that are coming in over \$ 200,000 – well over the \$ 150,000 high-end threshold of the ICER analysis.

5. Budget impact

The table in Appendix 6 shows that, at a treatment cost of \$ 1.0 million, the incremental lifetime costs for both Kymriah and Yescarta are very similar and in the range of \$ 960,000 – 970,000 per patient. This means that, in both cases, less than 1,000 patients can be treated per year for each drug without crossing the \$ 915 million threshold. The combined patient pool for pediatric RR-ALL and DLBCL adds up to 6,840 according to ICER estimates. This means that only about 27 % of patients could be treated per year without crossing the ‘budget line’. This is clearly unacceptable.

6. Recommendations to ICER for therapy pricing

Over the past few months, David Mitchell (President of Patients for Affordable Drugs) and I, with assistance and guidance from Drs. Kesselheim (Harvard), Sarpatwari (Harvard) and Najafzadeh (Harvard), have modeled the product P&L's for both Kymriah and Yescarta using very detailed assumptions. Our analysis has shown that if Gilead and Novartis reduce the pricing for their products by 2/3 they still generate net operating income and monies for ongoing R&D that equal the average percent operating income and R&D set-aside for the top-10 pharmaceutical companies in the US (and that top-10 happens to include both Novartis and Gilead).

The table provided in Appendix 7 shows that the lifetime costs for both treatments decrease by about 35 % when the drug (Kymriah or Yescarta) costs are reduced by 2/3 from their current prices. This will work wonders for 'access' to these life-saving therapies as the costs will then come closer to allo-transplants. David Mitchell, or I, will be more than happy to provide you with the detailed results of our financial analysis for Kymriah and Yescarta.

As a blood/bone marrow cancer patient, and on behalf of all my fellow patients, I would like to request that ICER take a firm stand against the revolting prices of these breakthrough therapies. I would like to suggest that ICER's position with respect to CAR-T pricing also be extended for the upcoming treatments with anti-BCMA CAR-T's, specifically JCAR017 (Juno Therapeutics) and bb2121 (Blue Bird Bio). Phase III studies for both products are already underway, not only in Multiple Myeloma but also in other hematologic malignancies. We estimate that the Multiple Myeloma target patient pool is around 20,000 patients per year who relapse after they have become refractory to prior treatments. Our healthcare system cannot absorb the shock of this patient pool at incremental treatment costs of around \$ 650,000 per patient. Time has come for society to take a stand against CAR-T prices that generate corporate profits far in excess of what the marketers in question, or the pharmaceutical industry in general, have lived with historically. I hope that ICER will help us in this societal quest.

In the event you have questions feel free to contact me at pkleutghen@gmail.com

Sincerely,

Paul Kleutghen

Copy to :

David Mitchell
President
Patients for Affordable Drugs

APPENDIX 1 ESTIMATES OF PATIENT DEMAND FOR KYMRIAH ASSUMPTIONS

1. Future approved indications

Demand for Kymriah over the next decade will be driven by its future approved indications in addition to by pediatric and young adult relapsed/refractory (RR) acute lymphoblastic leukemia (ALL). These future indications will hinge on the outcomes of ongoing clinical trials, which we identified searching for “CTL-019” using ClinicalTrials.gov. Our findings and analysis follow:

- In total, we identified 35 clinical studies, including 3 trials supporting the recently approved pediatric and young adult RR ALL indication.
- Of the other 32 studies, we excluded 2 that assessed 4S-CTL019, Novartis’s fourth-generation CAR-T.
- We excluded 20 Phase I or Phase I/II trials as being too early-stage.
- We excluded 2 studies that were halted.
- We excluded 1 Phase II trial in high-risk multiple myeloma based on our belief that Kymriah will not be able to generate as much clinical benefit as second-generation CAR-Ts like bb2121.
- Finally, we excluded 1 expanded treatment protocol and 1 Phase II trial in mantle cell lymphoma in China that had enrolled only 2 patients.
- The remaining 5 studies were Phase II trials targeting the following conditions.
 - Adult ALL
 - Patients with minimum residual disease after up front treatment
 - Patients who have no other curative options
 - RR diffuse large B-cell lymphoma (DLBCL)
 - RR chronic lymphocytic Leukemia (CLL)
 - RR small lymphocytic lymphoma (SLL)
 - Other RR non-Hodgkin’s lymphoma (NHL)

We projected that Novartis would secure supplementary approval for these indications at some point over the next 10 years.

2. Indication-Specific Approval Time and Treated Population Estimates

We made the following indication-specific assumptions based in part on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program and ClinicalTrials.gov.

Pediatric and Young Adult RR ALL

Experts have estimated that 600 children and young adults have RR ALL. An additional 3,100 children and young adults develop ALL annually, of whom only 15% (n=465) will not be long-term, event-free survivors on non-CAR-T therapies. Based on these statistics and the number of centers currently equipped to administer Kymriah, we estimated that 300 children and young adults would receive treatment in 2018. We assumed that this number would rise to 600 in 2019 and—anticipating some spillover from patients not fully benefiting from another treatment but not having exhausted other options—800 in 2020. We projected 2% annual growth thereafter.

