NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy [ID1684]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy [ID1684]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the ACD from Kite, a Gilead Company**

3. **Consultee and commentator comments on the ACD** from:
   a. Anthony Nolan
   b. Blood Cancer UK
   c. Lymphoma Action
   d. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

4. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient/carer group - consultee	Lymphoma Action	We are concerned that this decision does not fully recognise the unmet need that this treatment could fill. There is an unmet need for patients who have not benefitted from available treatments. CAR T-cell therapy offers hope when other treatments have failed; it is potentially life-saving. The committee have noted that Axicabtagene ciloleucel is a life-extending treatment and that the clinical evidence suggests that Axicabtagene ciloleucel improves how long people live compared with standard care but it is uncertain by how much because the trial is not yet complete. However, Axicabtagene ciloleucel has the potential to provide this for patients who have relapsed after previous courses of treatment and is an important treatment that has the potential to improve outcomes for people who may have limited treatment options left to them.	Comment noted. The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness. The committee concluded that axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment should be recommended for use within the Cancer Drugs Fund.
2	Patient/carer group - consultee	Lymphoma Action	We are also concerned that decisions based off just cost effectiveness when there is uncertainty about changing costs of CAR T-therapies may result in life-saving therapies being missed out on.	Comment noted. The cost of delivering CAR T-cell therapy in the NHS has been further analysed after the first committee meeting, and has been accepted by the company, NHS England, and the committee. The FAD has been amended to reflect this - see FAD section 3.12
3	Professional group - consultee	NCRI-ACP-RCP-RCR	Axicel has been shown to be superior to SOC in 2nd DLBCL for patients with primary refractory disease or early relapse based on a well-designed large, multi-centre phase 3 randomised trial with all randomised patients analysed included in efficacy analysis. This is the best quality of evidence that can be provided in favour of this treatment and has established axicel as the new SOC for this clinical setting. It will be a dis-service to NHS patients if they are denied access to this therapy in 2nd line.	Comment noted. The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness. The committee concluded that axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment should be recommended for use within the Cancer Drugs Fund.
4	Professional group - consultee	NCRI-ACP-RCP-RCR	NICE decision not to recommend axicel in 2nd line DLBCL seems to be based primarily on ICER per QALY calculations. As is evident, these calculations vary widely based on several assumptions which may or may not be true and many a times are best estimates. Axicel retreatment for instance is not something that is either commissioned or used in UK clinical practice. This should not be included in the model.	Comment noted. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				Guide to the methods of technology appraisal section 5.1. The committee concluded that it was appropriate to include axicabtagene ciloleucel retreatment costs as there was no robust way of removing treatment benefit and it is important to align modelled costs and benefits. See FAD section 3.14.
5	Professional group - consultee	NCRI-ACP-RCP-RCR	We are concerned NHS patients will continue to receive intensive 2nd line chemotherapy which is destined to fail in more than 80% of patients. Clinically it is hard to justify subjecting patients to toxicity of intensive chemotherapy which is quite likely to fail when a better therapeutic alternative is available. The psychological impact of having to go through a treatment which is quite likely to fail has not been considered fully.	Comment noted. The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness. The committee concluded that axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment should be recommended for use within the Cancer Drugs Fund.
6	Professional group - consultee	NCRI-ACP-RCP-RCR	Zuma 7 PRO data shows quality of life scores are better for patients receiving axicel in 2nd line compared to those receiving intensive chemotherapy +/- transplant. Another important factor which may not have been fully captured in the decision-making process.	Comment noted. Patient reported outcomes of quality of life are included in the ICER calculation as part of the QALY (quality-adjusted life year).
7	Professional group - consultee	NCRI-ACP-RCP-RCR	Our experts believe that not having access to 2nd line axicel would not only disadvantage NHS patients but also mean, UK practice will lag behind the developed world in offering cutting edge novel therapies.	Comment noted. The innovative nature of the technology has been considered by the committee. See FAD section 3.19
8	Professional group - consultee	NCRI-ACP-RCP-RCR	Our experts believe it is important to note that Zuma 7 trial, though aimed at transplant eligible patients did not have an upper age limit. Several patients in the trial were >70 years of age. If available on the NHS, patients >70 years who are otherwise fit are likely to be offered axicel in 2nd line thereby reducing the age-related inequality relating to use of high dose chemotherapy and autologous stem cell transplant which is rarely offered to those >70 years of age.	Comment noted. The company proposed axicabtagene ciloleucel for a narrower population than its marketing authorisation. The committee considered the evidence that had been submitted. People for whom autologous stem cell transplant is not suitable but who could tolerate axicabtagene ciloleucel were not included in the submitted evidence. Age is a protected characteristic and was considered by the committee. See FAD section 3.20.
9	Patient/carer	Anthony	We are concerned that the significant benefit that this treatment could provide some patients has not been	Comment noted. The Committee

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	group - consultee	Nolan	adequately accounted for. Many patients who contacted Anthony Nolan for this appraisal who received axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma were very supportive of the availability of this treatment. Those who received axicabtagene ciloleucel after two or more systemic therapies were also highly supportive of the treatment option being made available sooner in the pathway. Patients described currently available comparator treatments as leaving them in 'excruciating pain' and 'so wiped out that I could hardly stand up'.	considered the patient perspectives alongside the evidence on clinical and cost effectiveness. The committee concluded that axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment should be recommended for use within the Cancer Drugs Fund.
10	Patient/carer group - consultee	Blood Cancer UK	There is an undeniably heavy burden that patients with relapsed / refractory diffuse large B-cell lymphoma face in both managing symptoms of disease combined with the toxicity of current standard of care. The negative recommendation means this chemo-resistant population will continue to face significant unmet need at the 2nd line (as standard of care fails in up to 70% of cases according to a consultant haematologist we spoke to) which Axi-cel has the potential to address. We are concerned the significance of this need is not being considered enough.	Comment noted. The Committee considered the patient perspectives alongside the evidence on clinical and cost effectiveness. The committee concluded that axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment should be recommended for use within the Cancer Drugs Fund.
11	Patient/carer group - consultee	Blood Cancer UK	We recognise and appreciate the committee's concerns around cost-effectiveness. However, we are equally concerned that an innovative, clinically effective and superior treatment such as Axi-cel, which represents a step-change in treatment, will not reach patients that will significantly benefit from access to it. We hope the issues can be addressed and an agreement can be reached with the company in a way that doesn't impede access to this potentially life-saving treatment for patients in the future.	Comment noted.
12	Patient/carer group - consultee	Blood Cancer UK	Whilst we recognise that the company positioned Axicabtagene ciloleucel in a narrower, transplant-eligible population, alternative options such as chemotherapy (for a seemingly chemoresistant population) and intensive stem cell transplantation isn't appropriate in all the population.	Comment noted. The company proposed axicabtagene ciloleucel for a narrower population than its marketing authorisation. The committee considered the evidence that had been submitted. People for whom autologous stem cell transplant is not suitable but who could tolerate axicabtagene ciloleucel were not included in the submitted evidence. Age is a protected characteristic and was considered by the committee. See FAD section 3.20.
13	Patient/carer group - consultee	Blood Cancer UK	We would also like to emphasise that Axicabtagene ciloleucel has been described by some clinicians as a treatment showing some of the "highest antitumour activity" they have seen their entire professional lives. There are quite simply no other treatments available at the 2nd line that rival Axicabtagene ciloleucel for its innovative	Comment noted. The innovative nature of the technology has been considered by the committee. See

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>potential to cure disease and that allow patients to regain their quality of life. This transformative impact should therefore be given further consideration.</td><td>FAD section 3.19</td></tr>
<tr><td>14</td><td>Company</td><td>Kite, a Gilead company</td><td>Following the information that has been shared from NHS England we have removed the costs included for the delivery of CAR-T from the model and replaced this with the £41.1k CAR-T delivery cost as communicated from NHS England.

