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

Response to Public Comments on Draft Evidence Report

February 15, 2018
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<td>1.  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. Patient heterogeneity is extensive and its relationship to response is poorly understood. On top of this, the therapeutic armamentarium of a handful of drugs is too small to address this huge patient and disease variation. Moreover, small numbers of patients 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.</td>
<td>We agree that the evidence base for clofarabine, blinatumomab, and tisagenlecleucel is limited: single arm trials with limited follow-up. We also agree that the lack of head-to-head trials raises issues of selection bias when comparing therapies. We have highlighted these issues throughout the report. However, patients, clinicians, guideline authors such as the NCCN, and payers need to make decisions about how to treat patients using these FDA approved medications.</td>
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<td><em>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.</em> 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. 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.</td>
<td>See response to #1 above. In addition, we recognize that tisagenlecleucel may be used after blinatumomab failure or vice versa as you describe below. This does not change the primary findings of the assessment.</td>
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<td><strong>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.</strong> 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 classification indicates only for relapsed or refractory B-ALL would meet criteria for the ultra-orphan framework, it is our understanding that tisagenlecleucel will be used for indications beyond R/R B-ALL, such as adult DLBCL and other indications, which result in a much larger potential patient population.</td>
<td>While therapies indicated only for relapsed or refractory B-ALL would meet criteria for the ultra-orphan framework, it is our understanding that tisagenlecleucel will be used for indications beyond R/R B-ALL, such as adult DLBCL and other indications, which result in a much larger potential patient population.</td>
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Response to Comments – CAR-T Therapies for B-Cell Cancers
framework sets a strong precedent for ICER to conduct this R/R B-ALL assessment under this same ultra-orphan framework.

4. **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, 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.

We agree that there remains uncertainty about the net health benefits of tisagenlecleucel; hence the B+ rating. In our estimation, the evidence supports substantial net health benefit with uncertainty. We did not think that the conceptual uncertainty including no benefit or harm compared with available therapies for pediatric patients with relapsed or refractory B-ALL was defensible. Hence the B+ rating.
chemotherapy in adult patients with R/R B-ALL in a randomized, controlled study. 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.

5. **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. 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.

We agree that there is considerable uncertainty about the best approach for sequencing the available therapies for pediatric R/R B-ALL. In patients with who meet criteria for use of tisagenlecleucel, if they have not yet been treated with blinatumomab, then some clinicians will elect to use blinatumomab first.

6. **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. RIALTO has many similarities to MT103-205, providing a significant increase in the number of subjects, We have added the preliminary data on the first 40 patients enrolled in the RIALTO study as reported at ASCO 2017 to the Tables in the report and appendices as well as the text.
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., ≥ 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.

### 7. 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.

### 8. 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.

We agree that there are potential issues with pooling the three trials but elected to include the pooled results because of the much longer follow-up in the B2101J trial. The curves for the B2202/ELIANA study in the recently published NEJM article are quite similar, though the median and maximum follow-up times are shorter.

We emphasized the AEs reported in the package insert for tisagenlecleucel for consistency with those available for axicabtagene ciloleucel. We have included the AEs available from all of the trials of tisagenlecleucel in the Appendix Table C13.

As we repeatedly point out in the review, selection bias (heterogeneity in the patient populations studied) is a critical issue that limits confidence in any cross-study comparisons that are made. This is one of the critical areas that introduce uncertainty in our analyses.

Ideally, there would be head-to-head RCTs or at least RCTs with a common comparator to allow for indirect comparisons to be estimated, but no such studies are available. Amgen suggests consideration of alternative methods as evaluated by NICE in their Technical Support Document (see reference #14 referred to by Amgen in their comments).
The NICE reference (14) states: “An unanchored MAIC or STC effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate.”

Since there is no consensus on the weighting of prognostic factors for OS or EFS for pediatric R/R B-ALL, the strong assumption is not met, and these methods cannot be used.

Indeed, Amgen in their later comments states “The precise direction and relative importance of the factors for predicting survival in these patients has not been established.”

9. The ELIANA and MT-103-205 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.

We agree that there are a number of differences in the patient populations and have highlighted them in our report.

10. 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., we found that patients in MT103-205 and

See our response under #8 above. We believe that there is the potential for significant bias applying these methods to
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, 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. Without this analysis, the conclusions on treatment effect and causation may be a function of other unrelated and coincidental variables.

11. 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.

We agree that the current state of uncertainty is not fully captured in a quantitative way through the one-way and probabilistic sensitivity analyses. There is a lack of best practices in regard to how to quantify uncertainty in single-arm survival curves. We explored variation of shape and scale parameters within the models that were produced by our curve-fitting algorithms, but this generated two potential flaws in the uncertainty findings: 1) the transition probabilities generated for a particular modeled intervention path did not produce plausible results (i.e. no one existing in the progressive alive state) and perhaps most importantly, 2) the uncertainty generated had no relative relationship to the comparator curve. If we had uncertainty around a hazard ratio, that accounted for the difference between intervention and comparator, we could fix one curve and vary the other intervention curve based on the hazard ratio uncertainty. However, without having this
Moreover, survival curves for immuno-oncologic agents differ from chemotherapy, cautions need to be taken while selecting the parametric distributions for survival. Therefore, the current conclusion that the CE model results are robust through one-way and probabilistic sensitivity analyses is unfounded.

The relative relationship, we would introduce too much noise around an intervention’s curve, compared to the comparator curve if we produced uncertainty around each curve, separately. Because of the challenge of making an unsupported assumption around randomness for this comparative exercise, we decided to not attempt to quantify curve uncertainty for shape and scale in each intervention. Lastly, parametric distributions were selected separately for each therapy and for each survival curve.

However, we added scenario analyses to account for uncertainty in the survival estimates beyond the observed trial time horizon. The first analysis introduced a lower bound survival estimate by removing the knot in the curve. This resulted in fewer life years and quality-adjusted life years gained from the base-case analysis. The second analysis added additional death after five years (based on proportions in the literature). Finally, we computed the value estimates for a range of time horizons in an attempt to aid decision makers who are wary to accept certain long-term assumptions within the model.

To the comment about B-ALL related death, we note that a standardized mortality ratio was already included in the base-case results for added mortality after five years.