Adult ALL

Number: We estimated that 346 (30%) of the 1,152 adults who die from ALL annually would receive treatment. We additionally estimated that 240 (10%) of the 2,400 adults newly diagnosed with ALL annually would receive treatment as patients who were MRD+ after upfront treatment. We projected that both numbers would grow 2% annually.

Timing: The Phase II trial in adult ALL patients with no other curative options had a target completion date of July 2019. We projected a US launch 12 months later in July 2020. The Phase II trial in adult ALL patients with minimum residual disease following upfront treatment had a target completion date of April 2018. We projected a US launch 15 months later in July 2019.

DLBCL

Number: We estimated that 11,400 (60%) of the 19,000 DLBCL patients on third-line treatment annually would receive CAR-T treatment, which would be split evenly between Kymriah (n=5,700) and Kite's Yescarta (n=5,700).

Timing: Novartis filed for supplementary approval of this indication in October 2017 and received a "breakthrough therapy" designation. We anticipated a US launch in July 2018.

CLL

Number: We estimated that 1,398 (30%) of the 4,660 patients who die each year from CLL would receive treatment and that this number would increase 2% annually.

Timing: The Phase II trial in adults with RR CLL or SLL had a target completion date of October 2019. We projected a US launch 15 months later in January 2021.

SLL

Number: We estimated that 132 (33%) of the 400 newly diagnosed SLL patients annually would relapse, and that 40 (30%) of these relapsed patients would receive treatment.

Timing: The Phase II trial in adults with RR CLL or SLL had a target completion date of October 2019. We projected a US launch 15 months later in January 2021.

Other NHL

Each year, about 5,000 people die from NHL (excluding DLBCL, CLL, and SLL). We estimated that 1,500 (30%) of these people would receive CAR-T treatment, which would be split evenly between Kymriah (n=750) and Yescarta (n=750).

Timing: The Phase II trial in adults with NHL had a target completion date of January 2018. We projected a US launch 12 months later in January 2019.

Appendix 2 : Kymriah Patient Pool Estimates

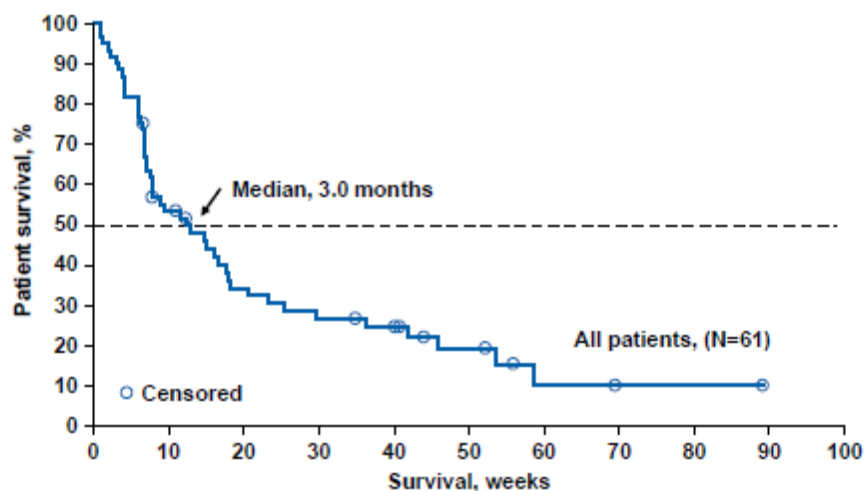
Patient subgroup US	Base and growth rate in %	2017	2018	2019	2020	2021	2022
Pediatric RR B-cell ALL	600						
	2%						
		50	300	600	800	816	832
Adult ALL - patients with MRD+ during upfront treatment	240						
	2%						
		0	0	120	240	245	250
Adult ALL - last resort treatment	640						
	2%						
		0	0	0	172	346	353
CLL	932						
	2%						
		0	0	0	0	1,398	1,426
DBCL	5700						
	2%						
		0	2,135	5,700	5,814	5,930	6,049
SLL	20						
	2%						
		0	0	0	0	20	40
All other NHL	750						
	2%						
	0	0	0	750	765	780	796

Worldwide market estimates		2017	2018	2019	2020	2021	2022
US		50	2,435	7,170	7,791	9,535	9,746

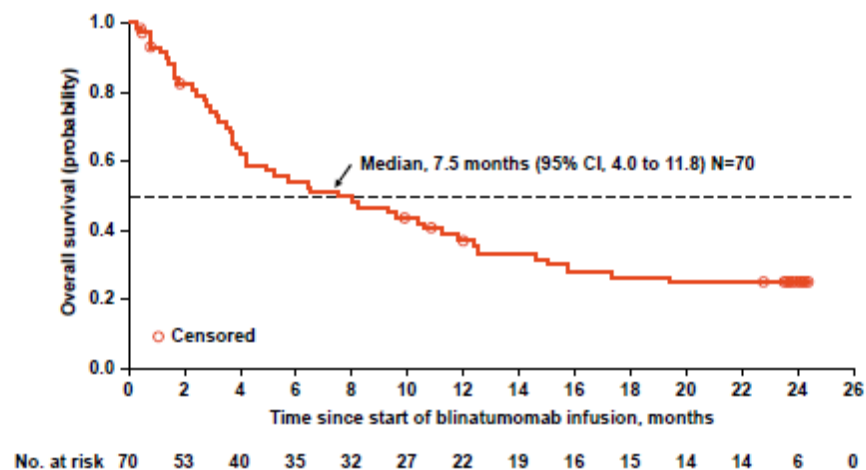
APPENDIX 3 KAPLAN-MEIER CURVES (OS) FOR CLOFARABINE AND BLINATUMOMAB⁴

Figure 2-1 Current outcomes for pediatric patients with r/r ALL

Clofarabine monotherapy: Phase-II trial in pediatric r/r ALL (N=61)