Using the updated PAS for axicabtagene ciloleucel and implementing the committee preferred assumptions this provides an ICER of £45,165.

<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>SoC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td></tr>
<tr><td>Axi-cel</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£45,165</td></tr>
</table>

As the ICER when adopting the committee preferences falls below the £50k willingness-to-pay threshold, whilst we accept there may still be minor unresolved issues such as the discount PAS levels of other treatments, we believe that we are likely to be cost effective and ask that the need for a second committee meeting is reviewed.</td><td>Comment noted. Above a most plausible ICER of £20,000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs, whether there are strong reasons to indicate that the assessment of the change in HRQL has been inadequately captured, and the innovative nature of the technology. Above an ICER of £30,000 per QALY gained, the case for supporting the technology on these factors has to be increasingly strong (see section 6.3 of the Guide to the methods of technology appraisal). The committee noted the high level of uncertainty, see FAD section 3.6.

When end of life weighting is applied and uncertainty is considered, the maximum acceptable ICER was substantially less than £50,000 per QALY gained. See FAD section 3.17</td></tr>
<tr><td>15</td><td>Company</td><td>Kite, a Gilead company</td><td>Section 3.8 – Axicabtagene ciloleucel overall survival extrapolation

We are concerned that the summary of approach does not refer to the company’s clinical plausibility concerns of the log-logistic curves, and therefore that these were not factored into the committee conclusion. The company preferred model was the generalised gamma distribution because it had good statistical fit, was validated by clinical experts, and provided clinically plausible survival extrapolations compared with observed 5-year data from later-line use of CAR T-cell therapy.

In line with the NICE reference case, “the external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources”. Unfortunately, there was limited time in the appraisal committee meeting (ACM) to discuss and appraise this clinical plausibility, but in</td><td>Comment noted. The committee considered the clinical plausibility of the log-logistic and generalised gamma extrapolations of axicabtagene ciloleucel overall survival. The committee concluded that both the generalised gamma and log-logistic curves appeared plausible and believed that the log-logistic model was appropriate given the uncertainty. See FAD section 3.9..</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			essence the committee's preferred extrapolation infers patients treated with axicabtagene ciloleucel at third- or later-line who are alive at 2 years, have a better future prognosis than the second-line patients treated with axicabtagene ciloleucel at the same time point. This goes beyond what can be considered simply 'conservative' to a place that is clinically implausible. ZUMA-1 provides 5-year data for relapsed and refractory diffuse large B-cell lymphoma (R/R DLBCL) patients treated with axicabtagene ciloleucel after two or more systemic treatments (equivalent to third- or later-line use), with the majority of patients (64%) having received at least three prior treatments.[1] With appropriate caveats around naïve comparisons, which had been acknowledged and supported by the external assessment group (EAG), outcomes from ZUMA-1 provide the best available data source to validate the extrapolation of outcomes with earlier use of axicabtagene ciloleucel in the R/R DLBCL disease setting. In the observed 2-year data available from both trials we see an approximate 10% absolute improvement in 2-year overall survival (61% vs 50%) and in complete response rates (58% vs 65%) between patients treated with axicabtagene ciloleucel in ZUMA-7 compared with ZUMA-1.[2, 3] Clinical experts consulted considered such a magnitude of improved treatment effect with earlier use of axicabtagene ciloleucel to be reasonable over the longer-term, with consideration of the worsening prognosis across later treatment lines (due to increasing tumour burden, comorbidities, morbidity and mortality impacts of prior treatments and associated decreased 'window of opportunity' to access CAR T-cell treatment).[4] When applying a log-logistic curve model to extrapolate ZUMA-7 data, the resulting 5-year overall survival estimate is 46%; this represents a 3% absolute improvement compared with the observed 5-year overall survival rate of 43% in ZUMA-1.[3] In comparison, when applying a generalised gamma model to extrapolate ZUMA-7 data, the resulting 5-year overall survival estimate is 51%; this better represents the previously observed and expected approximate 10% absolute improvement, and therefore represents the most clinically plausible estimate based on the best available evidence. In contrast to the clinically implausible committee preferred extrapolation, the company preferred extrapolation is on the conservative side of being clinically plausible. For those patients alive at 2 years, our extrapolation in effect implies an equivalent mortality rate between those who received axicabtagene ciloleucel at third- or later-line and those who received it in second-line. In reality, the survival prospects of those receiving axicabtagene ciloleucel earlier would continue to be better than the cohort treated at third- or later-line.	
16	Company	Kite, a Gilead company	**Section 3.11 – CAR T-cell administration costs**	Comment noted. The cost of delivering CAR T-cell therapy in the NHS has been further analysed after

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Since the first committee meeting for this appraisal, an agreed administration cost of £41.1k for CAR T-cell therapy has been accepted for the parallel cancer drugs fund review of axicabtagene ciloleucel for treating DLBCL after 2 or more systematic therapies [ID3980] (administration costs cover the first 3 months of care, excluding the cost of bridging therapy, consolidation SCT and hypogammaglobulinemia management). We believe that NHS England have confirmed that £41.1k (with the costs for bridging chemotherapy drugs and its administration, SCT and IVIg in addition to this) would appropriately reflect the cost of delivery of treatment for this appraisal, we therefore provide an appendix to this response document with updated cost-effectiveness analyses using this administration cost and applying an updated patient access scheme (PAS) discount. Across the post-ACD company preferred base-case, committee-preferred base-case and the EAG preferred base-case, axicabtagene ciloleucel clearly demonstrates cost-effectiveness with ICERs falling below the accepted threshold for end-of-life treatments in all cases at £42,464, £45,165 and £46,940 per quality adjusted life year gained, respectively. Whilst we believe that the tariff issue is resolved at £41.1k when appropriate like for like changes have been made, we feel we need to reiterate our objection to the original position in the ACD. Following the first committee meeting for this appraisal, the Committee adopted a CAR-T administration cost of £60,000. We are confident the issue of the uncertainty of cost of treatment has now been resolved by NICE and NHS England as set out above, but as £60,000 is referred to in the published ACD would like to take the opportunity to reiterate that we remain deeply concerned about any use of this figure, given the lack of the clarity on the proposed tariff coverage, and apparent over-estimation of costs proposed by NHS England as previously communicated. Discussions prior to issue of the ACD appear to have given little consideration to the concerns shared by the company and the EAG who provided a detailed critique of the proposed tariff, emphasizing the need for further transparency and avoidance of double counting and proposing six alternative scenarios to cost the delivery of CAR T cell therapy. The lack of clarity on tariff coverage is further reflected in the committee preference to add the cost of an additional consultation for neurological adverse events to the NHS England tariff which has previously been stated to include “all costs of care from when a person is identified for CAR T-cell therapy to 100 days after infusion”. Discussion informing this preference is not captured in the appraisal consultation document, additionally highlighting the company concerns over a lack of transparent consideration of the costing approach proposed. In the absence of transparency from UK real-world evidence, Gilead have looked to resource and cost data associated with CAR T-cell administration from the broader evidence base. Focused literature searches identified six recently published studies that provide absolute or	the first committee meeting, and has been accepted by the company, NHS England, and the committee. The FAD has been amended to reflect this - see FAD section 3.12

