NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

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 Appraisal Consultation Document from Kite, a Gilead Company**

There were no comments on the Appraisal Consultation Document received through the NICE website

3. **Evidence Review Group critique of company comments on the Appraisal Consultation Document**

4. **NHS England CAR-T delivery costs summary**

5. **Gilead response to NHSE CAR-T delivery costs documents**

6. **Evidence Review Group additional analysis post-committee meeting, including NHSE CAR-T delivery costs**

7. **Evidence Review Group post-committee analysis including updated NHSE CAR-T delivery costs**

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 low-grade non-Hodgkin lymphoma [ID1685]

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	Consultee	Kite Pharma, a Gilead company	**Section 3.6 – Survival data are immature and uncertain** We agree with the Committee that survival data are immature and thus uncertain at this time, hence why we believe axicabtagene ciloleucel (axi-cel) is a suitable candidate for the cancer drugs fund (CDF) that is intended to facilitate access to promising treatments such as axi-cel while further evidence is collected. Every effort was taken to use data that were available at the time of submission to inform and validate the survival modelling, including longer-term data available for axi-cel and other chimeric antigen receptor (CAR)-T cell therapies in other indications. More recently, five-year outcomes for patients with relapsed or refractory follicular lymphoma (FL) who were treated with tisagenlecleucel were published in a letter to the editor of the New England Journal of Medicine.[1] Of the patients with FL, 43% of patients were progression-free at 5 years, suggesting that the [redacted] progression-free at 5 years estimated from the axi-cel FL survival modelling may be a conservative estimate. Additional data are also now available from a 36-month data cut of ZUMA-5, which further support the modelling extrapolations (see Appendix). The overall survival Kaplan-Meier curve for the full analysis set (FAS) of patients with centrally confirmed FL who had received three or more lines of prior therapy (n = 75) shows clear signs of a plateau at around [redacted] survival occurring after approximately [redacted] (confidential data on file). As well as supporting the long-term survival assumptions, this also aligns with the [redacted] overall survival at 5 years estimated from the axi-cel FL survival modelling. Overall survival analyses for the inferential analysis set (IAS) show a similar plateau. Median overall survival is still [redacted] but median progression-free survival is estimated at [redacted] (confidential data on file). As a reminder of	Thank you for your comment. The committee concluded that the results of the updated data cut and post-hoc analysis shows that that axicabtagene ciloleucel reduces the risk of disease progression in people with relapsed or refractory follicular lymphoma, but there is uncertainty about its long-term treatment effect. Please see section 3.6 of the FAD.

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			expected survival with current care, SCHOLAR-5 estimated median overall survival of [redacted] and median progression-free survival of [redacted].[2] Post-hoc sensitivity analyses have also been conducted to explore the potential impact of allogeneic stem cell transplant (allo-SCT) after treatment with Yescarta which the committee felt may impact the overall mean survival for ZUMA-5. Censoring of patients at the time of allo-SCT results in a 24-month overall-survival rate estimate of [redacted] compared with a 24-month overall-survival rate estimate of 8[redacted] without censoring for subsequent allo-SCT (confidential data on file). With appropriate caveats around potential areas of bias with these exploratory analyses, they do suggest subsequent allo-SCT is not having a positive impact on the survival estimates associated with Yescarta.	
2	Consultee	Kite Pharma, a Gilead company	**Section 3.8 – SCHOLAR-5 population alignment to ZUMA-5** We are surprised that the non-alignment of SCHOLAR-5 and ZUMA-5 due to the inclusion of the DELTA cohort of patients is considered an issue since this was resolved during technical engagement via the removal of the DELTA cohort of patients from standard of care arm. We agreed with the Committee and the review group that patients within the DELTA cohort were not aligned to clinical practice in England due to the use of idelalisib. For this reason, the DELTA cohort was removed from the analysis prior to the Committee meeting (during technical engagement), and the revised company base case did not include these patients. Note that as expected this change was favourable for axicabtagene ciloleucel since patients in the DELTA cohort on average lived longer than patients receiving standard of care more aligned to NHS England current practice.	Thank you for your comment. The FAD has been amended to reflect that the information within your response was considered by the committee.
3	Consultee	Kite Pharma, a Gilead company	**Section 3.9 – Company approach to adjusting the SCHOLAR-5 data** The statistical analysis plan for the SCHOLAR-5 analyses was informed by best practice, including NICE DSU Technical Support Document (TSD) 18 as well as more recent developments in the wider literature. The design of the analyses is as recommended in NICE DSU TSD 17. We agree with the ERG and the committee that propensity score weighting improved the comparability of ZUMA-5 and SCHOLAR-5, and	Thank you for your comment. The committee took this additional information provided into its decision making. The committee concluded that, because of the complexity in the methods to adjust the SCHOLAR 5 data, and the potential biases, the results of the unanchored comparisons were very uncertain. Please see section 3.8 of the FAD.

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			that propensity score weighting methods should ideally adjust for all treatment effect modifiers and prognostic variables. However, this does have to be balanced with sample size and in the case of the SCHOLAR-5 population, we do have limited patient numbers reflecting the rarity of disease. It was therefore considered appropriate to focus on identification and inclusion of covariates strongly correlated with outcomes. A data model was developed specifically for the SCHOLAR-5 study that predicted variable selection. A comprehensive list of all potential variables of relevance plus standardised ranges for each was created, based on published literature, clinical guidelines or standardised test reference values. In parallel, primary investigators from select sites reviewed the list of variables to rank them as high, medium and low priority. Within each category variables were further ranked numerically to guide decisions about variable selection if the need arose. Nine variables were ultimately included in the final base case model: these variables represented all available variables from the dataset that were pre-specified to be of 'high' or 'medium' importance in R/R FL. The high importance variables (in order of deemed importance) were disease progression within 24 months of first anti-CD20 combination therapy (POD24), number of prior lines of therapy, refractory vs relapsed disease and prior stem cell transplant (SCT). The medium importance variables (in order of deemed importance) were time from last treatment, best response to last therapy, tumour bulk of the largest lesion, age, and prior anti-CD20 + alkylating agent. The committee commented that they would like to see other methods explored in more detail. In addition to propensity score weighting, sensitivity analyses were conducted using doubly robust and propensity score matching methods as well as inverse probability treatment weighting (IPTW). Alternative methods were also explored, including G-estimation and the 'E value'. All sensitivity analyses were consistent with the base case analysis findings, that is, axi-cel was shown to improve response and survival outcomes compared with current care. In general, results of the sensitivity analyses were more in favour of axi-cel.	
4	Consultee	Kite Pharma, a Gilead company	**Section 3.12 – Long term survivor predictions** As requested, we have presented a graph with the modelled overall survival stratified by long-term and non-long-term survivors in the	Thank you for your comment. The committee took this additional information provided stratified by long-term survivors and long-term survivors into its decision making. It also discussed other scenarios provided

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			Appendix to these responses.	during the committee meeting. The committee concluded that the presented analyses did not resolve uncertainties about the company's long-term and non-long-term survivor assumptions. Please see section 3.11 of the FAD.
5	Consultee	Kite Pharma, a Gilead company	**Section 3.13 – Long-term survivor utility** While the impact is minor, we note that the Committee has not followed precedent regarding the rebound to general population utility after achieving long term survival. This assumption was applied consistently with existing appraisals where long-term survival is modelled, where the same assumption, with a similar evidence base has been approved by the Committee. While it is recognised that this assumption was discussed and critiqued during these previous appraisals, it was ultimately accepted by the Committee. This includes a previous appraisal for the same product in a different indication (diffuse large B-cell lymphoma [DLBCL]) [TA559].[3]	Thank you for your comment. The committee took this information provided into its decision making. The committee recognised that there are some uncertainties with this approach. The committee concluded that the ERG's approach of using a utility decrement for long-term survivors was more appropriate. The committee also noted that the assumption of a rebound to general population utility for long-term survivors favoured axicabtagene ciloleucel. Please see section 3.12 of the FAD.
6	Consultee	Kite Pharma, a Gilead company	**Section 3.15 – Inclusion of NHS England CAR-T delivery tariff** We are deeply concerned about the inclusion of the NHS England CAR-T delivery tariff after this was raised during the Committee meeting on 5 July 2022, both in terms of the implications for a fair and transparent procedure in this appraisal and the ramifications this is likely to have for patient access to CAR-T therapies generally in England. In line with the Methods Guide NICE must consider what the *true cost* of the treatment is to the NHS. The cost analysis submitted by Gilead followed recommended NICE methods and the relevant hierarchy of evidence, Gilead's cost analysis therefore included our best estimate of the costs of delivering CAR-T therapy, using an approach which included systematic identification of evidence using published sources and clinical validation. However, during the Committee meeting, a tariff for delivering CAR-T therapy in England of £96,016 (the **NHS Tariff**) was raised, which led the Committee to conclude that Gilead's cost model may not be reflective of NHS practice, and ultimately not recommend that the product be made available to NHS patients. The Appraisal Committee recognised that there is a lack of transparency about what costs the NHS Tariff included, that	Thank you for your comment. Comment noted. The cost of delivering CAR T-cell therapy in the NHS has been further analysed after the second committee meeting, and has been accepted by the company, NHS England, and the committee. Please see section 3.15 of the FAD.