12. 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 base case analysis for tisagenlecleucel assumes payment for responders only at one month. This was selected as the base-case based on comments made by the manufacturer and by CMS. However, we present other payment scenarios as a sensitivity analysis, and the results and conclusions were robust.

Due to the difficulties mentioned, mark-up determination was a challenge. We engaged multiple stakeholders and heard
the pediatric R/R B-ALL patients. The model also underestimates the cost of B-cell aplasia. Ranges from no mark-up (0%) to a mark-up similar to that of other oncology drugs (ASP+152%). We selected our mark-up approach based on comments and feedback from the stakeholders we engaged. However, we note the uncertainty in the mark-up and thus vary it over a large range (with the lower bound being no mark-up) in the sensitivity analyses.

Regarding the cost per hospital day, we have now updated the cost to be specific to pediatric leukemia hospitalizations.

Thanks for pointing out the issue with the B-cell aplasia cost. In order to capture the variation in B-cell aplasia cost, we now vary B-cell aplasia within a sensitivity analysis from a duration of 0 months to lifetime for those with hypogammaglobulinemia.

13. 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.

These are primarily references that were incorrect: we have removed the old citations and replaced them with the correct citation. The methodologic issues have been addressed in the early comments. None of these changes have any impact on the findings of the evidence review or cost model.

Genentech

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

We agree that the evidence base for clofarabine, blinatumomab, tisagenlecleucel, and axicabtagene ciloleucel is limited: single-arm trials with limited follow-up. We also agree that the lack of head-to-head trials raises issues of selection bias when comparing therapies. There is no common comparator, so usual methods for indirect comparisons (network meta-analyses) cannot be used. We have highlighted these limitations throughout the report and will ensure that this is adequately addressed during the public meeting.
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. Further, a significant bias in patient selection is introduced due to the manufacturing time of 17 days for axicabtagene ciloleucel treatment. 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. 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 data cut be used to update the model. 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 data cut; we updated the survival curves from the recent NEJM publication that included progression-free survival (not duration of response) and overall survival. These results are updated in our revised report.

To address uncertainty in the survival estimates beyond the trial time horizon, we added scenario analyses. The first analysis introduced a lower bound survival estimate by removing the knot in the curve. This resulted in fewer life years and quality-adjusted life years gained from the base-case analysis. The second analysis added additional death after five years (based on proportions in the literature). Finally, we computed the value estimates for a range of time horizons in an attempt to aid decision makers who are wary to accept certain long-term assumptions within the model.
mPFS 5.8 months from 8/11/2017 data cut). 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.

### 3. 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. 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. There are noted differences in patient characteristics, histologies, treatment exposure and outcomes between Schirmbeck et al. 2016 and SCHOLAR-1. 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).

### 4. 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 are the same in responders vs. non-responders. Overall survival is the key driver of the model, and that was available for SCHOLAR-1. We assumed the proportional relationship to get at the proportion who were progression free to estimate the utilities. We recognize this action required assumptions, but do not believe that this assumption would highly impact the long-term costs or outcomes produced from the model.

To add more uncertainty in the survival estimates beyond the trial time horizon, we added scenario analyses. The first analysis introduced a lower bound survival estimate by removing the knot in the curve. This resulted in fewer life years and quality-adjusted life years gained from the base-case analysis. The second analysis added additional death after five years (based on proportions in the literature). Finally, we computed the value estimates for a range of time horizons in an attempt to aid decision makers who are wary to accept certain long-term assumptions within the model.
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). 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.

### 5. 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. 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

We did not have all of the data elements needed to run a mixture cure model (i.e., access to patient-level data with a comparator arm); therefore, we developed a modified parametric approach to account for the flattening observed in the curve. Even the mixture cure model without a comparator arm would struggle to quantify the relative uncertainty between intervention and comparator.

Clinicians in the field provided feedback and supported this modeling approach and the time point used for assumed flattening. We agree that our approach does not quantitatively account for all uncertainty. Because of the challenge of
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.

making an unsupported assumption around randomness for this comparative exercise, we decided to not attempt to quantify curve uncertainty for shape and scale in each intervention.

To address uncertainty in the survival estimates beyond the trial time horizon, we added scenario analyses. The first analysis introduced a lower bound survival estimate by removing the knot in the curve. This resulted in fewer life years and quality-adjusted life years gained from the base-case analysis. The second analysis added additional death after five years (based on proportions in the literature). Finally, we computed the value estimates for a range of time horizons in an attempt to aid decision makers who are wary to accept certain long-term assumptions within the model.

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<td>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. 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.</td>
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<td>The cost of R-DHAP was evaluated with other commonly used regimens (R-ICE and R-CHOP) and the costs were similar across the three.</td>
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<tr>
<th>7.</th>
<th>Additional comments for consideration</th>
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<td></td>
<td>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.</td>
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<td>We now report chemotherapy treatment costs separately from palliative chemotherapy costs.</td>
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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 + cytarbene 2g/m² every 12 hours for 2 doses on day 2 + cisplatin 100 mg/m² on day 3.

**Juno Therapeutics**

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 study 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 studies 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 study and 50% of the treatments in the LY. Thus, the use of the
| 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. |
| **Please refer to Table D10 and Table D11 for utilization, administration and monitoring costs.** | Regarding treatment regimens and the number of administrations, detail is provided in Table D2. If there were multiple drugs administered on the same day and/or time, an add-on sequence cost was used (from Table D10). If drugs were administered on different days or at different times, different administration costs were used. Our approach is consistent with what you described. |

| 3. | Improved transparency is also needed on the 31- and 15-inpatient hospital days of therapy for KYMRIAH™ and YESCARTA™ 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. YESCARTA™ patients are expected to have an inpatient stay of between 7 and 10 days. 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. |
|---------------------------------------------------------------|
| **We were provided with these values by the manufacturer. They are now cited as such in Table D11.** |

| 4. | Lastly, ICER’s calculated future healthcare costs are substantially lower for chemotherapy patients than for YESCARTA™ 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. |
|---------------------------------------------------------------|
| **Thanks for bringing up this issue. Detail on future healthcare costs was mistakenly omitted from the draft report. Discussion of this has been added to the revised report. Future healthcare costs were included for those considered long-term survivors (those alive after five years). There were fewer patients alive after five years following chemotherapy—thus, this treatment had fewer future healthcare costs (fewer people alive after five years).** |

| 5. | 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 |
|---------------------------------------------------------------|
| **The evidence obtained from the curves suggested convergence at a period of less than five years (i.e., around two years) and was, therefore, accounted for in our model. However, there was not a** |
NICE evaluation specific to ALL, it is not aligned with the literature findings ICER cites in their report. For the lymphoma population, ICER discusses a 2014 publication which suggests that event-free survival of two-years is a reasonable surrogate outcome for a cure, while also citing an additional publication 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.