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			comparative cost data for axicabtagene ciloleucel, alternative CAR T-cell therapy and/or autologous stem cell transplant (auto-SCT).[5-10] These studies are summarized in an appendix to this response document. Across all studies, the mean total hospitalization costs associated with inpatient CAR T-cell administration was £35,402 (converted value); costs specific to axicabtagene ciloleucel and costs specific to a DLBCL population were £33,641 and £30,783, respectively (converted values). In a large-scale process analysis study in Switzerland, total costs associated with CAR T-cell therapy administration were shown to be 29% lower than costs associated with auto-SCT administration including 29% lower staff costs, 69% lower concomitant medication and material costs and 9% lower surcharge costs.[5] A further large-scale healthcare database analyses of 852 patients treated with CAR T-cell therapy or stem-cell transplant (SCT) across 37 hospital systems in the US has been presented at the American Society of Hematology conference this month.[11] Data from this study reported a lower mean index non-pharmacy cost for CAR T-cell therapy than SCT with CAR T-cell therapy non-pharmacy costs being 20% lower than the auto-SCT non-pharmacy costs. This is broadly aligned with the company costings, where the auto-SCT costs equates to £37,736 and the CAR T administration costs equate to £28,674, a 24% difference. Among inpatient-treated patients, the mean length of stay for patients treated with CAR T-cell therapy was 18 days; this is aligned with data for axicabtagene ciloleucel from ZUMA-7 ([redacted] days) and was higher than the mean length of stay for patients treated with SCT (21 days for auto-SCT, 28 days for allogeneic SCT). Total intensive care unit (ICU) costs were also lower for CAR T-cell therapy; 16.4% of patients treated with CAR T-cell therapy (n=208) had an ICU stay with a mean length of stay of 7 days. Adjusting the original company model base case to align with these real-world ICU data showed minimal impact on the incremental cost effectiveness ratio (ICER), increasing marginally from £51,154 to £51,701. Of patients treated with auto-SCT (n=595), 28.1% had an ICU stay with a mean length of stay of 17 days. These data and data comparisons to the ZUMA-7 data and company modelling demonstrate that the company estimates are robust and aligned with available real-world data.	
17	Company	Kite, a Gilead company	**Section 3.13 – Retreatment costs** We are concerned that the inclusion of retreatment costs contradicts the NICE reference case which clearly states, *"exclude costs that are unrelated to the condition or technology of interest"*. As acknowledged in the ACD, retreatment with axicabtagene ciloleucel is not part of the marketing authorization and does not have a role in clinical practice, as clearly stated by clinical experts during the appraisal committee meeting. Gilead have completed [redacted]	Comment noted. The committee concluded that it was appropriate to include axicabtagene ciloleucel retreatment costs as there was no robust way of removing treatment benefit and it is important to align modelled costs and benefits. See FAD section 3.14.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			[redacted]. As such, the inclusion of retreatment costs does not therefore reflect a conservative approach but rather an unrealistic one. While we recognize the concerns of the committee that the exclusion of retreatment costs would create misalignment in modelled costs and benefits, we maintain that the benefit of retreatment is negligible. A small minority of people enrolled to ZUMA-7 received axicabtagene ciloleucel retreatment ([redacted]) and only one retreated patient had an ongoing response of [redacted] months at the time of primary analysis data cut-off (data on file). Considering this negligible benefit, the potential direction of bias resulting from inclusion of retreated patients in the benefits analyses is against axicabtagene ciloleucel and therefore considered a more conservative approach than an informed censoring removal of such patients from the analyses. We would therefore challenge the committees' conclusion that it is appropriate to include axicabtagene ciloleucel cost, when this creates an unrealistic scenario, contradictory of the NICE reference case, in the context of inconsequential benefit that if anything biases against axicabtagene ciloleucel.	

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kite, a Gilead company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

<table>
<tr><th>Comment number</th><th>Comments

Insert each comment in a new row.
Do not paste other tables into this table, because your comments could get lost – type directly into this table.</th></tr>
<tr><td>1</td><td>Following the information that has been shared from NHS England we have removed the costs included for the delivery of CAR-T from the model and replaced this with the £41.1k CAR-T delivery cost as communicated from NHS England.

Using the updated PAS for axicabtagene ciloleucel and implementing the committee preferred assumptions this provides an ICER of £45,165.

<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER incremental (£/QALY)</th></tr>
<tr><td>SoC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td></tr>
<tr><td>Axi-cel</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£45,165</td></tr>
</table>

As the ICER when adopting the committee preferences falls below the £50k willingness-to-pay threshold, whilst we accept there may still be minor unresolved issues such as the discount PAS levels of other treatments, we believe that we are likely to be cost effective and ask that the need for a second committee meeting is reviewed.</td></tr>
<tr><td>2</td><td>Section 3.8 – Axicabtagene ciloleucel overall survival extrapolation

We are concerned that the summary of approach does not refer to the company's clinical plausibility concerns of the log-logistic curves, and therefore that these were not factored into the committee conclusion. The company preferred model was the generalised gamma distribution because it had good statistical fit, was validated by clinical experts, and provided clinically plausible survival extrapolations compared with observed 5-year data from later-line use of CAR T-cell therapy.

In line with the NICE reference case, "the external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources". Unfortunately, there was limited time in the appraisal committee meeting (ACM) to discuss and appraise this clinical plausibility, but in essence the committee's preferred extrapolation infers patients treated with axicabtagene ciloleucel at third- or later-line who are alive at 2 years, have a better future prognosis than the second-line patients treated with axicabtagene ciloleucel at the same time point. This goes beyond what can be considered simply 'conservative' to a place that is clinically implausible.

ZUMA-1 provides 5-year data for relapsed and refractory diffuse large B-cell lymphoma (R/R DLBCL) patients treated with axicabtagene ciloleucel after two or more systemic treatments (equivalent to third- or later-line use), with the majority of patients (64%) having received at least three prior treatments.[1] With appropriate caveats around naïve comparisons, which had been acknowledged and supported by the external assessment group (EAG), outcomes from ZUMA-1 provide the best available data source to validate the extrapolation of outcomes with earlier use of axicabtagene ciloleucel in the R/R DLBCL disease setting.

In the observed 2-year data available from both trials we see an approximate 10% absolute improvement in 2-year overall survival (61% vs 50%) and in complete response rates (58% vs 65%) between patients treated with axicabtagene ciloleucel in ZUMA-7 compared with ZUMA-</td></tr>
</table>

	1.[2, 3] Clinical experts consulted considered such a magnitude of improved treatment effect with earlier use of axicabtagene ciloleucel to be reasonable over the longer-term, with consideration of the worsening prognosis across later treatment lines (due to increasing tumour burden, comorbidities, morbidity and mortality impacts of prior treatments and associated decreased 'window of opportunity' to access CAR T-cell treatment).[4] When applying a log-logistic curve model to extrapolate ZUMA-7 data, the resulting 5-year overall survival estimate is 46%; this represents a 3% absolute improvement compared with the observed 5-year overall survival rate of 43% in ZUMA-1.[3] In comparison, when applying a generalised gamma model to extrapolate ZUMA-7 data, the resulting 5-year overall survival estimate is 51%; this better represents the previously observed and expected approximate 10% absolute improvement, and therefore represents the most clinically plausible estimate based on the best available evidence. In contrast to the clinically implausible committee preferred extrapolation, the company preferred extrapolation is on the conservative side of being clinically plausible. For those patients alive at 2 years, our extrapolation in effect implies an equivalent mortality rate between those who received axicabtagene ciloleucel at third- or later-line and those who received it in second-line. In reality, the survival prospects of those receiving axicabtagene ciloleucel earlier would continue to be better than the cohort treated at third- or later-line.