Blinatumomab: Phase-I/II trial in pediatric r/r ALL (N=70)

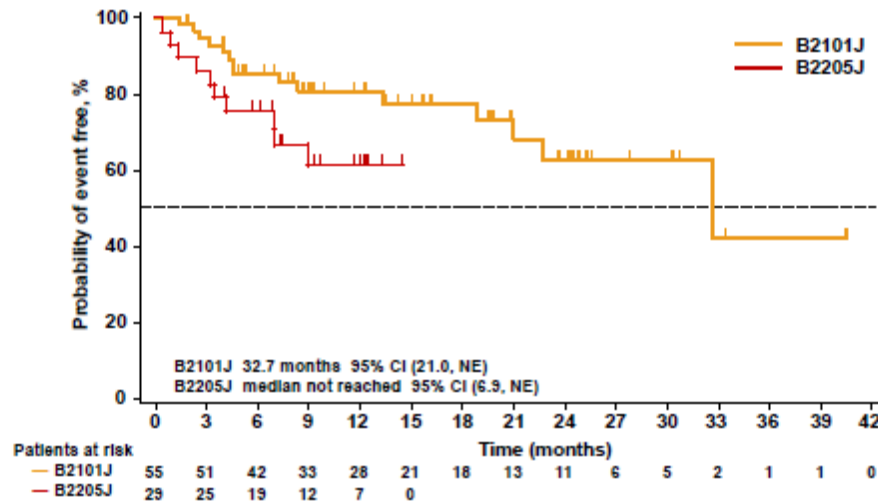


ALL Acute lymphoblastic leukemia; CI Confidence interval; r/r Relapsed/refractory

⁴ Novartis. Tisagenlecleucel (CTL019) for the treatment of pediatric and young adult patients with relapsed/refractory b-cell acute lymphoblastic leukemia. *FDA Advisory Committee Briefing Document*. 2017.

APPENDIX 4 KAPLAN MEIER CURVES OS NOVARTIS STUDIES B2101J AND B2205J⁵

Figure 5-2 Overall survival – Studies B2101J and B2205J



CI Confidence interval; NE Not estimable; OS Overall survival

⁵ Novartis. Tisagenlecleucel (CTL019) for the treatment of pediatric and young adult patients with relapsed/refractory b-cell acute lymphoblastic leukemia. *FDA Advisory Committee Briefing Document*. 2017.

APPENDIX 5

EXAMPLES OF REPORTED CAR-T TREATMENT COSTS

- a. A recent editorial in JAMA⁶ quotes Dr. Leonard Saltz *“If you’ve paid half a million dollars for drugs and half a million dollars for care, and a year later your cancer is back, is that a good deal?”*
- b. Liz Szabo, writing for Kaiser Health News⁷ states :

“The total costs of the country’s first gene therapy will be far higher than many have imagined, reaching \$1 million or more per patient, according to leading cancer experts. The therapy, a leukemia drug from Novartis called Kymriah, was approved in August with an eye-popping sticker price of \$475,000 for a one-time treatment. But that price doesn’t include other essential parts of treatment, such as hospitalizations or the costs of managing side effects, said Dr. Hagop Kantarjian, a leukemia specialist and professor at the University of Texas MD Anderson Cancer Center, who estimates the total cost of care could be \$1.5 million.”

- c. Cortez et al., writing for Bloomberg⁸ make the following statement :

“MD Anderson, which has more than 100 patients on a waiting list, has started treatment for a few, after getting them to sign waivers that they will be responsible for the costs if insurance doesn’t pay. Bishop, of the University of Chicago Medicine, said he doesn’t want to turn down any patients, but the prospect of losing \$1 million per patient is unsustainable. The hospital has 10 people on its waiting list.”

⁶ “FDA Approval of Tisagenlecleucel: Promise and Complexities of a \$475 000 Cancer Drug”, authored by Bach et al. JAMA. 2017; doi: 10.1001/jama.2017.15218 (September 20, 2017)

⁷ “New gene therapy treatment could hit \$1M per patient because of additional costs”, published in USA Today, issue of October 16, 2017.

⁸ ‘Months after approval, breakthrough cancer patient given to just five patients’ Cortez et al., Bloomberg, December 14, 2017.