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<th>6. Societal Perspective</th>
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<tr>
<td>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 KYMRIAH™ and $1,171 per life year for YESCARTA™. 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.</td>
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<td>The societal perspective was designed as a limited perspective. Our goal was to avoid double counting of future productivity gains with the utility score; therefore, we only calculated costs associated with treatment. Again, we acknowledge that this is a limited societal perspective. We did not include costs of travel for chemotherapy. Chemotherapy could be administered at various centers and isn’t reliant on a patient visiting a specialized center for CAR-T. Regarding inpatient versus outpatient administration of CAR-T, our objective was to model what happened (inpatient), not what might happen (outpatient).</td>
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7. 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. 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.

The only adverse event that we identified with an additional disutility outside of treatment was CRS. The additional disutility was only applied to those with CRS and the disutility's duration was eight days. Because the additional disutility on CRS had such a minimal impact, it was not a key driver in the model. Our approach for this was in line with the approach of the mock HTA.

8. 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 D10 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 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 Guide 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

We acknowledge that lacking a uniform source for cost data represents a study limitation. We have added it as a factor in our section on limitations.
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.

9. 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. When considering that rates of grade 1-2 CRS are 35% for Kymriah™ 20 and 81% for Yescarta™, 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.

Our intent with this review was not to compare one CAR-T therapy to another CAR-T therapy. That comparison represents a challenging undertaking due to the many differences between CAR-T treatments, such as disease, classification of adverse events, definitions of response, and definitions of adverse events.

10. 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. While the current model framework adequately captures the relative benefit of Survival curves stratified by response status were not available for all curves. Further, we heard from stakeholders and clinical experts that definitions for response varied widely between therapies. Our results should be interpreted as the average cost-effectiveness for the average patient initiating therapy. As noted in our draft

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Response to Comments – CAR-T Therapies for B-Cell Cancers
CAR-Ts compared to chemotherapy, a more granular estimation of survival, using stratified responses, is necessary for any future comparisons between CAR-T therapies.

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.

Kite Pharma (A Gilead Company)

1. 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.

2. 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-
3. 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

From the third-party payer perspective, the costs of the CAR-T intervention and its administration are included. We recognize that multiple stakeholders are involved in the delivery of CAR-T and therefore, multiple stakeholders are responsible for the long-term cost-effectiveness findings.

Regarding mark-up for CAR-T, we had extensive conversations with stakeholders. Input from stakeholders suggested a range of possible mark-up 0% to a mark-up comparable to other oncology therapies (ASP+152%). To accommodate for the challenge of accounting for hospital mark-up, we varied the mark-up percentage in a one-way sensitivity analysis. The lower bound for the mark-up in the sensitivity analysis is 0%. Further, the threshold analyses suggest the price that the total of the mark-up and acquisition cost need to meet. This informs the price that payers would need to pay in total, either through negotiations with the hospital mark-up, drug acquisition cost, or both.
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.

4. 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.

For the cost of hospitalization, we have now updated the cost of hospitalization to be disease specific. Previously, we used the average adult cost per hospital day for adult cancer patients (axicabtagene ciloleucel) or for pediatric cancer patients (tisagenlecleucel). However, after receiving your feedback, we realized it would be more suitable to use disease-specific costs. As such, we made necessary adjustments and accounted for inflation to 2017 USD. Now we use the cost per hospital day for pediatric leukemia (tisagenlecleucel) and cost per hospital day for non-Hodgkin’s lymphoma (axicabtagene ciloleucel).

5. 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.

The cost of a CAR-T hospital admission included the per diem cost for hospital days and the costs of therapies administered during the hospitalization because the bundled payment mechanism was unknown. Our assumption was that the bundled payment will approximate the cost of the resources used under a fee-for-service framework.

Without known bundled payments (or DRGs), we estimated what the bundled payment might be by using a per diem cost for hospital days and adding on the cost of therapies administered. We assumed the bundled payment would approximate the cost of the resources used under this fee-for-service framework.

6. 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. These costs are well below the $60K hospitalization cost plus add-on costs of AEs employed by ICER.
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.

| 7. | 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. | In the base-case analysis, we assumed B-cell aplasia for 11.4 months for patients with hypogammaglobulinemia. However, in the one-way sensitivity analysis, we vary the duration of IVIG for those with hypogammaglobulinemia from 0 months to a lifetime. Therefore, the one-way sensitivity analysis can be reviewed to identify the cost-effectiveness estimate assuming no IVIG or lifetime IVIG use for those with hypogammaglobulinemia. Based on the literature by Casulo provided by the reviewer, we now account for the 6.6% of those receiving R-DHAP who... |
| 8. | 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... | See detailed and itemized responses above. |
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.

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<th>9.</th>
<th>FUTURE MEDICAL COSTS: Adhere to established best practices</th>
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<td>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 CEA. 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).</td>
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<td>We included future healthcare costs based on recommendations from the Second Panel of Cost-Effectiveness. More detail on the future healthcare costs have been added to the report. These were added for CAR-T long-term survivors (those alive and responding to treatment after five years). These were important to include for CAR-T, a potentially curative therapy, due to the potential for people to be alive and responding to treatment after five years.</td>
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| 10. | 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 |
| The societal perspective was designed as a limited societal perspective. We wanted to avoid the potential of double counting future productivity gains with the utility score; therefore, we only calculated societal costs associated with treatment. Again, we acknowledge that this is a limited societal perspective and include this as a limitation in the report. It is important to note that this is a scenario |
11. 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.

We have added additional text to the methods section to detail the inclusion of future healthcare costs. This was mistakenly omitted from the draft report.