3	**Section 3.11 – CAR T-cell administration costs** Since the first committee meeting for this appraisal, an agreed administration cost of £41.1k for CAR T-cell therapy has been accepted for the parallel cancer drugs fund review of axicabtagene ciloleucel for treating DLBCL after 2 or more systematic therapies [ID3980] (administration costs cover the first 3 months of care, excluding the cost of bridging therapy, consolidation SCT and hypogammaglobulinemia management). We believe that NHS England have confirmed that £41.1k (with the costs for bridging chemotherapy drugs and its administration, SCT and IVIg in addition to this) would appropriately reflect the cost of delivery of treatment for this appraisal, we therefore provide an appendix to this response document with updated cost-effectiveness analyses using this administration cost and applying an updated patient access scheme (PAS) discount. Across the post-ACD company preferred base-case, committee-preferred base-case and the EAG preferred base-case, axicabtagene ciloleucel clearly demonstrates cost-effectiveness with ICERs falling below the accepted threshold for end-of-life treatments in all cases at £42,464, £45,165 and £46,940 per quality adjusted life year gained, respectively. Whilst we believe that the tariff issue is resolved at £41.1k when appropriate like for like changes have been made, we feel we need to reiterate our objection to the original position in the ACD. Following the first committee meeting for this appraisal, the Committee adopted a CAR-T administration cost of £60,000. We are confident the issue of the uncertainty of cost of treatment has now been resolved by NICE and NHS England as set out above, but as £60,000 is referred to in the published ACD would like to take the opportunity to reiterate that we remain deeply concerned about any use of this figure, given the lack of the clarity on the proposed tariff coverage, and apparent over-estimation of costs proposed by NHS England as previously communicated. Discussions prior to issue of the ACD appear to have given little consideration to the concerns shared by the company and the EAG who provided a detailed critique of the proposed tariff, emphasizing the need for further transparency and avoidance of double counting and proposing six alternative scenarios to cost the delivery of CAR T cell therapy. The lack of clarity on tariff coverage is further reflected in the committee preference to add the cost of an additional consultation for neurological adverse events to the NHS England tariff which has previously been stated to include “all costs of care from when a person is identified for CAR T-cell therapy to 100 days after infusion”. Discussion informing this preference is not captured in the appraisal consultation document, additionally highlighting the company concerns over a lack of transparent consideration of the costing approach proposed. In the absence of transparency from UK real-world evidence, Gilead have looked to resource and cost data associated with CAR T-cell administration from the broader evidence base. Focused literature searches identified six recently published studies that provide absolute or comparative cost data for axicabtagene ciloleucel, alternative CAR T-cell therapy and/or autologous stem cell transplant (auto-SCT).[5-10] These studies are summarized in an appendix to this response document. Across all studies, the mean total hospitalization costs associated with inpatient CAR T-cell administration was £35,402 (converted value); costs specific to axicabtagene ciloleucel and costs specific to a DLBCL population were £33,641 and £30,783, respectively (converted values). In a large-scale process analysis study in Switzerland, total costs associated with CAR T-cell therapy administration were shown to be 29% lower than costs associated with auto-SCT administration including 29% lower staff costs, 69% lower concomitant medication and material costs and 9% lower surcharge costs.[5] A further large-scale healthcare database analyses of 852 patients treated with CAR T-cell therapy or stem-cell transplant (SCT) across 37 hospital systems in the US has been presented at the American Society of Hematology conference this month.[11] Data from this study reported a lower mean index non-pharmacy cost for CAR T-cell therapy than SCT with CAR T-cell therapy non-pharmacy costs being 20% lower than the auto-SCT non-pharmacy costs. This is broadly aligned with the company costings, where the auto-SCT costs equates to £37,736 and the CAR T administration costs equate to £28,674, a 24% difference. Among inpatient-treated patients, the mean length of stay for patients treated with CAR T-cell therapy

	was 18 days; this is aligned with data for axicabtagene ciloleucel from ZUMA-7 ([redacted] days) and was higher than the mean length of stay for patients treated with SCT (21 days for auto-SCT, 28 days for allogeneic SCT). Total intensive care unit (ICU) costs were also lower for CAR T-cell therapy; 16.4% of patients treated with CAR T-cell therapy (n=208) had an ICU stay with a mean length of stay of 7 days. Adjusting the original company model base case to align with these real-world ICU data showed minimal impact on the incremental cost effectiveness ratio (ICER), increasing marginally from £51,154 to £51,701. Of patients treated with auto-SCT (n=595), 28.1% had an ICU stay with a mean length of stay of 17 days. These data and data comparisons to the ZUMA-7 data and company modelling demonstrate that the company estimates are robust and aligned with available real-world data.
4	**Section 3.13 – Retreatment costs** We are concerned that the inclusion of retreatment costs contradicts the NICE reference case which clearly states, *"exclude costs that are unrelated to the condition or technology of interest"*. As acknowledged in the ACD, retreatment with axicabtagene ciloleucel is not part of the marketing authorization and does not have a role in clinical practice, as clearly stated by clinical experts during the appraisal committee meeting. Gilead have completed [redacted]. As such, the inclusion of retreatment costs does not therefore reflect a conservative approach but rather an unrealistic one. While we recognize the concerns of the committee that the exclusion of retreatment costs would create misalignment in modelled costs and benefits, we maintain that the benefit of retreatment is negligible. A small minority of people enrolled to ZUMA-7 received axicabtagene ciloleucel retreatment ([redacted]) and only one retreated patient had an ongoing response of [redacted] months at the time of primary analysis data cut-off (data on file). Considering this negligible benefit, the potential direction of bias resulting from inclusion of retreated patients in the benefits analyses is against axicabtagene ciloleucel and therefore considered a more conservative approach than an informed censoring removal of such patients from the analyses. We would therefore challenge the committees' conclusion that it is appropriate to include axicabtagene ciloleucel cost, when this creates an unrealistic scenario, contradictory of the NICE reference case, in the context of inconsequential benefit that if anything biases against axicabtagene ciloleucel.