APPENDIX 6
ECONOMICS OF CAR-T TREATMENT COST AT \$ 1.0 MILLION

Key statistics for CAR-T treatment at \$ 1.0 million				
	Kymriah - ALL	Kymriah - DLBCL	Kymriah - weighted	Yescarta - DLBCL
Treatments costs	\$ 1,000,000	\$ 1,000,000	\$ 1,000,000	\$ 975,000
Future Healthcare costs	\$ 45,901	\$ 99,293	\$ 90,454	\$ 99,293
End of life costs	\$ 1,563	\$ 1,473	\$ 1,488	\$ 1,473
Total lifetime costs	\$ 1,047,464	\$ 1,100,766	\$ 1,091,942	\$ 1,075,766
Comparator lifetime costs	\$ (268,658)	\$ (104,658)	\$ (131,808)	\$ (104,658)
Incremental lifetime costs	\$ 778,806	\$ 996,108	\$ 960,134	\$ 971,108
Patient population	617	3,110	3,727	3,110
Incremental LYs	7.91	4.34	4.93	4.34
Incremental QALYs	7.18	3.59	4.18	3.59
CE Ratio per LY	\$ 98,458.41	\$ 229,517.97	\$ 207,821	\$ 223,757.60
CE Ratio per QALY	\$ 108,468.80	\$ 277,467.41	\$ 249,490	\$ 270,503.62

A few comments with respect to this table :

- The \$ 25,000 difference between the Yescarta and the Kymriah treatment costs reflects the difference between the Yescarta price and the 'discounted' Kymriah price.
- As indicated earlier in this letter, I feel that the ICER analysis for Kymriah needs to reflect the near-term approval for Kymriah in DLBCL and that this patient population needs to be included.
- Although I disagree with ICER's estimates for the patient pool for NHL, I have chosen to use the ICER number of 6,223 patients and have allocated them equally to both Novartis and Gilead.
- I have inserted an extra column to reflect the weighted average for the relevant statistics for Kymriah and have used the respective patient pools for pediatric RR-ALL and DLBCL as weights.

APPENDIX 7
CAR-T LIFETIME TREATMENT COSTS AT
DRUG COST EQUAL TO 1/3 OF ITS CURRENT COST

Key statistics for CAR-T treatment with drug costs at 1/3 of current				
	Kymriah - ALL	Kymriah - DLBCL	Kymriah - weighted average	Yescarta - DLBCL
Treatments costs	\$ 733,360	\$ 733,360	\$ 733,360	\$ 726,180
Future Healthcare costs	\$ 45,901	\$ 99,293	\$ 90,454	\$ 99,293
End of life costs	\$ 1,563	\$ 1,473	\$ 1,488	\$ 1,473
Total lifetime costs	\$ 780,824	\$ 834,126	\$ 825,302	\$ 826,946
Comparator lifetime costs	\$ (268,658)	\$ (104,658)	\$ (131,808)	\$ (104,658)
Incremental lifetime costs	\$ 512,166	\$ 729,468	\$ 693,494	\$ 722,288
Patient population	617	3,110	3,727	3,110
Incremental LYs	7.91	4.34	4.93	4.34
Incremental QALYs	7.18	3.59	4.18	3.59
CE Ratio per LY	\$ 64,749.18	\$ 168,080.18	\$ 150,974	\$ 166,425.81
CE Ratio per QALY	\$ 71,332.31	\$ 203,194.43	\$ 181,365	\$ 201,194.43

Clinical trials for tisagenlecleucel posted on ClinicalTrials.gov

Study Number	Target Patient Groups	Study Phase	Study Size	Date Started	Status
NCT02935543	Adult Lymphoblastic Leukemia (Patients with MRD+ during up front treatment !!)	Phase II	24	Oct-16	Recruiting
NCT01626495	Patients With Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma (Pedi CART19)	Interventional - Phase I/II	76	Aug-11	Ongoing but no longer recruiting
NCT02906371	Tocilizumab Optimization Timing for CART19 Associated Cytokine Release Syndrome - RR B-cell acute lymphoblastic leukemia	Interventional	30 (2 cohorts of 15) - high and low tumor burden	Aug-16	Recruiting
NCT01029366	B-Cell Leukemia or Lymphoma That Are Resistant or Refractory to Chemotherapy	Phase I - Pilot study	26	Jul-09	
NCT02640209	Patients with chronic lymphocytic leukemia and small lymphocytic lymphoma (SLL) - CAR-T with ibrutinib	Phase I - Pilot study	15	Dec-15	Recruiting
NCT02794246	High risk MM after auto SCT (within 9 months of start of RVd treatment)	Phase II	25	Jun-16	Ongoing but no longer recruiting
NCT01747486	RR CLL or SLL	Phase II - dose optimization	61	Dec-12	Ongoing but no longer recruiting
NCT02476734	Follicular Lymphoma (FL), Diffuse Large B-cell Lymphoma (DLBCL), and Mantle Cell Lymphoma (MCL)	Phase I - early	9	Aug-14	Ongoing but no longer recruiting
NCT02030834	RR Non-Hodgkins Lymphoma (NHL)	Phase II	57	Feb-14	Recruiting
NCT01551043	ALL relapsed after allo SCT	Phase I	2	Aug-10	Completed