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			greater transparency is required to explore potential issues of double counting, and noted that the clinical experts as well as Gilead strongly disagreed with the figure used by NHS England. However, it nevertheless concluded that the NHS Tariff estimate represented the best available source to inform the cost that the NHS is paying currently. No explanation for this conclusion is provided, although we infer that the figure is used by NHS England in practice. In the absence of any transparency for the NHS Tariff figure, this approach is both procedurally unfair and unreasonable. Since the Committee meeting, we have used our best efforts to understand what the NHS Tariff includes and how it has been calculated, so that we can compare it to our cost analysis. Our understanding is that this tariff was established by NHS England in 2019 with the introduction of CAR-T therapies. After the Committee meeting, NHS England provided to us and to NICE the same high-level summary of what is included in the NHS Tariff. However, this summary does not give any detail on what specific elements comprise the NHS Tariff and does not provide sufficient transparency nor resolve the issues highlighted by the Committee in the appraisal consultation document. For example, it is not possible to explore potential issues of double counting. There remains no transparency on the methods used to calculate, nor on evidence used to substantiate, the value of the NHS Tariff. It remains unclear whether the NHS Tariff is reliable or includes costs which are not relevant to a NICE appraisal. In circumstances where the tariff value is central to this appraisal and to any consideration of CAR-T therapies, it is clearly essential that this is fully transparent and can be understood and tested by stakeholders. We therefore requested more specific information, including an itemised breakdown of the pathway costs reflecting resource utilisation across the patient pathway for patients meeting the standard care patient pathway and patients on the complex patient pathway, assumptions on the proportion of patients meeting the standard care pathway and the complex patient pathway and related validation. NHS England have assessed our request as a request under the Freedom of Information Act. Under that Act, NHS England have until 6 September 2022 to respond. Despite the apparent introduction of the NHS Tariff some years ago it was not raised at any point during the ERG review or technical engagement, and has not been considered appropriate by NICE for inclusion in any other CAR-T guidance to date. This included the prior guidance for	

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			axicabtagene ciloleucel in 3L DLBCL in 2019 (TA559), and the appraisal of KTE-X19 in Mantle Cell in 2021 (TA677). While the NHS Tariff was noted in the ERG response in TA677 the value (£92k at that time) is redacted from public view and the ERG noted the lack of transparency in how the NHS Tariff was arrived at and the fact that the value was due to be re-evaluated following the appraisal (NHS England have confirmed that the NHS Tariff remains under review); ultimately the NHS Tariff was not included in the final decision. Any decision to adopt a different approach in the current appraisal should be justified by clear reasoning; this is currently absent. In order to carry out a general assessment of the NHS Tariff figure, we have obtained evidence from the Adelphi Real World DLBCL DSP™, a real-world point-in-time survey of haematologists, haem-oncologists, and medical oncologists and their patients with DLBCL in the UK, Germany, Spain, Italy, France and Canada in 2021. The analysis considered the 100 days following CAR-T administration. A total of [redacted] patients received CAR-T at 3rd line in the DSP UK sample; in European countries (UK, Germany, Spain, Italy and France), there were a total of [redacted] patients who received CAR-T at 3rd line. The analysis found that [redacted] patients in the UK who received CAR-T were hospitalised as an inpatient for an average of [redacted] nights within the first 100 days of administration (within the European countries this value was [redacted] nights). Additionally, UK patients had an average of [redacted] outpatient visits (within European countries this value was [redacted] visits). Applying a daily hospitalization cost of £903.20 per inpatient bed day (aligned with the cost-effectiveness model) and a cost of £217.00 per outpatient visit (NHS Reference Costs 2020/21[6]; Outpatient Attendance; 370 (Medical Oncology)), this results in a cost of [redacted] for UK patients ([redacted] for European patients) which is a small fraction of the NHS Tariff figure. These findings also align with the [redacted] day hospitalisation and outpatient visits resulting in the [redacted] cost associated with CAR-T infusion included within the company cost-effectiveness model. Given the lack transparency surrounding the NHS Tariff and the uncertainty in how the value was derived and its constituents, the inconsistency with the evidence of the NICE appointed clinical experts and real world evidence and the approach followed in previous appraisals of	

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			CAR-T therapies, a recommendation based on the use of this NHS Tariff would clearly be procedurally unfair and, in the absence of reasoning appears arbitrary and unreasonable. Further, such a decision would lack credibility, conflicting with NICE's reputation for transparent, evidence based decision-making and for facilitating accelerated patient access to transformative therapies. If there is uncertainty around clinical costs, the only fair and reasonable conclusion the Committee can reach based on the evidence it has been provided with is to include the cost of treatment shown in our cost analysis, calculated using NICE recommended methods and based on evidence, in preference to the NHS Tariff figure until any uncertainty is resolved. If, following consultation on this ACD, the Committee still believes that the clinical costs associated with CAR-T therapy are uncertain, we would propose that as a potential solution the health care resource use following CAR-T infusion could be studied carefully, and accurately determined during a period of CDF access in order to help establish a methodical, evidence-based treatment cost for future NICE appraisals. CAR-T therapies have an extremely high manufacturing cost due to their innovative and personalised nature, which limits the level of discount which can be offered. If imposed across the CAR-T class, the NHS Tariff, which is wholly lacking in transparency and we believe to be substantially incorrect, will have the effect of Gilead's provision of CAR-T therapy almost certainly not being cost effective without a level of discount which will not be commercially viable. This will result in new patients, such as those with FL, not gaining access to these innovative, life-saving therapies, but also existing patient groups losing access as currently available therapies exit the CDF. NHS England is known as a world leader in cell therapy and the potential loss of future and current access will be to the detriment of patient outcomes and to the reputation of the UK as an early adopter of transformative science. Given the potentially huge impact on patients we strongly urge the Committee to consider the consequences of this decision in full.	
7	Consultee	Kite Pharma, a Gilead company	**Section 3.16 – End of life** While we accept that the expected survival for a patient treated with best support care is likely marginally greater than 24 months, we are	Thank you for your comment. The committee considered that the short life expectancy criterion of less than 24 months was not met because the life expectancy of people who would have axicabtagene ciloleucel would normally be longer than 24 months. It

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			disappointed not to be considered for end of life. As validated by clinicians axi-cel would be expected to be adopted as an end-of-life therapy in England when other treatment options are no longer effective, in patients with a short life expectancy. Further, there is a substantial disease burden and unmet need for patients, and under revised NICE methods a severity of disease modifier greater than 1 would have been applicable. We understand that the assessment has taken place under old methods, but we are disappointed to have been disadvantaged by a change in NICE processes, and we regret a lack of flexibility which may result in patients' not gaining access to a potentially life-saving therapy.	concluded that axicabtagene ciloleucel does not meet the criteria to be considered a life-extending treatment at the end of life. Please see section 3.16 of the FAD.
8	Consultee	Lymphoma CSG	We are concerned that in paragraph 3.15 it is suggested that instead of using the NHS costing tool to calculate treatment delivery costs that the national NHS tariff, of £96,106 should be used. This would be a significant change to previous CAR-T evaluations when the treatment delivery costs were calculated by the companies based on the NHS costing tool and the NHS tariff was not applied. We are aware that brexucabtagene autoleucel –TECARTUS (a similar product to axicel) was approved for relapsed/refractory mantle cell lymphoma in February 2021 by NICE and delivery costs were estimated using the NHS costing tool and were significantly lower compared to the NHS tariff, which has been in place since several years. Hence, we have a clear precedent that a CAR-T therapy has been NICE approved using the estimated delivery costs based on the NHS costing tool. Introduction of a change in calculating delivery cost is therefore inconsistent with prior applications and appears to disadvantage the current and future CART funding applications.	Thank you for your comment. The NHS England is also undertaking urgent work to provide alternative costs to NICE and the company. Please lee section 3.15 of the FAD.
9	Consultee	Lymphoma CSG	In paragraph 3.16 we note that the life expectancy for follicular lymphoma (FL) patients who have failed at least 3 lines of therapy is estimated to be between 30-36 months based on the Scholar-5 study. Clinical experience would suggest that this is an overestimate and might be due to the fact that the data were collected from large academic centres, which have an inherit population bias towards fitter and healthier patients. We are fully aware that there are no good outcome data in FL patient treated after 3 failed lines but we estimate this is less than 30-36 months and probably closer to 2 years or even less as treatment options are limited. By this time point, patients will already have failed rituximab or obinutuzumab in combination with chemotherapy, which typically includes bendamustine, alkylating agents and anthracyclines. So the only options left are either to	Thank you for your comment. The committee considered that the short life expectancy criterion of less than 24 months was not met because the life expectancy of people who would have axicabtagene ciloleucel would normally be longer than 24 months. It concluded that axicabtagene ciloleucel does not meet the criteria to be considered a life-extending treatment at the end of life. Please see section 3.16 of the FAD.