References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *New England Journal of Medicine*. 2017; 377(26):2531-44.
2. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med*. 2021.
3. Jacobson CA, Locke FL, Ghobadi A, et al. Long-term (4- and 5-year) overall survival in ZUMA-1, the pivotal study of axicabtagene ciloleucel in patients with refractory large B-cell lymphoma. ASH Annual Meeting. Virtual & Atlanta, GA, USA. 10-14 December 2021.
4. Kite Pharma Inc. Yescarta 2L DLBCL_External Strategy Meeting Report. 28 January 2022. Data on file.
5. Ring A, Grob B, Aerts E, et al. Resource utilization for chimeric antigen receptor T cell therapy versus autologous hematopoietic cell transplantation in patients with B cell lymphoma. *Ann Hematol*. 2022; 101(8):1755-67.
6. Huguet M, Raimond V, Kaltenbach E, et al. How much does the hospital stay for infusion of anti-CD19 CAR-T cells cost to the French National Health Insurance? *Bull Cancer*. 2021; 108(12):1170-80.
7. Fowler NH, Dickinson M, Ghosh M, et al. Assessment of Healthcare Resource Utilization and Hospitalization Costs in Patients With Relapsed or Refractory Follicular Lymphoma Undergoing CAR-T Cell Therapy With Tisagenlecleucel: Results From the ELARA Study. *Transplant Cell Ther*. 2022.
8. Hoda D, Richards R, Faber EA, et al. Process, resource and success factors associated with chimeric antigen receptor T-cell therapy for multiple myeloma. *Future Oncol*. 2022; 18(19):2415-31.
9. Keating SJ, Gu T, Jun MP and McBride A. Health Care Resource Utilization and Total Costs of Care Among Patients with Diffuse Large B Cell Lymphoma Treated with Chimeric Antigen Receptor T Cell Therapy in the United States. *Transplant Cell Ther*. 2022; 28(7):404 e1- e6.
10. Maziarz RT, Yang H, Liu Q, et al. Real-world healthcare resource utilization and costs associated with tisagenlecleucel and axicabtagene ciloleucel among patients with diffuse large B-cell lymphoma: an analysis of hospital data in the United States. *Leuk Lymphoma*. 2022; 63(9):2052-62.
11. Cui C, Feng C, Rosenthal N, et al. Hospital Costs and Healthcare Resource Utilization (HRU) for Chimeric Antigen (CAR) T-Cell Therapy and Stem Cell Transplant (SCT) in Patients with Large B-Cell Lymphoma (LBCL) in the United States (US). *Blood*. 2022; 140(Supplement 1):2161-2.

Appendix to company ACD consultation response

Updated base-case results

Base-case incremental cost-effectiveness analysis results

The discounted company base case results for axi-cel versus SOC are shown in Table 1. This analysis uses the post-ACD company preferred settings as below:

- Generalised gamma mixture cure model for axi-cel overall survival (OS)
- No retreatment costs associated with axi-cel
- Auto-SCT costs from NG52
- Post-event treatment distributions from ZUMA-7 (aligned with EAG redistribution)
- Post-event utility values from ZUMA-1

In addition, CAR T administration costs have been updated to £41,101 (with b-cell aplasia adverse event costs and bridging chemotherapy drug and administration costs included in addition to the CAR T administration costs) and an updated PAS discount of [redacted] is applied.

Axi-cel is associated with [redacted] incremental life years, [redacted] incremental QALYs, and incremental costs of [redacted] per patient, compared with SOC. The incremental cost-effectiveness ratio (ICER) is £42,464 per QALY gained.

Table 1: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,464

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care.

Sensitivity analyses

Scenario analysis

Updated scenario analyses are presented below in **Table 2**. This includes additional scenarios with CAR T delivery costs of £48,313 (including all costs for the delivery of CAR T) instead of £41,101 (excluding costs for bridging therapy, consolidation SCT and hypogammaglobulinemia management), a scenario assuming committee preferred assumptions and CAR T delivery costs of £41,101, and a scenario with EAG preferred assumptions and CAR T delivery costs of £41,101.

Table 2: Scenario analyses results

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
Base case	-	[redacted]	[redacted]	**£42,464**	**-**
CAR T delivery costs = £48,313 (including b-cell aplasia AEs)	CAR T delivery costs = £41,101 (excluding b-cell aplasia AEs)	[redacted]	[redacted]	£43,879	3.3%
Committee preferred assumptions: • Log-logistic MCM for axi-cel OS • Retreatment costs included • Auto-SCT costs according to NG52 • Post-event treatment distributions from ZUMA-7 • Post-event utility values from ZUMA-1 • CAR T delivery costs = £41,101	• Generalised gamma MCM for axi-cel OS • Retreatment costs excluded • Auto-SCT costs according to NG52 • Post-event treatment distributions from ZUMA-7 • Post-event utility values from ZUMA-1 • CAR T delivery costs = £41,101	[redacted]	[redacted]	£45,165	6.4%
EAG preferred assumptions • Log-logistic MCM for axi-cel OS • Retreatment costs included	• Generalised gamma MCM for axi-cel OS • Retreatment costs excluded • Auto-SCT costs according to NG52	[redacted]	[redacted]	£46,940	10.5%

• Auto-SCT costs according to SA26A (NHS reference costs) • Post-event treatment distributions from ZUMA-7 • Post-event utility values from ZUMA-1 • CAR T delivery costs = £41,101	• Post-event treatment distributions from ZUMA-7 • Post-event utility values from ZUMA-1 • CAR T delivery costs = £41,101				
Time horizon = 10 years	50 years	[redacted]	[redacted]	£90,065	112.1%
Time horizon = 20 years		[redacted]	[redacted]	£53,938	27.0%
Discount rates = 1.5%	3.5%	[redacted]	[redacted]	£33,362	-21.4%
Axi-cel OS = Weibull (MCM)	Generalised gamma (MCM)	[redacted]	[redacted]	£42,389	-0.2%
Axi-cel OS = Log-logistic (MCM)		[redacted]	[redacted]	£43,049	1.4%
Axi-cel EFS = Generalised gamma (MCM)	Log-logistic (MCM)	[redacted]	[redacted]	£42,214	-0.6%
SOC EFS = Weibull	Exponential (MCM)	[redacted]	[redacted]	£42,477	0.0%
SOC OS convergence with EFS at 5 years applied	No convergence applied	[redacted]	[redacted]	£40,953	-3.6%

No AE disutilities applied and on-treatment specific utilities applied	AE disutilities included and no on-treatment specific utility applied	[redacted]	[redacted]	£42,446	0.0%
Cure time point = 2 years	5 years	[redacted]	[redacted]	£41,146	-3.1%
Cure time point = 7 years		[redacted]	[redacted]	£42,979	1.2%
ITT analysis	Crossover adjusted	[redacted]	[redacted]	£20,529	-51.7%

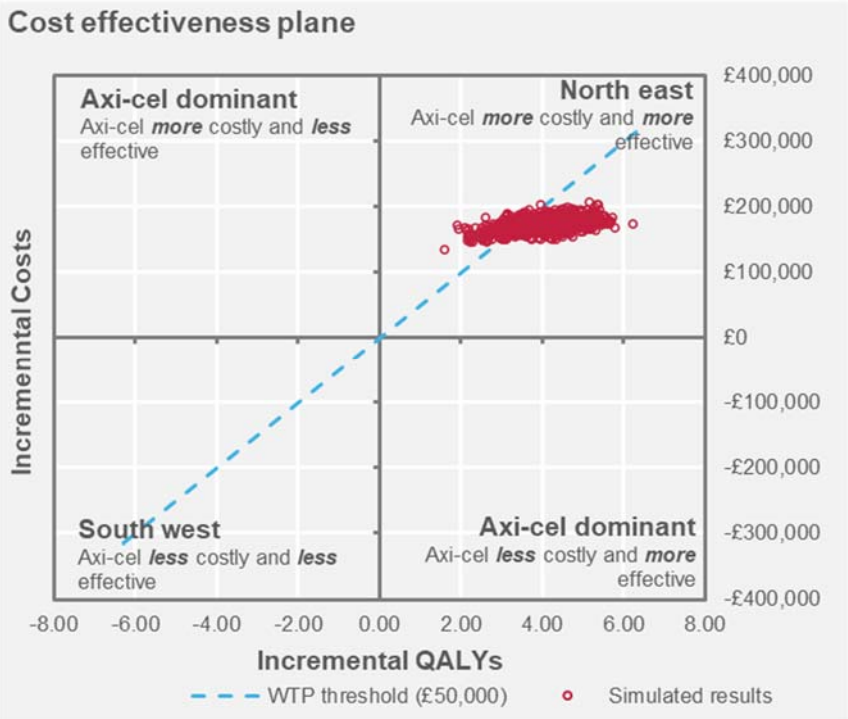
Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality adjusted life year.