Clinical trials for tisagenlecleucel posted on ClinicalTrials.gov

Target Completion	Age Group	Primary Time Frame measure	Secondary Time frame measure	# of centers
Apr-18	>= 18 (adult, senior)	MRD- at 28 days	OS, PFS at 1 year	1 U Penn
Aug-18	1 to 24	Safety - 2 years	Tumor response	1 Upenn
Feb-18	1 to 24	Frequency of Grade 4 CRS over 1 year	Tumor response at day 28 with MRD-	1 U Penn
May 2016, completed	> 18 (adult)	# of adverse events - 5 years	None	1 Upenn
Feb-18	> 18 (adult, senior)	# of adverse events - 26 months	None	1 Upenn
Dec-20	> 18 (adult, senior)	PFS - 3years	None	1 U Penn
Oct-19	> 18 (adult, senior)	# of adverse events - 12 months	None	1 U Penn
Feb-16	> 18 (adult, senior)	# of adverse events - 2 years	None	1 Upenn
Jan-18	> 18 (adult, senior)	# of adverse events - 18 months	None	1 Upenn
May-15	> 18 (adult, senior)	# of adverse events - 26 months	None	1 Upenn

Study Number	Target Patient Groups	Study Phase	Study Size	Date Started	Status
NCT02135406	Multiple Myeloma Patients With Early Relapse/Progression After Initial	Phase I	13	May-14	Ongoing but no longer recruiting
NCT02624258	RR Hodgkins Lymphoma (patients with limited prognosis , < 2 years)	Phase 1 - Early	10	Nov-15	Recruiting
NCT02030847	RR B-cell ALL (with no available curative options)	Phase II	30	Jan-14	Ongoing but no longer recruiting
NCT02465983	Pancreatic Cancer (unresectable, metastatic)	Phase I	12	May-15	Ongoing but no longer recruiting
NCT02650999	Relapse after CTL019 - treatment with pembroluzomab	Phase I DLBCL and Phase II MCL, Follic Lymph	12	Jan-16	Recruiting
NCT02277522	Hodgkin Lymphoma With no Available Curative Treatment Options	Phase I early	4	Oct-14	Terminated (unable to meet enrollment goal)
NCT02228096	Pediatric patients with r/r B-cell ALL and B-cell lymphoblastic lymphoma.	Phase II	67	Aug-14	Recruiting
NCT02435849	RR B-cell Acute Lymphoblastic Leukemia (childhood)	Phase II	100	Aug-15	Recruiting
NCT02445248	RR Adult diffuse large B-cell lymphoma (DBCL)	Phase II	130	Jul-15	Recruiting
NCT02374333	RR ALL or DBCL, possibly with prior auto SCT, but not eligible for all	Phase I	50	Mar-14	Recruiting
NCT02445222	Safety LTFU (15 year FU of all patients who were in CTL019 clinicals)	Safety - Study terminated - unable to meet recruitment goal	500	Nov-15	Ongoing
NCT02167360	Study of Efficacy and Safety of CTL019 in Adult ALL Patients	Study withdrawn prior to enrollment			

Target Completion	Age Group	Primary Time Frame measure	Secondary Time frame measure	# of centers
Dec-17	> 18 (adult, senior)	# of adverse events - 2 years	None	1 Upenn
Dec-18	18-24 (adult)	# adverse events - 18 months	None	1 Upenn
Jul-19	> 18, adult	# of adverse events - 18 months	None	1 Upenn
Jan-18	> 18 (adult, senior)	Safety - 2 years	None	1 UCSF + U Penn maybe ?
Jan-19	> 18 (adult, senior)	# of adverse events - 3 years	None	1 U Penn
Jun-17	> 18 (adult, senior)	# of adverse events - 2 years	None	1 U Penn
Oct-24	1-21 (child, adult)	6 months ORR - 12 months safety	None	13
Mar-22	3-21 (child, adult)	3 months - ORR	6 months is CR Cri rates & 5 years - OS	26
Jan-24	> 18 (adult, senior)	5 years - primary endpoint is ORR + OS	5 years	27
Mar-18	1-24 (child, adult)	6 months (March 2018)	none	1 - U Penn Carl June
Jul-05	all		15 years	All

Study Number	Target Patient Groups	Study Phase	Study Size	Date Started	Status
NCT03123939	Expanded Treatment Protocol in Acute Lymphoblastic Leukemia	Expanded acces to already approved indication- phase II			
NCT03027739	MRD Positive CD19+ ALL (indication already approved in US)	Phase II/III	20	Nov-16	Currently recruiting
NCT02799550	Elderly Relapsed/Refractory CD19+ ALL	Phase I	10	Oct-15	Currently recruiting
NCT02810223	B Cell Acute Lymphoblastic Leukemia	Phase I	20	May-16	Currently recruiting (?) - study should be completed by now
NCT03101709	Relapse and Refractory Patients With CD19+ B-cell Lymphoma	Phase I	30	Aug-16	Currently recruiting
NCT02924753	B-cell Acute Lymphoblastic Leukemia	Phase 1	20	Sep-16	Currently recruiting
NCT01864889	Relapsed and/or Chemotherapy Refractory B-cell Malignancy	Phase I	12	Apr-13	Currently recruiting
NCT03144583	Patients With CD19+ Leukemia or Lymphoma Refractory to Therapy (CART19-BE-01)	Phase I	10	Jun-17	Currently recruiting
NCT03118180	B Cell Lymphoma	Phase I/II	50	May-17	Currently recruiting
NCT02081937	Mantle cell Lymphoma and NHL	Phase II	2	Feb-14	