12. 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.

See itemized and detailed responses to these recommendations above.

13. 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 (Sorror 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.

Regarding mark-up for CAR-T, we had extensive conversations with stakeholders, and have used the same mark-up assumptions as in the cost-effectiveness model. Our mark-up in the budget impact model informs the budget impact for payers with a mark-up.

ICER’s budget impact threshold is perceived as a tool to help inform payers of a potential access alert based on the budgetary impact of a health technology, and is a standard feature of ICER’s potential budget impact analysis.
| 14. | **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. |
|     | Our approach was to model what has been stated publicly as the payment approach. |

| 15. | **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 drug. |
|     | 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. |
|     | The application of ICER’s ultra-rare framework is reserved for therapies with an anticipated target population of fewer than 10,000 individuals. We note that, in addition to current studies of axicabtagene ciloleucel in DLBCL, there are ongoing studies in both pediatric and adult acute lymphoblastic leukemia as well as mantle cell lymphoma, which will increase the likely target population size significantly. |

| 16. | **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. |
|     | Due to the immature long-term follow-up data, we opted to use shorter time horizons to show how long effects would need to be realized for a cost-effective finding. This was a scenario analysis. The base-case used a lifetime time horizon. |

<p>| 17. | <strong>MISCELLANEOUS CORRECTIONS</strong> |
|     | 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. |
|     | We have removed the phrase. |</p>
<table>
<thead>
<tr>
<th>Recommendation: Remove “ineligible for auto-SCT.”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>18.</strong> 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.</td>
</tr>
<tr>
<td>Recommendation: Update text to reflect new NCCN guidelines incorporating axicabtagene ciloleucel in lymphomas. We have updated the guidelines summary to reflect the most recent NCCN guidance issued in December 2017.</td>
</tr>
</tbody>
</table>

| 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. Table 4.3 (now 3.3) has been updated with the newly published data from the ELIANA trial. The table reports the ORR (CR + CRi). |

| 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.). Thank you. We have corrected the errors. |

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**Novartis**

| 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. 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 | Our model focuses on what occurred based on the outcomes data we used and not on what might occur in future circumstances. Probability of discontinuation before CAR-T infusion (due to adverse events, death, or manufacturing failure) was varied (with a lower bound of 0%), and this was not a key driver of the results. |
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%) 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.

2. 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 ALL and 28.6 months in the NCT02030834 trial in adult lymphoma. 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.

There is considerable controversy around this and we hope that this will be a good focus for panel and roundtable discussion. We have also received comments that the rating should be P/I.

The primary reason for the B+ rating is the considerable uncertainty in the survival curves and in comparisons to alternative therapies, such as blinatumomab.

The B2101J trial is problematic because the dosing was not standardized and the inclusion criteria were dissimilar from the other two trials.

Given the many areas of uncertainty, we believe that B+ is the appropriate rating.
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. 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). The FDA guideline for rare diseases states that controls may be concurrent or historical in these situations.

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. Novartis would welcome an opportunity to develop a different quality assessment methodology for rare and life-threatening diseases with no effective standard of care.

3. 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.

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

Our approach documents the total candidate population percentage that can be treated without crossing the threshold.

Our revised estimates of budget impact based on current model inputs and axicabtagene ciloleucel’s price suggest that 38% of the entire eligible cohort (or 2,243 patients) of 5,902 patients can be treated with axicabtagene ciloleucel without crossing the ICER budget impact threshold of $915 million. Based on the manufacturer’s stated manufacturing capacity and the analyst report estimates on uptake, we believe our estimate of 38% aligns closely with real-world market
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. 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.

4. **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, 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.

   - 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.

5. **Scenario analyses:**

   We suggest updating the societal perspective analysis in the draft report to consider long-term societal benefits. The societal perspective was designed as a limited perspective. To avoid the potential of double counting productivity gains with the utility score, we only included uptake and entry of other interventions, and is reasonable.
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.

**6.** Novartis recommends removing the scenario analysis of no active treatment therapy as a comparator (pgs 53-54), as the draft report 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.

We chose to include the scenario analysis for no active treatment therapy as a comparator in the draft report because it allowed us to show incremental costs and effectiveness of CAR-T therapy in the absence of other active treatments. This is a scenario analysis and not the base-case analysis.

**7.** 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. 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.

We have updated the cost of the hospital day to be disease specific. We recently updated all values in the draft report to account for inflation. All values now compensate for inflation at 2017 USDs.

**8.** 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. The UK mock technology appraisal also considered that all patients treated with clofarabine monotherapy would have one episode of non-elective hospitalization for treatment.

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.

Thank you for providing this literature. We have reviewed this literature and talked with clinical experts and now add an inpatient administration (for 22.5 days) of clofarabine.

**9.** 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), this rate actually reflects the proportion of patients

Thank you for providing this literature. We have reviewed and have re-calculated the size of the eligible population of tisagenlecleucel to 400 patients annually.
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.

Cooper et al. 2015 reported that 15%-20% of patients with newly diagnosed (ND) ALL will experience first relapse; 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.

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.

10. 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.

The value indicated is based on the weighted estimate for those that initiate treatment. The 14.8% was applied only to those that continued treatment all the way to assessment of response—not for those that discontinued or died before assessment of response was possible. This explains why the number is lower in Table 5.7 as the 14.8% was only applied to those that had assessment of response (and not the full cohort).

11. Please change progression-free survival to event-free survival in the context of ALL (Table D4-5).

This is now updated in the revised report.

12. 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.

We have updated the report to reflect the longer follow-up for B2101J and the ELIANA trial as reported in Maude NEJM 2018 after the release of the draft report.

13. 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.

Thank you. We look forward to additional information on the effectiveness of tisagenlecleucel for the treatment of adult lymphoma.
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.