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			enrol patients on an experimental study or recycle some of the chemo combinations used previously. Having CAR-T cells available in this setting would certainly open up a completely different treatment strategy with very good response rates, PFS and OS advantages.	

NICE National Institute for Health and Care Excellence

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

Consultation on the appraisal consultation document – deadline for comments 5pm on 17 August. 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 Pharma, 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]

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1	**Section 3.6 – Survival data are immature and uncertain** We agree with the Committee that survival data are immature and thus uncertain at this time, hence why we believe axicabtagene ciloleucel (axi-cel) is a suitable candidate for the cancer drugs fund (CDF) that is intended to facilitate access to promising treatments such as axi-cel while further evidence is collected. Every effort was taken to use data that were available at the time of submission to inform and validate the survival modelling, including longer-term data available for axi-cel and other chimeric antigen receptor (CAR)-T cell therapies in other indications. More recently, five-year outcomes for patients with relapsed or refractory follicular lymphoma (FL) who were treated with tisagenlecleucel were published in a letter to the editor of the New England Journal of Medicine.[1] Of the patients with FL, 43% of patients were progression-free at 5 years, suggesting that the [redacted] progression-free at 5 years estimated from the axi-cel FL survival modelling may be a conservative estimate. Additional data are also now available from a 36-month data cut of ZUMA-5, which further support the modelling extrapolations (see Appendix). The overall survival Kaplan-Meier curve for the full analysis set (FAS) of patients with centrally confirmed FL who had received three or more lines of prior therapy (n = 75) shows clear signs of a plateau at around [redacted] survival occurring after approximately [redacted] (confidential data on file). As well as supporting the long-term survival assumptions, this also aligns with the [redacted] overall survival at 5 years estimated from the axi-cel FL survival modelling. Overall survival analyses for the inferential analysis set (IAS) show a similar plateau. Median overall survival is still [redacted] but median progression-free survival is estimated at [redacted] (confidential data on file). As a reminder of expected survival with current care, SCHOLAR-5 estimated median overall survival of [redacted] and median progression-free survival of [redacted].[2] Post-hoc sensitivity analyses have also been conducted to explore the potential impact of allogeneic stem cell transplant (allo-SCT) after treatment with Yescarta which the committee felt may impact the overall mean survival for ZUMA-5. Censoring of patients at the time of allo-SCT results in a 24-month overall-survival rate estimate of [redacted] compared with a 24-month overall-survival rate estimate of [redacted] without censoring for subsequent allo-SCT (confidential data on file). With appropriate caveats around potential areas of bias with these exploratory analyses, they do suggest subsequent allo-SCT is not having a positive impact on the survival estimates associated with Yescarta.
2	**Section 3.8 – SCHOLAR-5 population alignment to ZUMA-5** We are surprised that the non-alignment of SCHOLAR-5 and ZUMA-5 due to the inclusion of the DELTA cohort of patients is considered an issue since this was resolved during technical engagement via the removal of the DELTA cohort of patients from standard of care arm. We agreed with the Committee and the review group that patients within the DELTA cohort were not aligned to clinical practice in England due to the use of idelalisib. For this reason, the DELTA cohort was removed from the analysis prior to the Committee meeting (during technical engagement), and the revised company base case did not include these patients. Note that as expected this change was favourable for axicabtagene ciloleucel since patients in the DELTA

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	cohort on average lived longer than patients receiving standard of care more aligned to NHS England current practice.
3	**Section 3.9 – Company approach to adjusting the SCHOLAR-5 data** The statistical analysis plan for the SCHOLAR-5 analyses was informed by best practice, including NICE DSU Technical Support Document (TSD) 18 as well as more recent developments in the wider literature. The design of the analyses is as recommended in NICE DSU TSD 17. We agree with the ERG and the committee that propensity score weighting improved the comparability of ZUMA-5 and SCHOLAR-5, and that propensity score weighting methods should ideally adjust for all treatment effect modifiers and prognostic variables. However, this does have to be balanced with sample size and in the case of the SCHOLAR-5 population, we do have limited patient numbers reflecting the rarity of disease. It was therefore considered appropriate to focus on identification and inclusion of covariates strongly correlated with outcomes. A data model was developed specifically for the SCHOLAR-5 study that predicted variable selection. A comprehensive list of all potential variables of relevance plus standardised ranges for each was created, based on published literature, clinical guidelines or standardised test reference values. In parallel, primary investigators from select sites reviewed the list of variables to rank them as high, medium and low priority. Within each category variables were further ranked numerically to guide decisions about variable selection if the need arose. Nine variables were ultimately included in the final base case model: these variables represented all available variables from the dataset that were pre-specified to be of 'high' or 'medium' importance in R/R FL. The high importance variables (in order of deemed importance) were disease progression within 24 months of first anti-CD20 combination therapy (POD24), number of prior lines of therapy, refractory vs relapsed disease and prior stem cell transplant (SCT). The medium importance variables (in order of deemed importance) were time from last treatment, best response to last therapy, tumour bulk of the largest lesion, age, and prior anti-CD20 + alkylating agent. The committee commented that they would like to see other methods explored in more detail. In addition to propensity score weighting, sensitivity analyses were conducted using doubly robust and propensity score matching methods as well as inverse probability treatment weighting (IPTW). Alternative methods were also explored, including G-estimation and the 'E value'. All sensitivity analyses were consistent with the base case analysis findings, that is, axi-cel was shown to improve response and survival outcomes compared with current care. In general, results of the sensitivity analyses were more in favour of axi-cel.
4	**Section 3.12 – Long term survivor predictions** As requested, we have presented a graph with the modelled overall survival stratified by long-term and non-long-term survivors in the Appendix to these responses.
5	**Section 3.13 – Long-term survivor utility** While the impact is minor, we note that the Committee has not followed precedent regarding the rebound to general population utility after achieving long term survival. This assumption was applied consistently with existing appraisals where long-term survival is modelled, where the same assumption, with a similar evidence base has been approved by the Committee. While it is recognised that this assumption was discussed and critiqued during these previous appraisals, it was ultimately accepted by the Committee. This includes a previous appraisal for the same product in a different indication (diffuse large B-cell lymphoma [DLBCL]) [TA559].[3]

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6	**Section 3.15 – Inclusion of NHS England CAR-T delivery tariff** We are deeply concerned about the inclusion of the NHS England CAR-T delivery tariff after this was raised during the Committee meeting on 5 July 2022, both in terms of the implications for a fair and transparent procedure in this appraisal and the ramifications this is likely to have for patient access to CAR-T therapies generally in England. In line with the Methods Guide NICE must consider what the *true cost* of the treatment is to the NHS. The cost analysis submitted by Gilead followed recommended NICE methods and the relevant hierarchy of evidence, Gilead's cost analysis therefore included our best estimate of the costs of delivering CAR-T therapy, using an approach which included systematic identification of evidence using published sources and clinical validation. However, during the Committee meeting, a tariff for delivering CAR-T therapy in England of £96,016 (the **NHS Tariff**) was raised, which led the Committee to conclude that Gilead's cost model may not be reflective of NHS practice, and ultimately not recommend that the product be made available to NHS patients. The Appraisal Committee recognised that there is a lack of transparency about what costs the NHS Tariff included, that greater transparency is required to explore potential issues of double counting, and noted that the clinical experts as well as Gilead strongly disagreed with the figure used by NHS England. However, it nevertheless concluded that the NHS Tariff estimate represented the best available source to inform the cost that the NHS is paying currently. No explanation for this conclusion is provided, although we infer that the figure is used by NHS England in practice. In the absence of any transparency for the NHS Tariff figure, this approach is both procedurally unfair and unreasonable. Since the Committee meeting, we have used our best efforts to understand what the NHS Tariff includes and how it has been calculated, so that we can compare it to our cost analysis. Our understanding is that this tariff was established by NHS England in 2019 with the introduction of CAR-T therapies. After the Committee meeting, NHS England provided to us and to NICE the same high-level summary of what is included in the NHS Tariff. However, this summary does not give any detail on what specific elements comprise the NHS Tariff and does not provide sufficient transparency nor resolve the issues highlighted by the Committee in the appraisal consultation document. For example, it is not possible to explore potential issues of double counting. There remains no transparency on the methods used to calculate, nor on evidence used to substantiate, the value of the NHS Tariff. It remains unclear whether the NHS Tariff is reliable or includes costs which are not relevant to a NICE appraisal. In circumstances where the tariff value is central to this appraisal and to any consideration of CAR-T therapies, it is clearly essential that this is fully transparent and can be understood and tested by stakeholders. We therefore requested more specific information, including an itemised breakdown of the pathway costs reflecting resource utilisation across the patient pathway for patients meeting the standard care patient pathway and patients on the complex patient pathway, assumptions on the proportion of patients meeting the standard care pathway and the complex patient pathway and related validation. NHS England have assessed our request as a request under the Freedom of Information Act. Under that Act, NHS England have until 6 September 2022 to respond. Despite the apparent introduction of the NHS Tariff some years ago it was not raised at any point during the ERG review or technical engagement, and has not been considered appropriate by NICE for inclusion in any other CAR-T guidance to date. This included the prior guidance for axicabtagene ciloleucel in 3L DLBCL in 2019 (TA559), and the appraisal of KTE-X19 in Mantle Cell in 2021 (TA677). While the NHS Tariff was noted in the ERG response in TA677 the value (£92k at that time) is redacted from public view and the ERG noted the lack of transparency in how the NHS Tariff was arrived at and the fact that the value was due to be re-evaluated following the