Target Completion	Age Group	Primary Time Frame measure	Secondary Time frame measure	# of centers
				EU study sites
Dec-18	Jan-60	1 year (leukemia free)		1 - China
May-18	> 60	6 months Leukemia free		1 - China
Dec-17	Jan-60	Adverse events		1 - China
Jul-19	18 -70 (adult to senior)	Adverse events	Efficacy 24 months	1 - China
Jul-19	4-70 (child - adult - senior)	Safety - adverse events	Survival of cells in 2 years	1 - China
Apr-17	5 to 90	Adverse events - 24 weeks	Anti-tumor response - 24 weeks	1 - China
Jul-12	2 to 80	Mortality, Toxicity	Response rate	1 - Spain
Dec-20	Up to 65	ORR		
Dec-19	50 to 80	ADR's	Clinical respons	1 - China

Study Number	Target Patient Groups	Study Phase	Study Size	Date Started	Status
NCT02968472	Relapsed and Refractory B Cell Leukemia using 4S-CART (4th gen)	Phase I	30	Mar-15	Currently recruiting
NCT03050190	Relapsed and Refractory B Cell Malignancies (4s-CART - 4th gen)	Phase I/II	200	Jul-13	Currently recruiting
NCT02813837	Refractory/Relapsed B Cell Hematologic Malignancies	Phase I/II	30	Jun-15	Currently recruiting

Target Completion	Age Group	Primary Time Frame measure	Secondary Time frame measure	# of centers
May-19	6 months and older	Safety of 4S-CART	Anti-tumor activity of 4S-CART	1 - China
Dec-19	6 months and older	Safety of 4S-CART	Anti-tumor activity of 4S-CART	1 -China
Jul-21	up to 60 years	ADR's	Anti-tumor response	1 -China

Comments of

David Mitchell
Multiple Myeloma Patient
President and Founder, Patients For Affordable Drugs

Regarding

Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value
Draft Evidence Report

January 24, 2018

Background

I am David Mitchell. I am president and founder of Patients For Affordable Drugs (P4AD), a national not-for-profit patient organization focused exclusively on policies to lower drug prices. P4AD does not accept funding from any organizations that profit from the development or distribution of prescription drugs.

More importantly, I am a relapsed multiple myeloma patient. Presently I am using a monoclonal antibody and proteasome inhibitor along with a steroid and various other drugs to prevent infusion reactions and unwanted side-effects. I am stable with blood cancer measures above complete response but well below symptoms. If one goes by the data, I will progress in the not-too-distant future. So CAR-T drugs are very important to me. The current CAR-T BCMA trials targeting myeloma are encouraging. It is likely I will receive a CAR-T treatment before all is said and done.

Value-Based Pricing and ICER Process

Right now, prescription drugs are priced without regard to the value they deliver to patients. Instead, corporations price their drugs based on maximizing profits. Value-based pricing for prescription drugs holds great promise as a framework that can move us away from pricing based only on the market power of drug corporations. The [Wall Street Journal](#) detailed how drug companies use that power and employ market research to determine what is the maximum price they feel they can get away with. Based on direct conversations with representatives of Novartis, we know it followed a similar process in arriving at its price for Kymriah. Instead, we believe value should be the starting point for negotiations with government, employers, insurers, and other payers.

The work of the Institute for Clinical and Economic Review (ICER) can be foundational to the creation of a new system to ensure that patients have access to drugs they need and that those drugs are accessible, affordable, and fairly priced. We applaud ICER for its work and for its inclusive and responsive process which engages patients like me, listens to concerns, and takes into account our real world experience.

Limitations of ICER Framework

The ICER value analysis is just one input that should be considered in arriving at the appropriate price for a new drug therapy. ICER does not address societal and ethical issues that are of the utmost importance for the health and well-being of patients and our nation.

ICER does not consider the role of taxpayers and government in the invention of new drugs. Because ICER does not consider appropriate returns for the drug manufacturer, it cannot take into account societal investment which reduces risk and should therefore reduce return to the company commercializing the drug.

ICER does not consider what is an appropriate price based on the investment to develop, produce, and distribute a drug. Given limited societal funds and necessary trade-offs when scarce resources are directed to unwarranted profits, this is an element that should be taken into account when arriving at a price.

Our Comments

These comments will address three key points—one within the ICER analytical framework and two that reside outside the framework, but must be taken into account in setting prices for these therapies.

- 1) By using only the populations for the initially approved indications, ICER is setting a benchmark that wildly underestimates the budget impact. Once set, the benchmark will embolden others to price follow-on drugs in the same range.
- 2) ICER should consider taxpayer investment that reduced risk to the drug corporations bringing the drugs to market. Taxpayers in the US should not pay twice for an expensive new drug—once by funding research and again by paying unjustifiably high prices.
- 3) ICER should consider the actual investment and cost to manufacture and distribute a drug. While this is often not possible because of drug company secrecy about costs, it is possible in the cases of both Kymriah and Yescarta.

1) ICER RELIANCE ONLY ON APPROVED INDICATIONS SETS A BENCHMARK THAT IS TOO HIGH AND UNDERESTIMATES BUDGET IMPACT

ICER elected to judge budget impact only on the initially approved indications. We think this is a mistake because we know about likely future approvals. The journal [Science](#) reported in January 2018 that there are 46 gene therapies in the pipeline right now. Even if only half of these are ultimately approved, the patient population will grow dramatically. In addition, if it is likely these treatments will move toward earlier use, meaning more patients getting them sooner. We analyzed the likely future patient population size and project almost 10,000 by 2022 just for Kymriah. (NOTE: These data are awaiting publication and we will share them with ICER within the next several weeks.)