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<table>
<thead>
<tr>
<th>14.</th>
<th>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. Therefore, conservatively, relapsed patients would have a 7-day stay.</th>
<th>This literature supported disease-related hospitalization, but was not clearly related to hospitalization for chemotherapy administration. We engaged stakeholders and clinical experts and did not hear that inpatient administration for chemotherapy was common.</th>
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<tbody>
<tr>
<td>15.</td>
<td>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. 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).</td>
<td>Thank you for providing this literature. We have reviewed and have re-calculated the size of the eligible population of axicabtagene ciloleucel to be 5,902 patients annually.</td>
</tr>
<tr>
<td>16.</td>
<td>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.</td>
<td>We now model SCT for non-responders in addition to responders.</td>
</tr>
<tr>
<td>17.</td>
<td>Only subsequent autologous SCT (autoSCT) was considered in the lymphoma evaluation (pgs 42 and 45). However, the</td>
<td>We have revised our model to include the alloSCT cost for those in ZUMA-1 and the</td>
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evaluation should consider both subsequent autoSCT and alloSCT:

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.

Patients enrolled in the ZUMA-1 trial received subsequent alloSCT.

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) and 3.9% of those without initial autoSCT received alloSCT (Van Den Neste et al. 2016). Novartis requests that these rates and the prior autoSCT rate (22%) in SCHOLAR-1 be used to estimate the alloSCT rate (7%).

| 18. | The average alloSCT cost during the first year after procedure was $473,005 (2016 USD). |
| 19. | 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. |
| 20. | 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. |
| 21. | Suggested corrections, organized by Table or Figure numbers [NOTE: These recommendations were presented in a table, which can be viewed in the PDF of the original comment submitted by Novartis] |

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**Clinical Societies and Clinical Experts**

Krishna Komanduri, MD, President, American Society for Blood and Marrow Transplant

1. 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 autoSCT cost for those from SCHOLAR-1. Based on inadequate data for both the intervention and comparator, we did not feel comfortable making assumptions suggested by the reviewer.

The FDA has approved these therapies, the NCCN has updated their guidelines to incorporate these therapies, and payers need to establish policies around coverage of the therapies. It is therefore critically-important to understand the value of CAR-T given the data currently available, even
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.

if the immaturity of the data contribute to significant uncertainty surrounding estimates for comparative effectiveness and value. We expect to update our analyses as more mature data become available.

2. 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.

Thank you. We strive to put the patient perspective first. We contact patient organizations before any other group and use their input for our draft scope and the key benefits and harms that we focus on in our reports.

3. 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

We had multiple conversations with stakeholders and experts related to mark-up. Feedback we received on potential mark-up ranged from 0% (no mark-up) to mark-up similar to other oncology drugs (ASP+152%). To accommodate for this uncertainty and possible range, we varied the mark-ups within a one-way sensitivity analysis. The lower bound of mark-up in the one-way sensitivity analysis is 0%, and thus those results can be reviewed to identify the incremental cost-effectiveness ratio under no mark-up.

We did not want to speculate on DRG payment as none are presently available. Instead, we followed a per-diem approach with the assumption that the bundled payment would approximate the fee-for-service amount.

Further, to add clarification to our perspective, we include the term "third-party payer".
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.

| 4. | 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 | We could not identify more appropriate literature. However, time to SCT was not a driver in the model results. Time would |
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.

5. There are more recent analyses of the costs of HCT that may be useful. Additional sources are suggested below.


6. 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.

7. 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 only affect the discounting of the cost of SCT.

Thank you for providing this literature. For the pediatric ALL population, we are using literature from Lin et al. for the cost of allo-SCT specific to this pediatric population. For adult SCT in the DLBCL population, we now use an allo-SCT cost for those that receive SCT after axicabtagene ciloleucel. The reference for the adult allo-SCT was by Maziarz et al., published in 2017. We elected to use this one over others provided in this comment due to the more recent publication year and longer follow up. Costs for adult auto-SCT were from Pelletier et al. The unit cost aligned with the range noted in the references provided in this comment; therefore, we didn’t update the reference used.

Thank you for this citation. We have added a description of Health Net’s Medi-Cal policy to the coverage policy section of the report.

Thank you for this citation. We have summarized the NGS policy in the revised report.
for allogeneic and autologous transplantation for the following types of lymphoma:

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Allogeneic</td>
<td>i. Primary refractory Hodgkin and non-Hodgkin lymphoma</td>
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<tr>
<td></td>
<td>b. Autologous:</td>
</tr>
<tr>
<td></td>
<td>i. Anaplastic large cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>ii. Large cell lymphoma/B-cell lymphoma</td>
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<tr>
<td></td>
<td>iii. Peripheral T-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>iv. Primary central nervous system lymphoma</td>
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</table>

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

8. 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.

The societal perspective was designed as a limited perspective. To avoid the potential to double count future productivity gains with the utility, we only calculated productivity costs associated with treatment. Again, we acknowledge that this is a limited societal perspective and mention it as such in the limitations.

9. 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.

Our model isn’t set up to be able to address this. Our survival and "relapse" data sources were from Kaplan-Meier curves, and therefore, we don't have an input for the probability of relapse.

10. 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.

In our base-case, we make our comparisons to chemotherapy. The supplemental scenario analysis for no active treatment was implemented to show the absolute costs and the effects as compared to no further treatment.

Susannah E. Koontz, PharmD, BCOP, FHOPA, 2017-2018 Hematology/Oncology Pharmacy Association President

1. 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:

   Thank you for your comments.

2. **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.

   Under interventions, we list tisagenlecleucel for both populations, but do not indicate that it has FDA approval. We knew that it was being actively studied for this indication.
On page 4 we state that tisagenlecleucel has FDA approval for ALL only and on page 8 we note that Novartis has applied to the FDA for tisagenlecleucel to have an indication for lymphoma. If FDA approval happened early enough, we would have built a cost model for tisagenlecleucel for adult lymphoma, but that has not happened.

3. On page 7, there is no mention of respiratory distress as related to CRS (only high fever and hypotension are mentioned).
   
   Thank you. We have added respiratory distress. We did not intend this to be an exhaustive list of the clinical features of CRS, so have not added additional symptoms and signs.

4. **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
   
   We have updated the guidelines summary to reflect the most recent NCCN guidance issued in December 2017.

5. On page 16, there is an error - ibrutinib is included in the CML active TKI list and imatinib is excluded.
   
   Thank you for identifying this error. We have corrected it in the revised report.

6. **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.
   