A scenario has been included investigating the ITT population with CAR T delivery costs of £41,101 and with the updated PAS. Whilst we do not believe this is a scenario of interest for the committee, we believe that we have demonstrated cost-effectiveness in this scenario and have displayed it for completeness.

Probabilistic sensitivity analysis

The updated probabilistic sensitivity analysis (PSA) is presented below. One thousand simulations were run, with the results presented as the probability of being cost-effective at a willingness-to-pay (WTP) threshold of £50,000 per QALY, to reflect the end-of-life criteria. The PSA cost-effectiveness plane is presented in Figure 1. This shows that all of the iterations fell in the north-east quadrant.

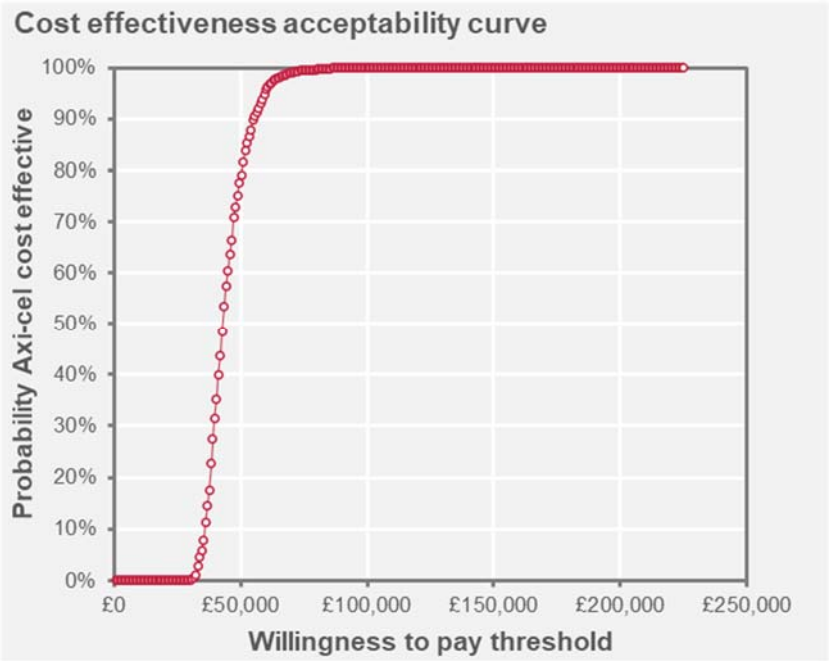
Figure 1: PSA scatter plot at £50,000 threshold



Key: QALYs, quality-adjusted life years, WTP, willingness-to-pay.

The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], giving a probabilistic ICER of £43,103. The cost-effectiveness acceptability curve is presented in Figure 2. This shows that at a willingness-to-pay threshold of £50,000, the probability of axi-cel being more cost-effective compared to SOC is [redacted]

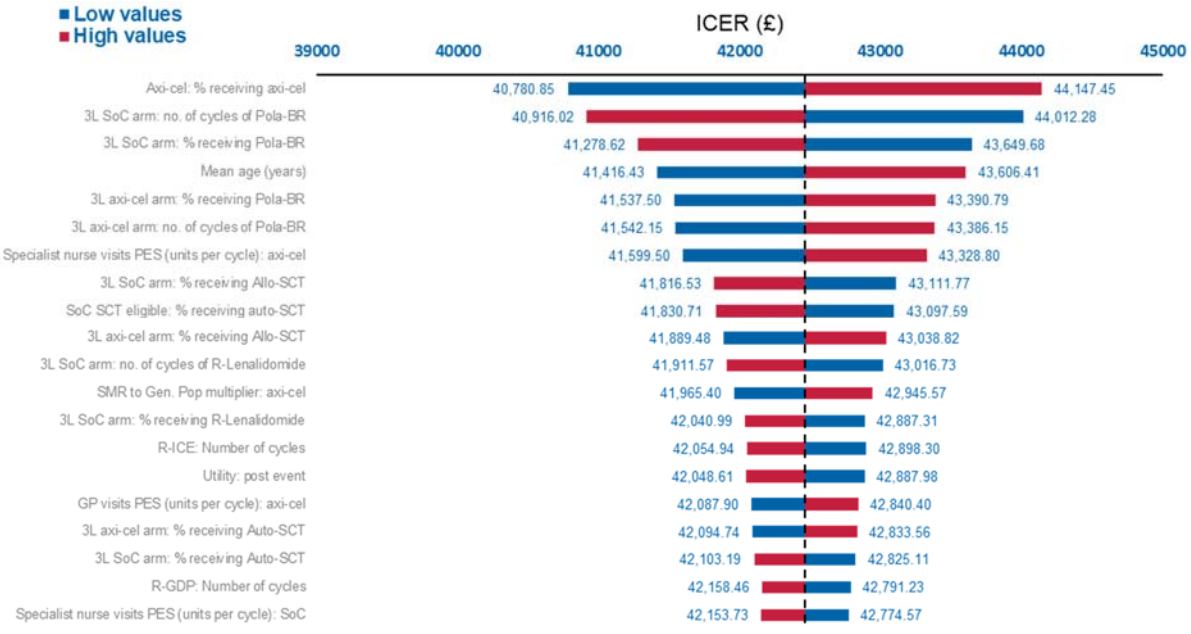
Figure 2: Cost-effectiveness acceptability curve



Deterministic sensitivity analysis

The updated one-way sensitivity analysis is present below. The top 20 influential parameters on the incremental cost-effectiveness ration (ICER) are presented as a tornado diagram in Figure 3. As shown in the tornado diagram, the three most influential parameters on the model results were the percentage of patients receiving axi-cel, the number of cycles of Pola-BR received in the 3L SOC arm and the proportion of people receiving Pola-BR in 3L SOC arm.

Figure 3: One-way sensitivity analysis, Tornado diagram



NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Anthony Nolan
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the significant benefit that this treatment could provide some patients has not been adequately accounted for. Many patients who contacted Anthony Nolan for this appraisal who received axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma were very supportive of the availability of this treatment. Those who received axicabtagene ciloleucel after two or more systemic therapies were also highly supportive of the treatment option being made available sooner in the pathway. Patients described currently available comparator treatments as leaving them in 'excruciating pain' and 'so wiped out that I could hardly stand up'.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Blood Cancer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Blood Cancer UK are disappointed and concerned by the negative recommendation for the use of Axicabtagene ciloleucel at the 2nd line. We reiterate the following key messages from our previous submission and would ask that these be reconsidered sufficiently before the final decision is reached: • Current treatment options do not offer a cure or produce durable remissions for all patients with diffuse large B-cell lymphoma. This demonstrates a persistent and significant unmet need for effective therapies earlier in the treatment course. Currently, patients with relapsed or refractory diffuse large B-cell lymphoma frequently endure constant fatigue, fear of relapse and anxiety about treatment side effects. • The most important aspects to patients with regards to treatments are its curative potential and ability to improve quality of life. Both have been expressed as being met by Axicabtagene ciloleucel by every patient we spoke to about this treatment. Axicabtagene ciloleucel's ability to meet patients' needs for new treatments should not be taken lightly. • Axicabtagene ciloleucel spares appropriate patients from undergoing futile treatments and associated side effects and gives them the opportunity to return to relative normality quicker which should not be overlooked. • Both the clinical and patient community have expressed that Axicabtagene ciloleucel at the 2nd line would mean a great opportunity for earlier use of a potentially curative treatment. It can spare chemotherapy toxicity and healthcare costs as successive futile treatments and follow ups can be avoided. • Many patients we spoke to describe the disadvantages, side effects or inconveniences caused by receiving Axicabtagene ciloleucel are far outweighed by the benefits it provides. This should be considered further.
2	There is an undeniably heavy burden that patients with relapsed / refractory diffuse large B-cell lymphoma face in both managing symptoms of disease combined with the toxicity of current standard of care. The negative recommendation means this chemo-resistant population will continue to face significant unmet need at the 2nd line (as standard of care fails in up to 70% of cases according to a consultant haematologist we spoke to) which Axi-cel has the potential to address. We are concerned the significance of this need is not being considered enough.
3	We recognise and appreciate the committee's concerns around cost-effectiveness. However, we are equally concerned that an innovative, clinically effective and superior treatment such as Axi-cel, which represents a step-change in treatment, will not reach patients that will significantly benefit from access to it. We hope the issues can be addressed and an agreement can be reached with the company in a way that doesn't impede access to this potentially life-saving treatment for patients in the future.
4	Whilst we recognise that the company positioned Axicabtagene ciloleucel in a narrower, transplant-eligible population, alternative options such as chemotherapy (for a seemingly