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	appraisal (NHS England have confirmed that the NHS Tariff remains under review); ultimately the NHS Tariff was not included in the final decision. Any decision to adopt a different approach in the current appraisal should be justified by clear reasoning; this is currently absent. In order to carry out a general assessment of the NHS Tariff figure, we have obtained evidence from the Adelphi Real World DLBCL DSP™, a real-world point-in-time survey of haematologists, haem-oncologists, and medical oncologists and their patients with DLBCL in the UK, Germany, Spain, Italy, France and Canada in 2021. The analysis considered the 100 days following CAR-T administration. A total of [redacted] patients received CAR-T at 3rd line in the DSP UK sample; in European countries (UK, Germany, Spain, Italy and France), there were a total of [redacted] patients who received CAR-T at 3rd line. The analysis found that [redacted] patients in the UK who received CAR-T were hospitalised as an inpatient for an average of [redacted] nights within the first 100 days of administration (within the European countries this value was [redacted] nights). Additionally, UK patients had an average of [redacted] outpatient visits (within European countries this value was [redacted] visits). Applying a daily hospitalization cost of £903.20 per inpatient bed day (aligned with the cost-effectiveness model) and a cost of £217.00 per outpatient visit (NHS Reference Costs 2020/21[6]; Outpatient Attendance; 370 (Medical Oncology)), this results in a cost of [redacted] for UK patients ([redacted] for European patients) which is a small fraction of the NHS Tariff figure. These findings also align with the [redacted] day hospitalisation and outpatient visits resulting in the [redacted] cost associated with CAR-T infusion included within the company cost-effectiveness model. Given the lack transparency surrounding the NHS Tariff and the uncertainty in how the value was derived and its constituents, the inconsistency with the evidence of the NICE appointed clinical experts and real world evidence and the approach followed in previous appraisals of CAR-T therapies, a recommendation based on the use of this NHS Tariff would clearly be procedurally unfair and, in the absence of reasoning appears arbitrary and unreasonable. Further, such a decision would lack credibility, conflicting with NICE's reputation for transparent, evidence based decision-making and for facilitating accelerated patient access to transformative therapies. If there is uncertainty around clinical costs, the only fair and reasonable conclusion the Committee can reach based on the evidence it has been provided with is to include the cost of treatment shown in our cost analysis, calculated using NICE recommended methods and based on evidence, in preference to the NHS Tariff figure until any uncertainty is resolved. If, following consultation on this ACD, the Committee still believes that the clinical costs associated with CAR-T therapy are uncertain, we would propose that as a potential solution the health care resource use following CAR-T infusion could be studied carefully, and accurately determined during a period of CDF access in order to help establish a methodical, evidence-based treatment cost for future NICE appraisals. CAR-T therapies have an extremely high manufacturing cost due to their innovative and personalised nature, which limits the level of discount which can be offered. If imposed across the CAR-T class, the NHS Tariff, which is wholly lacking in transparency and we believe to be substantially incorrect, will have the effect of Gilead's provision of CAR-T therapy almost certainly not being cost effective without a level of discount which will not be commercially viable. This will result in new patients, such as those with FL, not gaining access to these innovative, life-saving therapies, but also existing patient groups losing access as currently available therapies exit the CDF. NHS England is known as a world leader in cell therapy and the potential loss of future and current access will be to the detriment of patient outcomes and to the reputation of the UK as an early adopter of transformative science. Given the potentially huge impact on patients we strongly urge the Committee to consider the consequences of this decision in full.

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7	**Section 3.16 – End of life** While we accept that the expected survival for a patient treated with best support care is likely marginally greater than 24 months, we are disappointed not to be considered for end of life. As validated by clinicians axi-cel would be expected to be adopted as an end-of-life therapy in England when other treatment options are no longer effective, in patients with a short life expectancy. Further, there is a substantial disease burden and unmet need for patients, and under revised NICE methods a severity of disease modifier greater than 1 would have been applicable. We understand that the assessment has taken place under old methods, but we are disappointed to have been disadvantaged by a change in NICE processes, and we regret a lack of flexibility which may result in patients' not gaining access to a potentially life-saving therapy.

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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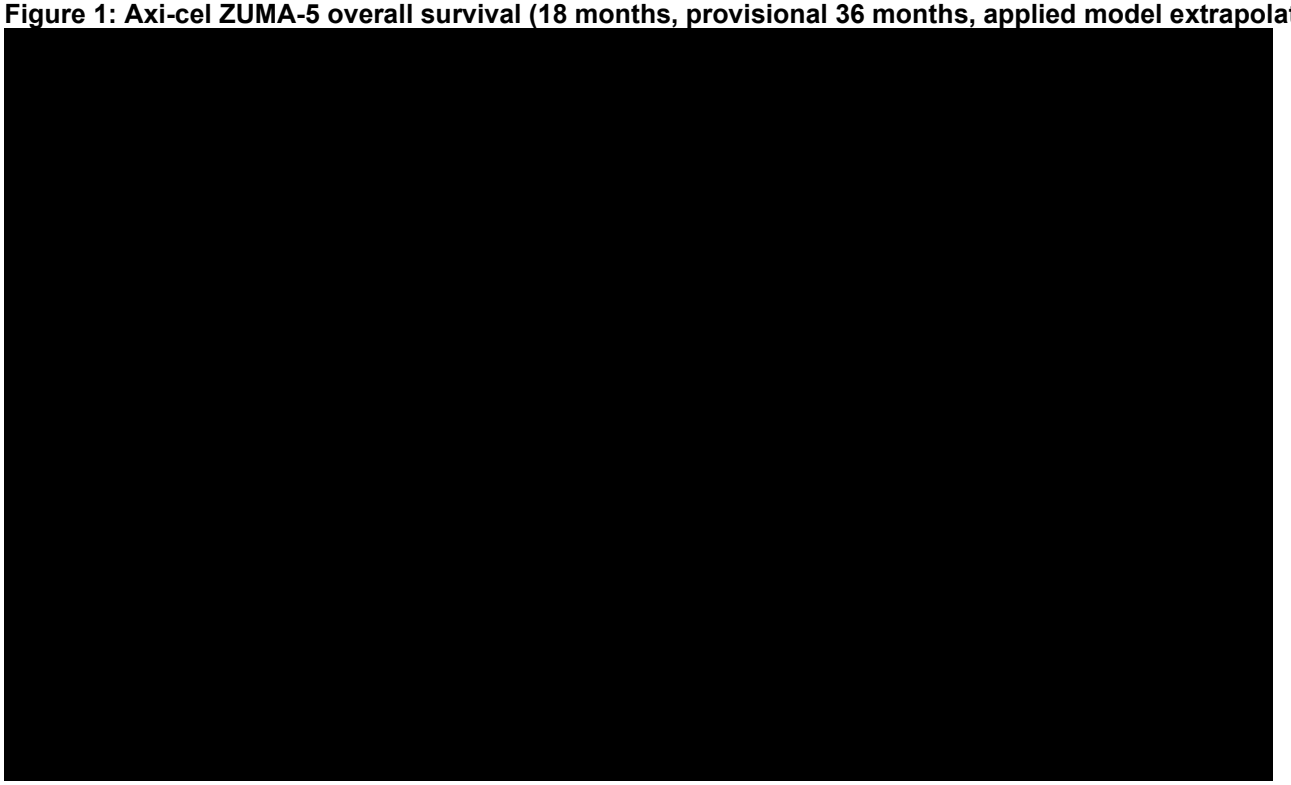
APPENDIX

Section 3.6 – Survival data are immature

The figure below presents the axi-cel overall survival Kaplan-Meier (dashed black line) and extrapolation (solid blue line) as applied in the cost-effectiveness model base case (Weibull function, with 25% assumed to be long-term survivors) overlayed with the provisional Kaplan-Meier from the 36-month data cut of ZUMA-5 (solid red line).

Figure 1: Axi-cel ZUMA-5 overall survival (18 months, provisional 36 months, applied model extrapolation)



Key: axi-cel, axicabtagene ciloleucel.

The 36M Kaplan-Meier plots for overall survival are provided for the FAS and IAS in Figure 2 and Figure 3. The 36M Kaplan-Meier plot for progression-free survival for the FAS is provided in Figure 4.