To buttress the point, the FDA has already granted priority review of Kymriah for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) who are ineligible for or relapse after autologous stem cell transplant (ASCT). And “the European Medicines Agency (EMA) also granted accelerated assessment to the Marketing Authorization Application (MAA) for Kymriah for the

treatment of children and young adults with r/r B-cell acute lymphoblastic leukemia (ALL) and for adult patients with r/r DLBCL who are ineligible for ASCT” according to [news reports](#).

By not addressing the reality of what’s coming down the road, ICER is setting a dangerous benchmark that is too high and is underestimating dramatically the budget impact of CAR-T. As the nominee to be the next Secretary of DHHS, Alex Azar, said: “I don’t know that there is any drug price of a branded product that has ever gone down from any company on any drug in the United States, because every incentive in this system is toward higher prices.”

We agree with Mr. Azar: History shows branded drugs under patent and exclusivity don’t go down in price—only up. We do not have faith in indication specific pricing to hold back the rising tide of cost that is going to roll in.

2) ICER DOES NOT CONSIDER THE POLICY AND ETHICAL RAMIFICATIONS OF TAXPAYER INVESTMENT TO INVENT A DRUG AND HOW THAT LOWERS THE RISK FOR CORPORATIONS BRINGING THE DRUG TO MARKET

One argument for high prices is that investors must be compensated for the high risk involved in doing the basic scientific research and clinical trials to bring a drug to market. Without that incentive, they say, new life-saving treatments will not be invented and made available to people who need them.

But in the case of CAR-T, [taxpayers took the risk](#), and the corporations moved to acquire the IP only after the treatment was shown to be viable. Taxpayers invested more than [\\$200 million](#) in research on CAR-T from 1993-2017. A [seminal paper](#) published by researchers at UPenn in August 2011 demonstrating success of the treatment was funded in part by NIH. It was only after publication of that paper that Novartis and Kite bought the IP for what has been named Kymriah and Yescarta. While both companies assumed some risk, it was by then dramatically lowered.

Corporations want to command a risk premium for these new drugs that is unwarranted. ICER should in fact discount the price to take into account the contribution by US taxpayers and the lower risk because of early taxpayer investment. ICER clearly believes it can look at societal factors outside of health care costs in arriving at an estimated price. ICER considered societal factors for the drug Luxturna, and suggested those would raise the value price for that drug. If societal considerations can raise an ICER price, then they should be able to lower it as well.

Taxpayer investment that lowers the risk for drug developers is a societal factor that ICER should consider. If taxpayers are going to underwrite the initial risk, they should receive a price reflecting the reduced risk borne by manufacturers. At least US taxpayers bore much of the cost to invent these drugs should pay no more than other similar OECD countries.

3) THIS ANALYSIS SHOULD CONSIDER THE APPROPRIATE PRICE TO MAXIMIZE ACCESS AND AFFORDABILITY WHILE ENSURING A ROBUST R&D PIPELINE AND REASONABLE PROFIT.

Life-saving drugs should be priced to maximize access and affordability while ensuring a robust research and development pipeline and a reasonable return to investors. Such a price is often difficult to determine but not so in this case. We have critical information about the investment costs of both Kymriah and Yescarta.

Kymriah

A painstaking analysis of Novartis's costs to develop, manufacture, and distribute Kymriah will soon be published, and we will make these data available to ICER when it is. Here are some of the highlights from that analysis:

- Former Novartis CEO Joe Jimenez disclosed his company's investment to bring Kymriah to market. According to [Forbes](#) "He puts a number on it, saying bringing Kymriah to market cost Novartis more than \$1 billion." It is very important to note that this is significantly less than the number \$2.6 billion from Tufts typically cited by the industry as the cost to develop a new drug. *And this is for the first in a completely new class of drugs.*
- The cost of goods was [revealed by Dr. Carl June](#), the principal inventor of tisagenlecleucel. He placed its production cost at \$20,000 per infusion, and noted that this price should decrease as Novartis scaled up production.
- The number of patients Novartis put through clinical trials has been publicly reported.
- Novartis told me directly in a meeting the cost of plants. The cost to outfit its plant in New Jersey was \$43 million and Novartis has three plants.
- Novartis received a 50 percent orphan drug tax credit for clinical trials, and an FDA priority review voucher worth approximately \$190 million, both of which further defray its development costs.
- Both publicly reported analyses and industry practice provide a good estimate of royalties paid to UPenn for the IP and Oxford Biomedica for the viral vector.
- We can estimate costs of staffing, patient support, patient registries, and after market surveillance.

We know enough to make a well-grounded estimate that at \$475,000—even discounting for the approximately 16 percent of patients who will not respond in four weeks—Novartis will realize profits of at least 84 percent on Kymriah. This for a drug that taxpayers invented and with development costs that are less than 40 percent of what the industry says is its benchmark.