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	chemoresistant population) and intensive stem cell transplantation isn't appropriate in all the population.
5	We would also like to emphasise that Axicabtagene ciloleucel has been described by some clinicians as a treatment showing some of the "highest antitumour activity" they have seen their entire professional lives. There are quite simply no other treatments available at the 2nd line that rival Axicabtagene ciloleucel for its innovative potential to cure disease and that allow patients to regain their quality of life. This transformative impact should therefore be given further consideration.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that this decision does not fully recognise the unmet need that this treatment could fill. There is an unmet need for patients who have not benefitted from available treatments. CAR T-cell therapy offers hope when other treatments have failed; it is potentially life-saving. The committee have noted that Axicabtagene ciloleucel is a life-extending treatment and that the clinical evidence suggests that Axicabtagene ciloleucel improves how long people live compared with standard care but it is uncertain by how much because the trial is not yet complete. However, Axicabtagene ciloleucel has the potential to provide this for patients who have relapsed after previous courses of treatment and is an important treatment that has the potential to improve outcomes for people who may have limited treatment options left to them.
2	We are also concerned that decisions based off just cost effectiveness when there is uncertainty about changing costs of CAR T-therapies may result in life-saving therapies being missed out on.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or

Please return to: **NICE DOCS**

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
1	Axicel has been shown to be superior to SOC in 2nd DLBCL for patients with primary refractory disease or early relapse based on a well-designed large, multi-centre phase 3 randomised trial with all randomised patients analysed included in efficacy analysis. This is the best quality of evidence that can be provided in favour of this treatment and has established axicel as the new SOC for this clinical setting. It will be a dis-service to NHS patients if they are denied access to this therapy in 2nd line.
2	NICE decision not to recommend axicel in 2nd line DLBCL seems to be based primarily on ICER per QALY calculations. As is evident, these calculations vary widely based on several assumptions which may or may not be true and many a times are best estimates. Axicel retreatment for instance is not something that is either commissioned or used in UK clinical practice. This should not be included in the model.
3	We are concerned NHS patients will continue to receive intensive 2nd line chemotherapy which is destined to fail in more than 80% of patients. Clinically it is hard to justify subjecting patients to toxicity of intensive chemotherapy which is quite likely to fail when a better therapeutic alternative is available. The psychological impact of having to go through a treatment which is quite likely to fail has not been considered fully.
4	Zuma 7 PRO data shows quality of life scores are better for patients receiving axicel in 2nd line compared to those receiving intensive chemotherapy +/- transplant. Another important factor which may not have been fully captured in the decision-making process.
5	Our experts believe that not having access to 2nd line axicel would not only disadvantage NHS patients but also mean, UK practice will lag behind the developed world in offering cutting edge novel therapies.
6	Our experts believe it is important to note that Zuma 7 trial, though aimed at transplant eligible patients did not have an upper age limit. Several patients in the trial were >70 years of age. If available on the NHS, patients >70 years who are otherwise fit are likely to be offered axicel in 2nd line thereby reducing the age-related inequality relating to use of high dose chemotherapy and autologous stem cell transplant which is rarely offered to those >70 years of age.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 14 December 2022. Please submit via NICE Docs.

the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

CONFIDENTIAL

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

ERG critique of the company's response to the Appraisal Consultation Document (ACD)

Produced by Aberdeen HTA Group

Authors Dwayne Boyers

Health Economics Research Unit, University of Aberdeen, UK

***C*orrespondence to** Dwayne Boyers (Senior Research Fellow)
University of Aberdeen, Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: d.boyers@abdn.ac.uk

Date completed: **09 January 2023**

Contains: **CIC/AIC**

Version: **1.0**

Overview

This report provides the ERG's brief commentary and critique of the company's (Kite, a Gilead company) submitted response to the appraisal consultation document (ACD) and in advance of the second AC meeting for this appraisal. The commentary/critique provided below should be read in conjunction with the company's submitted response to the ACD. A confidential appendix to this report describes a full set of results presented in this document and the company ACD response, applying confidential price discounts for subsequent treatments used in the economic model.

Updated analyses post ACD

The company provided a revised economic model and updated set of base case analyses in response to the appraisal consultation document. All analyses use the company model that was previously updated at technical engagement to include "post-FDA" analyses where overall survival (OS) curves for the comparator (standard care) arm of the model to account for [redacted] participants, originally thought lost to follow up in the ZUMA-7 study, who were subsequently identified as having died during the study follow up period.

The following describes three remaining areas of uncertainty / disagreement between the company and ERG.

1. Axi-cel overall survival extrapolation

The company and ERG remain in disagreement with regards to the most appropriate base case axi-cel overall survival mixture cure model. The company prefers the generalised gamma, whereas the ERG prefers the log-logistic model.

The ERG maintains the position that the most appropriate MCM for axi-cel OS is uncertain, but that both the generalised gamma and log-logistic MCMs may be clinically plausible. The ERG acknowledges that the company preferred generalised gamma MCM is slightly more optimistic than the ERG preferred log logistic MCM. Both have similar statistical fits (log-logistic slightly better) and generate 5- year OS estimates above the ZUMA-1 3rd line plus study, demonstrating clinical plausibility. As noted in previous documentation, on balance, the ERG prefers the use of the more conservative estimate for axi-cel given the substantial uncertainty regarding longer term OS outcomes. Further follow-up of the trial cohort is required to generate more robust estimates of long-term OS.

2. CAR-T delivery costs

The CAR-T delivery costs in the model were updated to £41,101, excluding the costs of bridging chemotherapy and immunoglobulins for b-cell aplasia.

The revised cost is consistent with a scenario analysis cost (scenario analysis 6) provided by the ERG in our CAR-T tariff critique document, dated October 21st, 2022, for this assessment

(See Table 3, analysis 6 and explanation of the calculation approach on pages 7-9 of that document).