   We agree that the lack of randomized trials and the lack of observational studies using techniques like instrumental variables or propensity score analyses introduces considerable uncertainty when making any comparisons between interventions. This is an essential caveat that pertains to all of the findings in our report.

7. 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.
   
   Thank you.

8. 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.
   
   Thank you. This is an important concern that warrants close attention to real world data about the use of CAR-T therapies.

9. 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.
   
   Thank you for raising these issues. Any comparison with historical data raises concerns about cohort effects due to changes in clinical care over time.
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<td><strong>10.</strong></td>
<td><strong>SCHOLAR-01:</strong> 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 editorial 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.</td>
<td>Thank you. We did highlight one of the editorials that called into question using SCHOLAR-1 as a benchmark for outcomes in patients with R/R adult lymphoma. The propensity-score matched analysis comparing outcomes for patients in ZUMA-1 to those in SCHOLAR-1 is likely to be more accurate, but still suffers from the issues of historical controls that you highlighted in your previous comment. There is really no substitute for a well-done randomized trial.</td>
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<td><strong>11.</strong></td>
<td><strong>ZUMA-1</strong> 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.</td>
<td>We agree that the comparisons across trials are challenging. You are correct that some of the subcategories of neurotoxicity are listed. It may be most helpful to compare the overall and Grade 3/4 neurotoxicities. It is primarily the CRS grading that differs by company, but assessing AEs in a standard, prospective way in the same study would give the most accurate assessment of the relative frequency of the adverse events.</td>
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<tr>
<td><strong>12.</strong></td>
<td>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.</td>
<td>Appendix Tables C1-C12 have more detailed summaries of demographics in the different trials.</td>
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<td><strong>13.</strong></td>
<td>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.</td>
<td>We agree that this is an important issue facing the field. At this time, we have the inclusion criteria for the pivotal trials and the FDA indications to guide us. Future studies will likely examine moving CAR-T therapy earlier in treatment sequencing. This will likely be an important topic of discussion during the policy roundtable, which moves the discussion beyond the currently available data.</td>
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<td><strong>14.</strong></td>
<td>Suggest including some comparison to data of both efficacy and pharmacoeconomics for these CAR T-cell therapies compared to SCT.</td>
<td>This is particularly relevant for the issues that you raise in your prior comment. Because several of the trials required patients to specifically not be eligible for SCT, we did not think that SCT was the appropriate comparator for our current report. It may become relevant for updates in the future.</td>
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<td>15.</td>
<td>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.</td>
<td>See the response to #14 above. It will be important to look at this going forward, but the current study populations do not allow us to address the comparison with SCT.</td>
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<td>16.</td>
<td>There have been no projections for repeat CAR T-cell infusions provided.</td>
<td>It is our understanding that repeat CAR-T cell infusions will not be the standard of care.</td>
</tr>
<tr>
<td>17.</td>
<td>The number for transplants post CAR T-cells in DLBCL may be underestimated.</td>
<td>This certainly should be monitored going forward. Given the limited data currently, a registry of all patients treated with CAR-T therapy is certainly feasible and would be enlightening.</td>
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<tr>
<td>18.</td>
<td>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.</td>
<td>We do not intend this report to be used as a clinical guideline for care. You certainly highlight a good point that is relevant for management of CRS and significant neurotoxicity: there is a tension between treating with corticosteroids to limit toxicity and the concern that the steroids would impair CAR-T cell function and replication.</td>
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<td>19.</td>
<td><strong>Section 5. Comparative Value</strong>  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.</td>
<td>For chemotherapy in ALL, we state that 14.8% of patients will have a SCT. This was accounted for in costs and in utilities.</td>
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<td>20.</td>
<td>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.</td>
<td>Because of this uncertainty, we did not model long-term productivity gains.</td>
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<td>21.</td>
<td>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.</td>
<td>In order to achieve a high level of consistency, we are modeling what was done with the response and survival evidence we obtained and used.</td>
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<td>22.</td>
<td>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</td>
<td>For consistency, we are modeling what was done—not what might occur in the future. Therefore, we are modeling inpatient utilization.</td>
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<td><strong>23.</strong> 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).</td>
<td>For consistency, we are modeling what was done—not what might occur in the future. Therefore, we are modeling inpatient utilization.</td>
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<td><strong>24.</strong> 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.</td>
<td>We are not modeling the intent of CAR-T as a bridge to chemotherapy. We include the costs and disutilities for SCT following CAR-T to mimic what occurred based on the outcome data we are using. Table 4.4 of the revised report (5.4 in the draft) presents the SCT rates. Patients may become eligible for SCT if they get to a response status from CAR-T.</td>
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<td><strong>25.</strong> 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.</td>
<td>We engaged multiple stakeholders and experts related to the mark-up for CAR-T. Input we received varied, with a range of potential mark-up from 0% (no mark-up) to a mark-up similar to other oncology drugs (ASP+152%). To accommodate for this uncertainty and range, we varied different mark-ups within a one-way sensitivity analysis. The lower bound of the mark-up was 0%; therefore, results of the one-way sensitivity analysis can be reviewed to identify the incremental cost-effectiveness estimate assuming no mark-up.</td>
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<td><strong>26.</strong> 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.</td>
<td>We have added text to refer readers to the regimen table so they are aware the costs presented are for unit costs.</td>
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<td><strong>27.</strong> 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</td>
<td>Drug doses were based on the weight that was reported in the trials.</td>
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<td><strong>28.</strong></td>
<td>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 &gt; 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.</td>
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<td>We assumed the per-diem hospitalization stay would include the costs of all adverse events, except for those that extended the length of stay (CRS) or those that extended beyond discharge (B cell aplasia). Note that Table 4.7 (5.7 in the draft report) shows the weighted adverse event costs (only including CRS and B cell aplasia). Not all patients experienced CRS as it is does not occur in 100% of patients that received therapy.</td>
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<td><strong>29.</strong></td>
<td>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.</td>
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<td>The societal perspective was a scenario analysis and has been limitations. It was not performed as the base-case analysis. To avoid the potential to double count future productivity gains with the utility score, we only calculated costs associated with treatment. Again, we acknowledge that this is a limited societal perspective.</td>
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<td><strong>30.</strong></td>
<td>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?</td>
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<td>We are not modeling any long-term productivity gains or losses due to this uncertainty.</td>
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<td><strong>31.</strong></td>
<td>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.</td>
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<td>We are not modeling any long-term productivity gains or losses due to this uncertainty.</td>
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<td><strong>32.</strong></td>
<td>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 survival. 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.</td>
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<td>We engaged stakeholders, clinical experts, and product inserts to inform IVIG utilization and duration. We heard that those with hypogammaglobulinemia would receive IVIG. The duration was less certain, however literature supported 11.4 months. We varied the duration of IVIG from 0 months to a lifetime for those with hypogammaglobulinemia in one-way sensitivity analyses.</td>
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<td><strong>33.</strong></td>
<td>Costs associated with travel to centers for treatment, housing and caregiving were not mentioned.</td>
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<td>This is a limited societal perspective; however, we discuss transportation and</td>
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### hotel costs in the scenario analysis