Kymriah is wildly overpriced. In fact, we estimate that at the retail price of \$160,000 per patient, Novartis can maintain its historic 19 percent R&D spend which generously covers both its successes and failures and realize its healthy historic profit level of 27 percent. Putting this profit into context: Pharma companies earn average profits of about 22 percent—which is already three times the S&P 500.

Given these factors, ICER's price should be dramatically reduced to maximize accessibility and affordability while maintaining a robust innovation pipeline and excellent returns for investors.

Yescarta

Yescarta is simpler. We know from SEC filings that Kite invested \$317 million to bring the drug to market before selling to Gilead. It will also receive a 50% orphan drug tax credit for the cost of clinical trials further defraying the cost of development.

At least two patents in which taxpayers still hold an interest transferred to Gilead with the Kite sale. So taxpayers directly played a role in underwriting the development of the drug. Many of the other cost factors from the Novartis analysis pertain to Gilead.

But the initial Gilead patient population is much larger, so the budget impact is greater and the price necessary to gain a fair return is lower. We estimate the Yescarta retail price should be approximately \$155,000.

Conclusion

Drugs must be priced to maximize accessibility and affordability while maintaining a well-stocked innovation pipeline and providing fair returns for investors. The ICER analytical framework is an important input for arriving at an appropriate price for new drugs. But this analysis of CAR-T drugs explores only two dimensions of pricing—value to patients and value to the system. It does not account for significant societal and ethical issues that must be considered when looking at allocation of scarce resources, and what is in the best interests of patients and our health care system. While ICER analytical framework may not be designed to incorporate these issues directly in determining an ICER price range, they at least should be referenced in the final ICER report so the VA and other payers—including government and private sector payers—can take these into account in negotiations. Then we can reach a broader measure of value to society.

Disclosure: Patients For Affordable Drugs is partially funded by the Laura and John Arnold Foundation which also funds ICER.



January 23, 2018

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

RE: Draft Evidence Report and Voting Questions---Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers

Dear Dr. Pearson:

On behalf of Patients Rising Now, we appreciate the opportunity ICER allows for stakeholders, including patient advocates and patients themselves, to comment on ICER's draft evidence report and voting questions on Chimeric Antigen Receptor T-Cell (CAR-T) for B-Cell Cancers.

In assessing ICER's draft evidence report and voting questions, we choose to view through the lens of a patient, and gauge how the assessment would impact their access to the therapy under review, the future innovation of this and other therapies, and the reforms that may be needed in ensuring utilization of both. With this as our guide, we must first state our serious concerns and enduring objections.

The ICER website states: *'Patients are at the core of ICER's mission to help provide an independent source of analysis of evidence on effectiveness and value to improve the quality of care that patients receive.'*

Though we acknowledge ICER has made some improvements in relations with patients and advocates, this draft evidence falls short of both the letter and the spirit of ICER's stated core and mission.

- I. ***It's Far Too Early:*** As long as ICER insists on reviewing therapies at what we believe are questionable times – generally right before a new therapy comes to market – then the evaluation will remain fundamentally flawed. Attempting to create a value framework for a therapy in its infancy fails any serious attempt at the scientific method, and ultimately serves to cheat patients by impacting undetermined coverage policies that could suppress patient access. We strongly encourage ICER once again to commit to developing a standard for *when it will assess new therapies*, and we believe that it should allow a significant period of time to gather real world data within the analysis.
- II. ***Updating Assessments:*** It is unwise for ICER to continue to resist consensus calls to update early assessments in a way that is consistent with logic and practice. If ICER

continues to assess treatments right before or as they hit the market – which is not a reliable standard – what will be the determining factor for how often you will reassess your findings? Without a standard in place for updating patient data, ICER cannot claim to truly be helping patients.

- III. ***Lack of Meaningful Patient Engagement:*** While we acknowledge ICER’s work with some selected organizations, an authentic patient perspective is obviously absent – and profoundly so in this case. In our experience, so many patients living with chronic and life-threatening illnesses develop an advanced scientific knowledge in their specific disease and are experts in its impact on their body. This is also absolutely true among the parents of younger patients. And yet, these vital voices of value are consistently excluded from your “expert panel.” Does living with a disease and in many instances fighting for your life not qualify as a worthwhile expertise?
- IV. ***Beyond Clinical Value:*** While we understand ICER’s purpose in evaluating the clinical and economic data for selected therapies, trying to create a universal assessment in a precision medicine world is simply not possible for certain therapies and certain types of patients. Surely, ICER should understand this. We respect and encourage the trend toward value and will continue to lead meaningful conversations and a deeper dialogue around its impact for patients. We believe patients voices need to be a part of defining and assessing the value of their treatment plan and the cost of all aspects of their treatment plan with their doctors.
- V. ***Budget Impact Analysis:*** How can ICER possibly assess a budget impact analysis on something with so many unknown outcomes and variables? The only budget analysis anyone should really be assessing is the patient’s out of pocket costs across the board. Patients Rising Now believes that by focusing on those unsustainable numbers, the societal budget impact will automatically be addressed by creating a more transparent, easier to understand payment system for patients.

It is for these reasons – and others – that we call on your organization to reexamine and reassess its current course and gain very needed credibility among the entire health care ecosystem that supports the crucial truth of patient access.

Thank you again for the opportunity to comment.

Sincerely,



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