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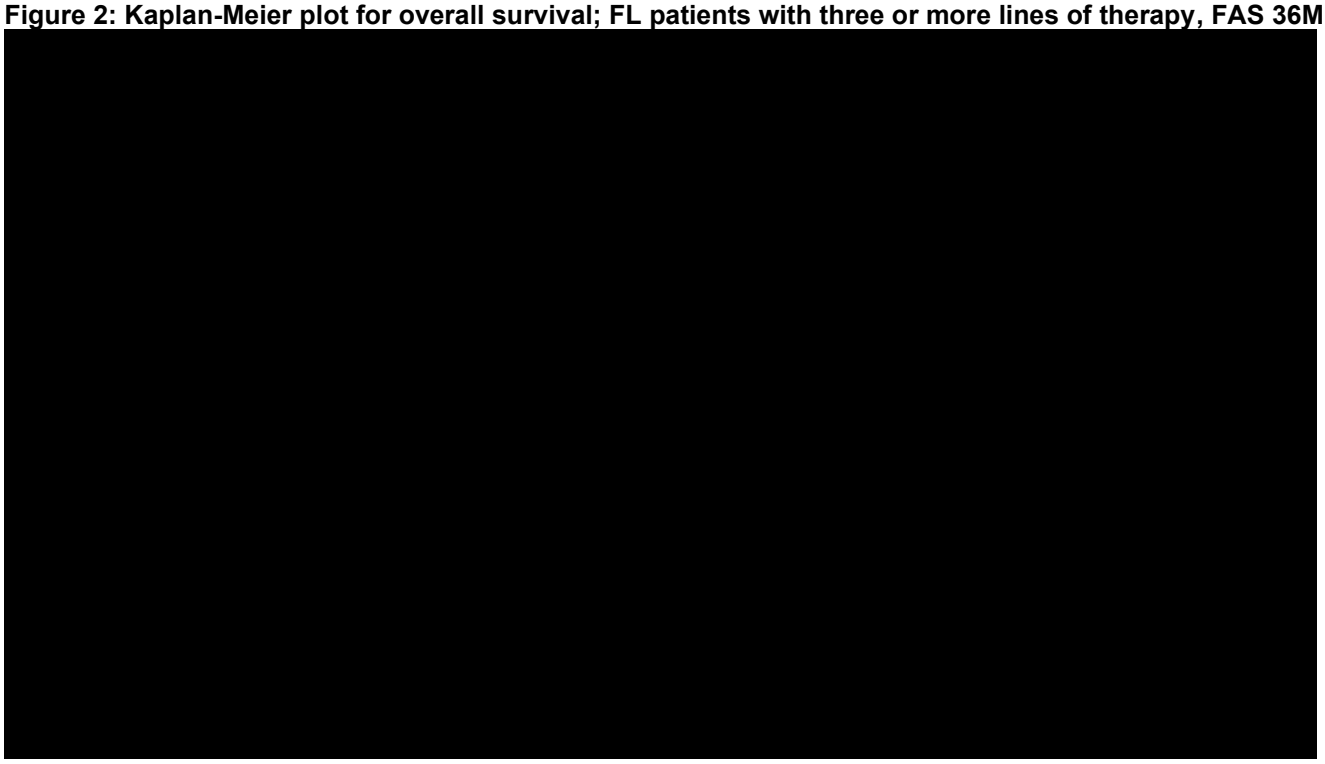
Figure 2: Kaplan-Meier plot for overall survival; FL patients with three or more lines of therapy, FAS 36M



Key: CI, confidence interval; FAS, full analysis set; FL, follicular lymphoma; M, month; NE, not estimable.
Source: Confidential data on file.

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Figure 3: Kaplan-Meier plot for overall survival; FL patients with three or more lines of therapy, IAS 36M

Key: CI, confidence interval; FL, follicular lymphoma; IAS, inferential analysis set; M, month; NE, not estimable.
Source: Confidential data on file.

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Figure 4: Kaplan-Meier plot for progression-free survival; FL patients with three or more lines of therapy, FAS 36M

Key: CI, confidence interval; FAS, full analysis set; FL, follicular lymphoma; M, month; NE, not estimable.
Source: Confidential data on file.

Section 3.12 – Long term survivor predictions

As requested, we have presented a graph with the modelled overall survival stratified by long-term and non-long-term survivors below.

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Figure 5: Cost-effectiveness model overall survival extrapolations stratified by long-term and non-long-term survivors

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Revised PAS

The confidential PAS submitted has been revised from [redacted].

Revised deterministic base case, probabilistic sensitivity analysis (PSA), one-way sensitivity analyses (OWSA), and scenario analyses are presented below. Results are consistent with the revised company base case (excluding DELTA) presented at the Committee meeting with reduced treatment acquisition costs resulting in a revised ICER of £40,584.

Table 7: Revised mean PSA results versus deterministic results (with PAS)

Technology	Total costs (£)		Total QALYs		ICER (£/QALY)	
	Revised PSA	Revised deterministic	Revised PSA	Revised deterministic	Revised PSA	Revised deterministic
Current 4L+ care	[redacted]	[redacted]	[redacted]	[redacted]		
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]		
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	£42,291	£40,584

Key: 4L, fourth line; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

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Figure 6: Revised cost-effectiveness plane and cost-effectiveness acceptability cure (with PAS)

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Key: 4L+, fourth-line plus; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

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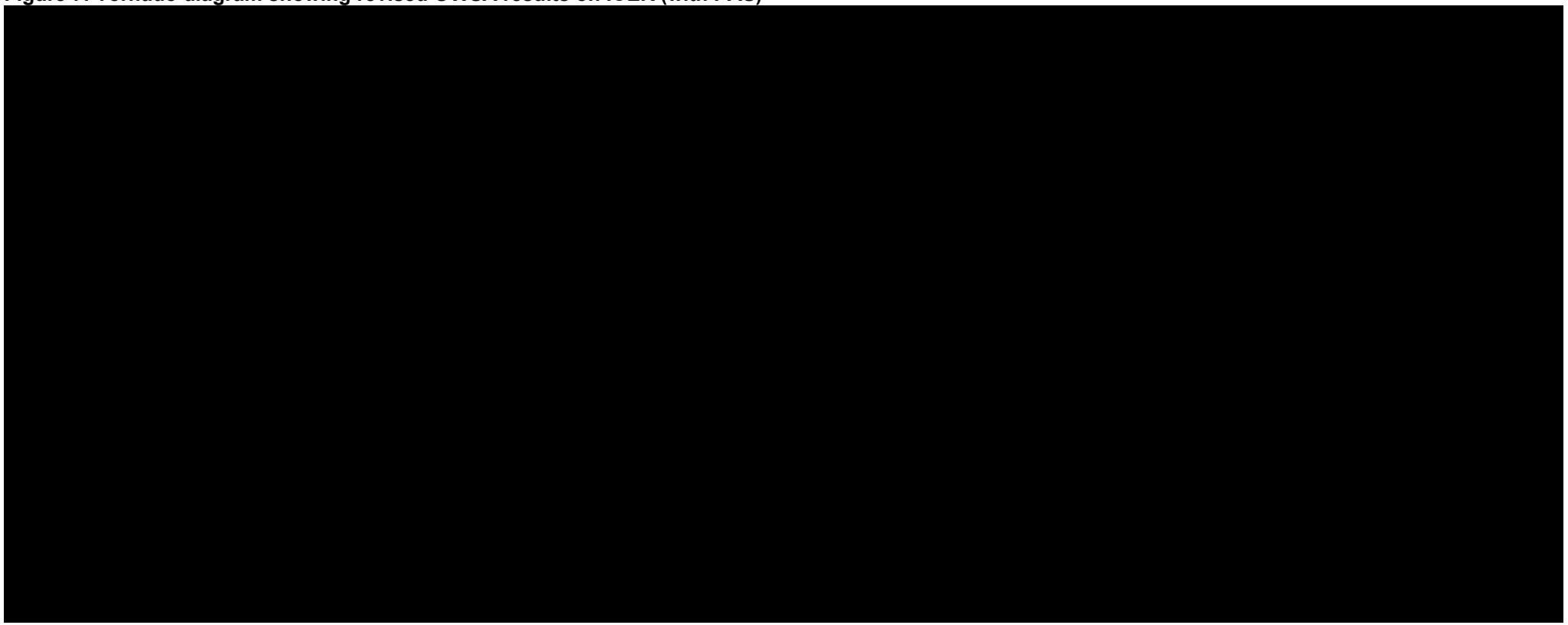
Figure 7: Tornado diagram showing revised OWSA results on ICER (with PAS)



Key: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme.