**34.** There appears no accounting for the use of blood products or colony stimulating factors. The use of blood products and colony stimulating factors should be accounted for in the cost for the hospital stay.

**35.** 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 are using the information provided to us from the manufacturer related to healthcare utilization for administration, monitoring, and adverse event management. Uncertainty in these values is then accounted for in the sensitivity analyses.

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### Patients and Patient Advocacy Organizations

Nellie Wild, Executive Director, Aimed Alliance

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<td><strong>1.</strong> Acute lymphoblastic leukemia (ALL) is a type of childhood cancer that most often occurs in children ages one to eleven. Each year, approximately 3,000 children under the age of 20 receive an ALL diagnosis, making it an ultra-rare disease. While 98 percent of children with ALL go into remission within weeks after starting treatment and are cured (i.e., 10 years of remission), children with refractory or relapsed ALL have a prognosis of 5 percent long-term survival when treated with chemotherapy or stem cell transplantation. 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. Thank you for the summary.</td>
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<td><strong>2.</strong> 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. 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. 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. Thank you. As noted above, there is ample reason for caution given the potential for selection bias when comparing across trials in these two populations.</td>
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<td><strong>3.</strong> 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. We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more detail on the ICER Evidence Rating Matrix. They are also only one component of the value assessment. Specifically, many of the issues your raise are part of the Other Benefits and Contextual Considerations section, which are essential in assessing value.</td>
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Response to Comments – CAR-T Therapies for B-Cell Cancers
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)). Yet, only 3 to 5 percent of children with ALL are Ph+. 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.

4. 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 access for children and seniors who need them.

The FDA has approved these therapies, the NCCN has updated their guidelines to incorporate these therapies, and payers need to establish policies around coverage of the therapies. It is therefore critically-important to understand the value of CAR-T given the data currently available, even if the immaturity of the data contribute to significant uncertainty surrounding estimates for comparative effectiveness and value. We expect to update our analyses as more mature data become available.

For example, see comment #1 from the Hematology/Oncology Pharmacy Association

In addition, Novartis has presented cost-effectiveness models for tisagenlecleucel...
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.

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<th>Saira Sultan, Executive Director, The Haystack Project</th>
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<tr>
<td><strong>1.</strong> 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;</td>
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<td><strong>2.</strong> 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</td>
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<td><strong>3.</strong> ICER should proactively and exponentially increase its engagement with the patient and caregiver community throughout its process.</td>
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<td><strong>4.</strong> 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.</td>
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<td>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.</td>
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<td>5. 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.</td>
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<td>6. 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.</td>
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outcomes are rarely captured in clinical trials.

ICER publicly posts the timeline for each review when it is announced to help stakeholder organizations plan to participate in each public comment opportunity. While we appreciate that some organizations may find it challenging to meet these deadlines, we feel we have struck an appropriate balance between extending our comment periods and ensuring that our reports are released on as timely a basis as possible.

Paul Kleutghen

1. 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.

Thank you for your comments.

2. **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 FDA 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 letter 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.

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<td>US</td>
<td>50</td>
<td>2,435</td>
<td>7,170</td>
<td>7,791</td>
<td>9,535</td>
<td>9,746</td>
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</table>

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.” 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.

<table>
<thead>
<tr>
<th>3. Kaplan-Meier curves</th>
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<tr>
<td>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.</td>
</tr>
<tr>
<td>We did not believe blinatumomab was the most appropriate comparator for tisagenlecleucel due to the heterogeneity in patient characteristics (age, bone marrow blast level, previous treatment histories, etc.).</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Separate cost effectiveness findings presented at ASH from a different economic model produced results similar to our model, as compared to clofarabine monotherapy consistent assumptions (e.g., 20-year time horizon, etc.). The ASH model also included blinatumomab as a comparator and the incremental cost-effectiveness ratio presented was very close to the clofarabine monotherapy comparison. Therefore, we do not expect the results or conclusions to be sensitive to comparator selection.</td>
</tr>
<tr>
<td>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.</td>
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<table>
<thead>
<tr>
<th>4. Simulation concerns</th>
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<tbody>
<tr>
<td>I was pleased to see that 5,000 simulations were run by the ICER team. Still, I would like to raise several concerns.</td>
</tr>
<tr>
<td>Normal distributions were not used with cost. Gamma distributions, which are limited to only positive values, account for the rightward skew.</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

We did not believe blinatumomab was the most appropriate comparator for tisagenlecleucel due to the heterogeneity in patient characteristics (age, bone marrow blast level, previous treatment histories, etc.).
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 a 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.

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.

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 we have yet to see any substantive result from the three Novartis studies.

| Table D6 indicates patients that received the infusion. Table 3.4 (4.4 in the draft report) uses the entire cohort, so it includes patients that discontinued prior to infusion. That is why the observed values are lower. | The Kaplan-Meier curve for tisagenlecleucel was developed with pooled data provided by the manufacturer. It is a single curve that integrates all data with the N represented. |
though there seems to 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.

7. 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.

We had extensive conversations with stakeholders that ranged from 0% mark-up to equitable mark-ups for other oncology drugs with an ASP+152%. Note that, if interested, a no mark-up is included in our one-way sensitivity analysis.

As for the first bullet point, the standard error was 10% of the base-case. Because the base-case value varied (because of the different drug prices and the $100,000 cap), the range varied as well.