Briefly, the scenario analysis updates the calculation approach used in the company model as follows:

1) *Calculation of cost per day for a lymphoma patient corrected to incorporate average length of stay in source HRG for lymphoma (i.e. weighted average: HRG code: SA31 (A-F)).*
2) *Assuming a nurse: patient ratio in the base lymphoma tariff of 1:6; and CAR-T of 1:2, then staff costs were uplifted by a factor of 3. Assuming all other resources increase by a similar factor, the cost per bed day calculated in a above was multiplied by 3 to capture the likely increased resource use required to deliver CAR-T treatment.*
3) *Hotel costs were added based on the assumption that the NHS pays the costs of local accommodation from the point of discharge ([redacted] days) up to day 28 following infusion. It was assumed that 50% of patients do not live locally and require accommodation at a unit cost of £150 per night to include accommodation and subsistence.*

The ERG would like to re-iterate that the true costs of CAR-T delivery from a UK NHS perspective are unknown and further micro-costing work in a UK setting would be required to reduce uncertainty. The company has attempted to source alternative costing data from the literature, identifying studies conducted in Switzerland and the USA. The ERG acknowledges that these studies represent the only real-world data available. However, healthcare systems in the USA and Switzerland may have substantial differences to those in the UK. The way in which care is organized may mean that resource use estimates are not transferrable. Furthermore, the ERG is concerned that simple currency conversions may not be appropriate for decision making as unit costs per resource use may be different in different countries.

The ERG shares the company's concerns regarding the CAR-T tariffs provided at different stages of the assessment. The original and revised tariffs may not fully account for economies of scale that could be achieved once a CAR-T service is up and running. It is therefore feasible that the true longer-term cost may be lower than that suggested by the current tariffs. Based on the concerns with both the costing literature identified by the

company, and the UK CAR-T tariff, the ERG considers the company applied CAR-T administration cost of £41,101 (excluding bridging chemotherapy and b-cell aplasia treatment) to be appropriate given the information currently available.

3. Axi-cel re-treatment costs

The company prefer to exclude axi-cel re-treatment costs, on the grounds that re-treatment would not be considered in UK clinical practice.

The ERG agrees that re-treatment with axi-cel would be unlikely in UK clinical practice, and this has been confirmed by the ERG's clinical advisor. However, this does not negate the ERG's main concern with the company's approach. [redacted] patients ([redacted]) in the axi-cel arm of ZUMA-7 received re-treatment with axi-cel. Receiving a second axi-cel treatment may have positively influenced patient outcomes. The ERG therefore considers any analysis which removes the costs of re-treatment but not the benefits to be biased. Given the complexity of the analyses, including the need to conduct cross-over analyses, the ERG considers the most appropriate way in which to create a balance between costs and benefits is to retain the axi-cel re-treatment costs in the model. The ERG maintains our position with regards to this issue.

Intention to treat analyses

The company has provided an additional scenario analysis exploring the impact on the ICER of an intention to treat (ITT) OS analysis, where mixture cure models are fitted to the standard of care (SOC) arm for the ZUMA-7 study, without the need for cross-over analysis. As noted in previous ERG documentation, the decision around whether to use an ITT analysis is dependent on the decision reached by the NICE committee on whether or not to accept axi-cel as a 3rd line plus treatment for DLBCL. Should the committee choose to recommend axi-cel in the, shortly to be published, FAD for the CDF review of axi-cel as a 3rd line plus DLBCL treatment, an ITT analysis of axi-cel 2nd line would, in the ERG's opinion, be the most appropriate analysis. In response to the ACD, the company has provided a scenario analysis exploring the impact of an ITT analysis on the company preferred ICER.

The company preferred ITT analysis uses a generalised gamma MCM (as discussed in appendix Q of the original CS) and applies ZUMA-7 post-event treatment distribution [redacted] of

post-event patients receive CAR-T therapies, including (axi-cel: [redacted]; Breyanzi: [redacted]; Kymriah:[redacted]).

Should the committee wish to consider the ITT analysis in their decision making, it may be useful to re-appraise axi-cel against the end-of-life criteria. Using the company preferred ITT analysis (generalised MCM model for SOC OS), the economic model predicts SOC life year gains of mean: [redacted], median OS: [redacted] and 2-year OS of [redacted]. Incremental life year gains are [redacted]. The ERG notes that the mean LYGs are well above the 2 years typically considered for remaining life expectancy for the SOC group, though the median OS is close to the 2-year threshold. The incremental life year gains obtained from the modelled output suggest that axi-cel would meet the "life-extending" criteria required for end-of-life consideration.

The ERG has not been able to provide a complete critique and clinical validation of all parameters used in the company's ITT analysis as this was deemed out of the scope of the appraisal by NICE. However, we would like to point out that, following a brief review of the company evidence, there are several areas of uncertainty with regards to the ITT analysis that the committee should be aware of. The first is whether the chosen generalised gamma OS extrapolation is the most appropriate for decision making. This would benefit from further clinical expert opinion and validation. The ERG has provided 2 alternative MCM scenario analyses (LN and LL) that would appear to demonstrate good statistical fit to the KM data and provide reasonably plausible long-term OS predictions, with SOC OS cure fractions lower than the company preferred generalised gamma axi-cel OS cure fraction. The ERG acknowledges however, that if the committee maintains its preference for the log-logistic MCM for axi-cel OS, then only the company preferred generalised gamma SOC OS MCM would generate a cure-fraction below that of the log-logistic used for axi-cel. The most clinically plausible SOC MCM should therefore be considered together with the chosen MCM for axi-cel OS.

The second area of uncertainty relates to the most appropriate choice of post-event treatment distribution. Whilst the ERG generally prefers the use of a post-event treatment distribution that aligns with ZUMA-7, it is worth noting that the confidential discount available for axi-cel, leads to a substantially lower treatment acquisition cost for axi-cel compared to other CAR-T therapies (Breyanzi and Kymriah). The ERG explores the impact on the ICER of

assuming that axi-cel is the only available CAR-T treatment, and that the available discount is the same as for axi-cel 2nd line treatment. For this scenario to remain non-biased, the committee would need to be satisfied that all CAR-T therapies have similar effectiveness.

The impact of these scenarios, and combinations of scenarios on the ICER is presented in Table 1 below for the committee's information.

Table 1: Additional ERG scenario analyses applied to the company's ITT analysis (assuming axi-cel is accepted as 3rd line plus treatment).

Sc.	Scenario	Incremental Costs	Incremental QALYs	ICER
1	Company ITT analysis (Apply generalised gamma SOC OS curve and include costs of CAR-T treatments ([redacted]) post-event (axi-cel: [redacted]; Breyanzi: [redacted]; Kymriah:[redacted])	[redacted]	[redacted]	£20,529
2	CAR-T delivery costs = £48,313 (including b-cell aplasia adverse events)	[redacted]	[redacted]	£21,857
3	Log-Normal OS MCM for SOC	[redacted]	[redacted]	£25,660
4	Log-Logistic OS MCM for SOC	[redacted]	[redacted]	£25,671
5	Include costs of CAR-T treatments post event (axi-cel: [redacted])	[redacted]	[redacted]	£32,700
6	3 + 5	[redacted]	[redacted]	£43,254
7	Apply committee preferred assumptions from ACD to ITT analysis (Log-logistic MCM for axi-cel OS + include axi-cel re-treatment costs)	[redacted]	[redacted]	£37,471
8	5 + 7	[redacted]	[redacted]	£59,248

Summary.

In summary, the ERG and company preferred base case analyses are now aligned with regards to the most appropriate CAR-T delivery costs, with only two areas of discrepancy remaining (inclusion of axi-cel re-treatment costs and the most appropriate axi-cel OS

MCM). The ERG notes that the company has increased the patient access scheme discount for axi-cel from [redacted] to [redacted] and that this reduces the ICER substantially. Should the committee wish to consider an ITT analysis, then it would be important to consider the substantial uncertainty that remains regarding the most appropriate extrapolation curve and post-event treatment distribution for use in the model.