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Table 8: Revised scenario analysis (with PAS)

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£40,584	N/A
Discount rate for costs and health outcomes	3.5%	0.0%	[redacted]	[redacted]	£27,446	-£13,138
		1.5%	[redacted]	[redacted]	£32,741	-£7,843
		6.0%	[redacted]	[redacted]	£51,531	£10,947
Time horizon	40 years	30 years	[redacted]	[redacted]	£41,188	£604
		20 years	[redacted]	[redacted]	£46,477	£5,893
OS extrapolations	• Current 4L+ care, gamma • Axi-cel, Weibull (25% of treated patients long-term survivors)	• Current 4L+ care, exponential • Axi-cel, Weibull	[redacted]	[redacted]	£40,784	£200
		• Current 4L+ care, Weibull • Axi-cel, Weibull	[redacted]	[redacted]	£41,198	£613
		• Current 4L+ care, gamma • Axi-cel, log-logistic	[redacted]	[redacted]	£35,549	-£5,035
		• Current 4L+ care, exponential • Axi-cel, log-logistic	[redacted]	[redacted]	£35,699	-£4,885
		• Current 4L+ care, Weibull • Axi-cel, log-logistic	[redacted]	[redacted]	£36,009	-£4,575
		Axi-cel, log-logistic (no long-term survivorship)	[redacted]	[redacted]	£40,086	-£498
Long-term survivorship proportion	25% of treated axi-cel patients are captured as long-term survivors	[redacted] of treated patients (i.e., all in PFS at 5 years)	[redacted]	[redacted]	£37,865	-£2,720
		10% of treated patients	[redacted]	[redacted]	£47,185	£6,600
Long-term survivorship SMR	SMR = 1.09	1.00	[redacted]	[redacted]	£40,151	-£433
		1.20	[redacted]	[redacted]	£41,090	£506
	5 years	2 years	[redacted]	[redacted]	£37,695	-£2,889
		7 years	[redacted]	[redacted]	£42,491	£1,907

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Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Long-term survivorship time point		10 years	[redacted]	[redacted]	£45,177	£4,593
Health state utility source for progression-free and progressed disease	Wild et al. (with general population utility for those alive and free of progression beyond 5 years)	• Progression-free, general population (TA627) • Progressed, general population with AUGMENT decrement (TA627)	[redacted]	[redacted]	£39,676	-£908
		GADOLIN	[redacted]	[redacted]	£40,117	-£467
		AUGMENT, R^2	[redacted]	[redacted]	£39,238	-£1,346
		AUGMENT, R-mono	[redacted]	[redacted]	£39,414	-£1,170
Utility value for those alive and progression-free beyond 5 years	General population	Adjust general population utility (98.6%)	[redacted]	[redacted]	£40,879	295

Key: ICER, incremental cost-effectiveness ratio; N/A, not applicable; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; R^2, lenalidomide with rituximab; R-mono; rituximab monotherapy; SMR, standardised mortality ratio; TA, technology appraisal.

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

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Date completed: **25 August 2022**

Contains: [redacted]

Following the first appraisal committee meeting, the committee were minded to not recommend Axicabtagene ciloleucel within its marketing authorisation. In response to appraisal consultation document (ACD) the company have addressed seven points of concern raised by the committee. They have retained their based case modelling assumptions but offered a revised patient access scheme which reduces the ICER.

In this document, the ERG comments on the company's response and provides further cost-effectiveness scenarios addressing uncertainties that the company's scenarios have not covered. It should be read in conjunction with the company's response to the ACD. The ERG has also provided a further cPAS appendix, which reproduces the company's revised analyses using confidential prices available for comparator/subsequent therapies in the model.

Section A – Critique of Company's response to the ACD

1. Section 3.6 – Survival data are immature and uncertain

The company acknowledge that the survival data from ZUMA-5 are immature and uncertain, but defend their base case extrapolations and suggest axi-cel is a suitable candidate for the cancer drugs fund.

To further support their case, they reference the five year survival outcomes of a small cohort of relapsed or refractory FL patients recently published in a letter to NEJM (Chong et al. 2021), and the provisional analysis of a new (36-month) data cut from ZUMA-5 (see appendix of the company response).

The letter published in NEJM provides a Kaplan-Meier (KM) plot for 14 relapsed or refractory FL patients treated with tisagenlecleucel with a median of 60.7 months follow-up. The company note that "43% of patients were progression-free at 5 years, suggesting that the [redacted] progression-free at 5 years estimated from the axi-cel FL survival modelling may be a conservative estimate" (Company ACD response).

The KM curve for overall survival (OS) based on provisional analysis of the 36 month data cut from ZUMA-5, for patients with centrally confirmed FL and three or more lines of prior therapy (n = 75), shows five year survival of around [redacted]. The company argue that there are clear signs of a plateau from about [redacted] (see figure 2 of the company response document). The company suggest this aligns with their model-based 5-year survival projection of [redacted]. Median PFS based on the 36 month data cut is [redacted] (see company ACD response).

The ERG has the following observations:

The external PFS data reported for relapsed or refractory FL patients treated with tisagenlecleucel is based on a small number of patients, with PFS outcomes affected by censoring and only 6 patients remaining at risk from three years. This makes the five year progression free estimate of 43% uncertain (95% CI, 18% to 66%).

The KM estimates of OS and PFS from the ZUMA-5 36 month data cut are broadly aligned with the company's model extrapolations out to five years (with median PFS slightly underestimated by the model). There are also signs that the curves are flattening from three years. The data, however, do start to be more heavily affected by censoring from around this time point, making longer term projections more uncertain.

It is not clear why the number at risk at time zero ([redacted]) in these updated analyses is slightly different from the number in the mITT analysis set (n=78) used to inform the company's model.

The company also partially address committee concerns that the use of allo-SCT following axi-cel treatment in ZUMA-5 may be influencing the survival estimates. The company report on an exploratory analysis that censors patients at the time of allo-SCT, which results in a very similar 24-month overall-survival probability compared to the main analysis; [redacted] This, they note, suggests that allo-SCT is not having a positive impact on the survival estimates associated with axi-cel.

The ERG would note that it is perhaps too early at 24 months to determine if allo-SCT following CAR-T therapy has a positive impact on OS. The data may be too immature for this purpose. Without longer-term evidence, it is difficult to address this. If allo-SCT is used in practice following CAR-T therapy, or current care, this adds further cost that is not included

in the model. It may be noted, however, that only [redacted] had an SCT following axicel treatment in ZUMA-5 ([redacted]). It is not clear how many there were in the relevant 4L+ cohort. Likewise, it is not clear what percentage of patients had a subsequent SCT in the SCHOLAR-5 cohort following 3 or more lines of prior therapy.

2. Section 3.8 – SCHOLAR-5 population alignment to ZUMA-5

The company note that they agree with the committee and the review group that patients within the DELTA cohort were not aligned to clinical practice in England due to the use of idelalisib. They note that the DELTA cohort was removed from the analysis prior to the Committee meeting (during technical engagement), and the revised company base case did not include these patients. They further note that this change was favourable for axicabtagene ciloleucel since patients in the DELTA cohort on average lived longer than patients receiving standard of care more aligned to NHS England.

The ERG note that the company's account is factually accurate. The ERG would add, however, that it became apparent during technical engagement that patients from the DELTA cohort fed into the original SCHOLAR-5 OS analysis from the point of progression on idelalisib, not from initiation on idelalisib. Thus, the case for the DELTA OS outcomes being ungeneralisable to NHS England were less clear cut than the ERG had originally thought. The ERG noted this in its critique of the company's technical engagement response, and suggested that inclusion of the DELTA patients may still provide a useful scenario analysis given the uncertainty around the OS survival outcomes expected for relapsed of refractory FL patients following three or more prior lines of therapy in routine NHS clinical practice.

3. Section 3.9 – Company approach to adjusting the SCHOLAR-5 data

In response to the committee's concerns, the company have provided more details/clarity on the comparative analysis of SCHOLAR-5 with ZUMA-5, noting its design and analysis are in line with NICE DSU guidance. The SCHOLAR-5 study was designed to provide comparative evidence for those meeting the eligibility criteria for ZUMA-5, and the company describe how prognostic and potentially effect modifying variables were identified and prioritised for inclusion in propensity score weighting. They note that the ideal of including all such variables needs to be balanced with sample size implications. They also highlight the sensitivity analysis they undertook to explore alternative methods, including propensity score matching and inverse probability treatment weighting (IPTW) – which produced consistent findings.

The ERG acknowledges the company's points, and note that full details were provided in a separate technical report at the time of the main submission (Kite, confidential data on file). There are obvious challenges to estimating comparative effectiveness estimates from real world data, particularly when available sample sizes are small and not all prognostic and effect modifying variables can be adjusted for. The committee note that FL subtype was not included in propensity score

weighting, but there were in fact more lower grade subtypes in SCHOLAR-5 than in ZUMA-5, which failure to adjust for may bias in favour of current 4L+ care. There will be substantial uncertainty around the magnitude of the relative and absolute survival benefit whichever statistical approach is used. Of further importance is the selected approach to extrapolating the weighted Kaplan-Meier data for current 4L+ care in the model. As noted in the original ERG report, the parametric curves with best statistical fit to the propensity score weighted OS data from SCHOLAR-5 were dismissed due to implausibility of their long-term extrapolations, and more pessimistic curves with poorer statistical and visual fit to the observed data were favoured. Further uncertainty relates to the inclusion/exclusion of the DELTA cohort. All these issues contribute to substantial uncertainty regarding the long-term survival outlook for those treated with current 4L+ care in the NHS, and the relative and absolute magnitude of benefit that can be expected with axi-cel treatment.