For mark-up percentages, refer to the mark-up assumptions that are different by population. There are different assumptions based on disease and setting.

We have now updated the lower bound of CRS to be the cost of tocilizumab plus the lower bound of ICU cost.

8. 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

The costs and outcomes presented in the results are weighted. Not every patient in the CAR-T pathway received the CAR-T infusion, or responded to treatment, or received a SCT, or experienced CRS, etc. However, we now add a table to the appendix (D13) that shows the costs for certain sub-categories of the cohort.
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.

9. **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.

10. **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 incremental lifetime discounted costs, which are weighted based on receipt of infusion, response to treatment, receiving a SCT or experiencing an adverse event, of tisagenlecleucel and axicabtagene ciloleucel relative to their respective comparators in their relevant target populations are approximately $329,000 and $462,000, respectively. Our potential budget impact analysis suggests that the entire eligible incident population for tisagenlecleucel could be treated without exceeding more than 12% of the ICER annual potential budget impact threshold, and 38% of the eligible incident population for axicabtagene ciloleucel can be treated without exceeding the ICER annual budget impact threshold.

While we appreciate that there is ongoing discussion relating to appropriate levels of manufacturer profit, taxpayer participation in clinical development, and other such concerns, ICER is singularly focused on determining whether current pricing (however it is derived) is in alignment with the clinical benefits to the patient, based on current evidence.
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.

David Mitchell, President, Patients for Affordable Drugs

1. 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

Thank you for your comments.
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.

2. **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.

3. **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

   We agree that more CAR-T therapies are likely to be approved by the FDA, and that currently-approved CAR-Ts are also likely to receive expanded indications. This was one of the major reasons we elected not to apply our modified framework for ultra-rare conditions to this review.

   The results presented in the current reviews apply only to the patient populations who are currently indicated for treatment per the FDA label. Should the label of either CAR-T expand, we would need to review evidence specific to that indication, as well as potential budget impact over relevant comparator treatments, before determining a new benchmark.

   This is also a reason why we include an analysis of potential budget impact on our reports – to assess whether a treatment would strain access and affordability at its current price, and to facilitate discussions
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.

4. **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

Thank you for raising these important points. While they are outside the realm of our framework for assessing value, they are important elements of the drug pricing discussion overall.
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.

<table>
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<th>5.</th>
<th><strong>THIS ANALYSIS SHOULD CONSIDER THE APPROPRIATE PRICE TO MAXIMIZE ACCESS AND AFFORDABILITY WHILE ENSURING A ROBUST R&amp;D PIPELINE AND REASONABLE PROFIT.</strong></th>
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<td></td>
<td>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.</td>
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**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 companie 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.

6. **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.

7. 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.

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

1. 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.

2. **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.

The FDA has approved these therapies, the NCCN has updated their guidelines to incorporate these therapies, and payers need to establish policies around coverage of the therapies. It is therefore critically-important to understand the value of CAR-T given the data currently available, even if the immaturity of the data contribute to significant uncertainty surrounding estimates for comparative effectiveness and value. We expect to update our analyses as more mature data become available.

For example, see comment #1 from the Hematology/Oncology Pharmacy
3. **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.

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<th>Association. Many other stakeholders encourage us to release our reports as close as possible to the date of FDA approval.</th>
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<td>In addition, Novartis has presented cost-effectiveness models for tisagenlecleucel at ASH and in other venues, suggesting that they acknowledge the importance of a value assessment at product launch. The value assessment makes a number of assumptions and extrapolations and will need to be refined as more data become available. We have tried to highlight these uncertainties throughout the report.</td>
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| ICER has recently announced that it will begin updating its reviews periodically. These updates will typically occur after the release of important new data that could be expected to impact the results of a review and/or the approval of new therapies in the same clinical area. Depending on the extent of these data, the review update may take the form of a brief “New Evidence Update,” as was done when new outcomes data for PCSK9 inhibitors were made available, or as an update to an entire report, as we are currently doing with our 2016 review of targeted therapies for plaque psoriasis. |

4. **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?

| We disagree with this characterization of our patient engagement process. For each review, we seek out input from the major disease-specific patient advocacy organizations and patients who are living with the condition that is the subject of our review. Our process also includes multiple opportunities for feedback from the broader patient and advocacy communities, including explicit review of early drafts of our report. In addition, we invite patients with the condition under review to participate in our public meetings through both oral comments and formal participation throughout the meeting as part of a policy roundtable. |

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<th>©Institute for Clinical and Economic Review, 2018</th>
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<td>Response to Comments – CAR-T Therapies for B-Cell Cancers</td>
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ICER has also recruited patients and patient advocates to serve on the voting panels of its core public programs. These voting panels are composed of patients, clinicians, and health policy researchers with broad expertise in evaluating evidence on clinical effectiveness and comparative value. We have purposefully recruited the panel membership for a diversity in experience and background to ensure the objectivity of the deliberations at the meeting.

5. **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.

   While there are certainly challenges inherent in assessing the value of precision therapies, we believe that ICER’s framework is flexible enough to adapt to them given that it is fundamentally based in four domains that are common to all medical therapies – clinical effectiveness, long-term value for money, and any other benefits or contextual considerations that are important to consider.

   Furthermore, the uptake and use of precision therapies is naturally tied to the availability of subgroup data on particular patient types; if these data are available in a standardized fashion, ICER will surely evaluate them.

6. **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.

   ICER’s approach to assessing potential budget impact is described in detail in each report, and we believe the reader can assess whether our assumptions are appropriate.

   As we have stated elsewhere, budget impact is of great interest to health care payers, particularly those with fixed budgets, as they need to manage costs within 1-2 year cycles. ICER’s approach looks at potential budget impact over five years to account for the cost offsets that may accrue from effective during a longer time period.

   Out-of-pocket costs may vary greatly across payers and plans, so while we agree
that they are of the utmost importance to patients, there would be no way for us to reliably estimate these. In addition, they are inextricably linked to the treatment prices themselves. In theory, lower treatment prices would lead to lower copayment, thus improving patient access and affordability. When lower prices, either through reduced list prices or negotiated rebates, do not result in lower patient costs, we have in the past noted concern and issued recommendations for savings to be shared with patients – see our 2017 final report on multiple sclerosis as one example.