4. **Section 3.12 – Long term survivor predictions**

In response to the committee's concern, the company have provided a graph of the modelled overall survival form long-term and non-long-term survivors in the Appendix to their ACD response.

The graph reflects the assumptions that long-term survivors face a mortality rate that is 1.09 times higher that of that age/sex matched general population from five years, and non-long-term survivors face a mortality rate that is 1.2 times that projected by the chosen parametric survival curve that was fitted to the overall mITT population of ZUMA-5.

The graph provided by the company shows extrapolations of OS for long-term and non-long-term survivors, assuming all those alive at five years ([redacted]), when the assumptions apply, are in each group respectively. An alternative set of curves is provided below, showing the assumed proportional split of five year survivors between long-term and non-long-term survivors, which may help illustrate what is actually happening in the model.

It may be noted that the hazard of death remains lower in non-long-term survivors (NLTS) than it does for those on current 4L+ care over the survival duration of the current 4L+ care cohort. Further, the Weibull extrapolated hazard of mortality for NLTS, tends to the SMR adjusted general population mortality of long-term survivors (LTS) by [redacted], but is adjusted to remain 1.2 times higher (due to way the NLTS adjustment factor (=1.2) is applied to the chosen extrapolation curve).

Based on potential for the chosen Weibull curve to overestimate survival of NLTS, the ERG explored increases to the adjustment factor applied to the curve, to 1.5 and 2. The extrapolated survival is illustrated in figures 2 and 3 for these adjustments respectively.

The ERG also reimplemented a more pessimistic scenario whereby the generalised gamma curve is selected for extrapolation of axi-cel OS, but without upward

adjustment of the extrapolated mortality hazard for NLTS. This predicts a much steeper OS curve for NLTS (figure 4), with the cycle specific hazard of mortality exceeding that of the current 4L+ care arm from [redacted], when [redacted] and current 4L+ care cohort are still alive and [redacted] of the axi-cel cohort are NLTS.

Figure 1 Survival of long-term survivors, non-long-term survivors and the overall cohort (hazard of death in non-long-term survivors held 1.2 times higher than the chosen Weibull extrapolation curve).

Figure 2 Survival of long-term survivors, non-long-term survivors and the overall cohort (hazard of death in non-long-term survivors held 1.2 times higher than the chosen Weibull curve).

Figure 3 Survival of long-term survivors, non-long-term survivors and the overall cohort (hazard of death in non-long-term survivors held 1.2 times higher than the chosen Weibull curve).

Figure 4 Survival of long-term survivors, non-long-term survivors and the overall cohort (generalised gamma selected for extrapolation).

5. Section 3.13 – Long-term survivor utility

The company argue for the application of general population utility for the proportion considered long-term survivors from 5 years – the arguments are primarily based on precedent; i.e. what has been accepted in previous NICE TAs of CAR-T therapies in other indications.

The ERG acknowledges the company's points. The alternative assumption, of applying progression free utility to long-term survivors has minimal impact on the ICER, and the ERG have provided the scenario in Table 1 below which does this.

6. Section 3.15 – Inclusion of NHS England CAR-T delivery tariff

The company outline their concerns regarding the committee's conclusion in the ACD that the CAR-T NHS Tariff (£96,016) provides the best available source to inform the cost that the NHS is paying currently. They highlight the lack of transparency around its calculation and what it captures, and the fact that it has not been used in previous NICE appraisals of CAR-T therapies, including those published since its apparent introduction. The company have requested further details from NHS England under a freedom of information request.

From a methodological perspective, the costs included in an economic evaluation should reflect the value of all health care resources required to treat patients, including staffing, consumables, and justifiable allocations of shared capital and overheads. The ERG has no more information than the company on how the tariff has been calculated and agrees that further clarity and detail would be beneficial. Further, a more detailed costing study of CAR-T delivery, as the company suggest, could be beneficial if the committee chooses to recommend axi-cel for use on the cancer drugs fund.

The company's approach to costing in their submission applies an average hospitalisation cost per day to observed length of stay data from ZUMA-5, to estimate the average admission cost for infusion and monitoring. The average cost per day is calculated using a weighted average (by activity across complication and comorbidity score bands) of the NHS elective inpatient reference cost for "Malignant lymphoma, including Hodgkin and non-Hodgkin" (SA31), divided by mean length of stay data from the hospital episode statistics (see Table 38 of the company submission). Reflecting on this there is potential for the company's approach to underestimate the full economic cost of the infusion and monitoring admission. Based on its clinical expert advice, the ERG understands that the delivery of CAR-T therapy requires increased staffing and infrastructure compared to other admissions for Malignant lymphoma; for example, use of a positive air pressure room and highted staffing levels for intensive monitoring. Increased resource requirements may not be captured in the average HRG for Malignant lymphoma, but it is not clear if they could explain the large difference between the company's cost calculation and the tariff price. The company present further cost analysis in their response, using length of stay data for patients receiving CAR-T therapy in real world setting

(including UK patients) which aligns with their calculation based on ZUMA-5 length of stay data.

It is clear that increases in the cost of the admission will push the ICER for axi-cel upwards. To further explore this uncertainty, the ERG has added further scenarios to Table 1 (see below) that apply percentage increases to the infusion/monitoring admission cost.

7. Section 3.16 – End of life

The company accept that expected survival exceeds 24 months, but state they are disappointed not to be considered end of life. They suggest that axi-cel will be adopted as an end-of-life therapy if recommended for use in England, and used "when other treatment options are no longer effective, in patients with a short life expectancy". This appears to suggest that there could be judicious use of axi-cel in the r/r 4L+ FL population, with it being selected for use in patients most likely to meet end of life criteria.

The ERG accepts that there is heterogeneity in the life-expectancy of the r/r 4L+ FL population*, but no case has been made for the cost-effectiveness of using axi-cel in particular subgroups with shorter life expectancies, or for how such an approach would be operationalised. Based on its own clinical exert advice, the ERG believes that if axi-cel is recommended for use in the r/r 4L+ FL population, it will be used broadly in r/r 4L+ FL patients. Based on SCHOLAR-5 data, it does not meet end of life criteria in this population as a whole.*

The company suggest that had axi-cel been considered under the new TA methods (), then a severity of disease QALY weighting greater than 1 would have applied. They have not, however, provided their calculations.

Using the online QALY shortfall calculator published by the University of York (https://shiny.york.ac.uk/shortfall/), the ERG find that that the absolute QALY shortfall for the population under current care comes to [redacted] *(company base case), and the proportional shortfall comes to* [redacted]*, which does not qualify for a QALY weight >1 (NICE, 2022). Hence, the company's arguments of being disadvantaged by a change in NICE processes do not appear to hold. If the company believe these calculations to be incorrect, they should provide their alternatives.*

Section B - Further scenario analysis, conducted by the ERG, around the company's revised based case

Table 1 below provides the results of further scenario analysis conducted by the ERG, applying the company's revised PAS. This includes the scenarios presented in the ERG critique of the company response to technical engagement, and any additional scenarios identified in the text above.

Table 1 Additional scenario analyses around the company's revised based case

Setting	Company revised base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£40,584	N/A
OS and PFS extrapolation (Axi-cel)	OS, Weibull OS; PFS Weibull (25% of treated patients long-term survivors)	OS, Weibull OS; PFS generalised gamma (no long-term survivorship)	[redacted]	[redacted]	£48,100	£7,516
OS extrapolation (Axi-cel)	OS, Weibull, inflated by factor of 1.2 for non-LTS	OS, generalised gamma, no inflation factor applied to non-LTS	[redacted]	[redacted]	£48,829	£8,245
OS and PFS (Current 4L+ care)	OS, gamma; PFS, exponential (DELTA excluded prior to propensity score weighting)	OS, gamma; PFS, exponential (DELTA included in OS, as per original company submission)	[redacted]	[redacted]	£46,834	£6,250
		OS, lognormal; PFS, exponential	[redacted]	[redacted]	£47,369	£6,785
Health state utility of long-term survivors	Age/sex match general population norms	Progression free utility from Wild et al.	[redacted]	[redacted]	£41,178	£594

Setting	Company revised base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Comparator treatment costs	Capped on PFS	Capped on OS	[redacted]	[redacted]	£35,150	-£5,434
Long-term survivor proportion	25%	15%	[redacted]	[redacted]	£44,768	£4,184
		20%	[redacted]	[redacted]	£42,578	£1,994
Mortality ratio for non-long-term survivors versus full ZUMA-5 4L+ cohort	1.2	1.09	[redacted]	[redacted]	£39,661	-£923
		1.5	[redacted]	[redacted]	£42,806	£2,222
		2	[redacted]	[redacted]	£45,754	£5,170
Infusion and monitoring hospital admission cost	[redacted]	25% increase [redacted]	[redacted]	[redacted]	£41,306	£722
		50% increase [redacted]	[redacted]	[redacted]	£42,028	£1,444
		100% increase [redacted]	[redacted]	[redacted]	£43,472	£2,888

Setting	Company revised base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
		[redacted]	[redacted]	[redacted]	£58,582	£14,657

References

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2. Kite (a Gilead company). A comparison of clinical outcomes from ZUMA-5 (axicabtagene ciloleucel) and the international SCHOLAR-5 external control cohort in relapsed/refractory follicular lymphoma. Non-interventional Final Study Report. Data on File. 2021
3. NICE. NICE health technology evaluations: the manual. Published: 31 January 2022; www.nice.org.uk/process/pmg36

NICE National Institute for Health and Care Excellence

NHS England CAR-T tariff

Information provided to NICE as of 17 October 2022

Summary

- **Tariff value:** £65,415
- **Relevant technologies and indications:** applies to all CAR-T cell therapy technologies and indications currently used for people aged 18 or over
- **Methods overview:** Rapid review of financial inputs and costings of 6 NHS providers of CAR-T services
- **Confidentiality status:** not confidential

Description

Rationale: there is not a 22-23 HRG tariff price that could be used as a proxy for CAR-T tariff

Methods:

- Not a micro-costing approach
- Considered costs over pre-infusion, treatment and post-infusion phases
- Removed overheads from the calculations (about 30% reduction from initial tariff value)
- Adjustments to:
    - Length of stay and acuity of patient cohort
    - Proportion of patients who are able to receive their preconditioning in an ambulatory setting
    - Rebalanced the treatment phase to reflect more recent percentage of patients who are well enough to spend some of the first 28 days post infusion outside of hospital (often in a local hotel instead)
- Adjustments are applied as:
    - 20% reduction to pre-conditioning costs (-£1,734)
    - 33% reduction to inpatient admission costs (-£9,749)
    - 171% increase in the costs associated with hotel stays near the treating centre resulting from reduced hospital length of stay (room and subsistence) (+£1886)
    - Net reduction from original costing of £9,597

25th October 2022

Celia Mayers
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RE: Kite/Gilead response to NHS England CAR T Tariff

Dear Celia,

Thank you for the opportunity to respond to the proposed use by NICE of the revised NHS England CAR-T Tariff (**Revised NHS Tariff**) and related information provided to NICE by NHS England.

In the limited time available, we have reviewed the documents titled "*CAR-T tariff summary to stakeholders*" and "*CAR-T NHSE national costing summary reworked for NICE ID3980 FINAL with % distribution*" (both received on 18 October 2020) together with "*Car-T NHSE national costing original tariff by provider*" (received on 20 October 2022). We note with surprise that the breakdown included in this third document was not included in NHS England's response under the Freedom of Information Act on 1 September 2022 (**FOIA response**), despite the fact that our request specifically asked for an itemised breakdown of pathway costs.

We would be deeply concerned if NICE were to include the Revised NHS Tariff in its assessments as the cost of treatment for CAR-T. For the reasons set out below, we would consider this approach to be procedurally unfair and unreasonable, and with potential adverse ramifications on patient access.

The NHS tariff for CAR-T treatment is used primarily as a mechanism for NHS England to fund individual hospitals for CAR-T treatment and is not designed to represent the cost base that is evaluated by NICE in an appraisal. The current tariff has been embedded within NHS England for three years, without external consultation or validation. In their FOIA response, NHS England explained that "*a CAR-T Finance Working Group used the SmPC for individual products and trial experience of the initial products to establish the individual components of the pathway to build an overall projection of the costs associated with each patient. These overall estimations were then subject to national negotiation discussions between the provider cohort and NHS England to agree an overall tariff, which was considered acceptable to all parties*". The FOIA response further explained that the resulting tariff is a standard value to ensure "*appropriate service reimbursement overall without excessive administrative burden*."

Further, the FOIA response also explains that this service was developed by building on the requirements for allogenic blood and bone marrow transplantation. The proposed tariff is aligned with an allogenic transplant, rather than the autologous transplant, which is a closer match to the cost and treatment burden of CAR-T treatment.

We appreciate that there may be broader reasons why NHS England and trusts might favour retaining the current high level of tariff: for example, there may have been reasons to pay a higher tariff to introduce a new technology into the NHS England. There is a potential conflict in the construction of the tariff, in that it is in the interest of the trusts who provided the estimates to have a higher tariff, and for NHS England to maintain the existing tariff

structure which has been paid for since 2019 without external consultation or validation. How has NICE anticipated and adjusted for this potential conflict?

In line with its Methods Guide, NICE must consider what the true cost of treatment is to the NHS. NICE may consider, but is not bound to apply, the NHS England tariff when determining that cost of treatment. The recommendations that NICE make must apply a clear methodological approach, be evidence based and transparent.

The information provided by NHS England does not:

- provide sufficient transparency on the methods used to calculate the Revised NHS Tariff (or the original tariff on which it is based)
- indicate the evidence on which the calculation, including recent adjustments, was based

To the extent that information has been provided, it raises questions on whether the Revised NHS Tariff includes costs that are not relevant.

We have set out our detailed questions and concerns in the schedule to this letter.

Generally, the concerns that we raised in our response to NICE's ACD ID1685 continue to apply. The information provided does not allow potential issues of double counting to be explored, or a proper assessment of whether all costs reflected are appropriate for inclusion in a NICE assessment. There remain significant questions as to whether the Revised NHS Tariff reflects the true cost of treatment.

We ask that NICE does not incorporate this Revised NHS Tariff and instead applies the cost structure already agreed in the previous appraisals, ID3980 and ID1313.

As noted above, the NHS tariff for CAR-T has not been subject to external consultation or validation. Given its potential impact on access to CAR-T therapies generally (and not just those provided by Kite), full external consultation should take place before any NHS tariff is included in any NICE appraisals.

The requested base case analyses are provided in Appendix A-D of this response.

Please contact me if you have any further queries.

Yours sincerely

A. G. Lundie

Gordon Lundie

Executive Director, Market Access and Reimbursement

Schedule

True cost of treatment

NICE must consider the true cost of treatment that is relevant to the NICE appraisal, which may be different from the tariff cost paid by NHS England.

The information provided by NHS England shows a calculation that starts with the average of costs apparently reported by six Trusts in 2019/20. From the FOIA response, we understand that the original tariff was the result of negotiations to achieve a service reimbursement that was acceptable to all parties. This value has been uplifted to reflect costs in 2022/2023, and then reduced by 30% to remove overheads and further adjusted to reflect certain factors outlined in the *CAR T tariff summary to stakeholders.*

To assess if the Revised NHS Tariff reflects the current, true cost of treatment to the NHS, a number of questions should be addressed, including the following:

1. The Revised NHS Tariff is based on the original tariff, which, as the FOIA response explains, was the result of negotiations to achieve a service reimbursement that was acceptable to all parties. What factors were taken into account in this negotiation, beyond the true cost of treatment? How can the value of these factors be assessed and discounted when determining the appropriate cost of treatment for a NICE appraisal?

2. The original cost information was collected in 2019 and the FOIA response explains that it was based on trial experience of the initial products. Is this sufficiently reflected in the reduction of in-patient costs, or should there be further adjustments? Clinical opinion accepts that the initially anticipated patient burden and costs of CAR-T have not been realised, due to early advances in patient care and identification, and the wider, earlier use of steroids and tocilizumab [1]. Does the Revised NHS Tariff reflect the evolution of clinical practice since 2019?

3. The document *CAR-T NHSE national costing original tariff by provider* shows a breakdown of costs across six Trusts that supports the calculation of the original NHS tariff for CAR-T.
   If this breakdown was used to calculate the original NHS CAR-T tariff in 2019, why was this break down not provided in the FOIA response?

If this breakdown was not provided in the FOIA response because it was only produced after 1 September 2022, why was it produced to support the result of the 2019 calculation, rather than current CAR-T costs?
Why were only six Trusts asked to provide input?

Which Trusts were asked to contribute to the calculation of the original NHS CAR-T tariff in 2019? Were the same Trusts asked to provide the breakdown shown in CAR-T *NHSE national costing original tariff by provider* and also consulted on the allocation of costs in the document *Car-T NHSE national costing summary reworked for NICE ID3980*?

Was the original NHS CAR-T tariff adapted from the tariff or costing for another treatment? If so, with hindsight from 2022, did this provide a suitable basis?
We note from the FOIA response that the CAR-T service was developed by building on the requirements for allogeneic Blood and Marrow Transplantation (BMT) (see section 1.1 of the Service Specification provided with the FOIA response.) A number of elements of the breakdown of the original NHS CAR-T tariff reflect the complexity of bone marrow transplant (allogeneic stem cell transplant) – such as length of hospital stay, nature of apheresis and invasiveness of treatment (and associated costs). However, it has been recognised that CAR-T treatment is not as complex as bone marrow transplant but is more similar to autologous stem cell transplant (see below).

4. The clinical treatment most similar to CAR-T treatment in terms of complexity and NHS activity is autologous stem cell transplant – which has a tariff rate of £17,181 (inflated from 2019/2020 HRG tariff elective SA26A £16,668). What is the explanation for the significant difference that still remains between this tariff and the Revised NHS Tariff for CAR-T?

5. Is it possible to validate the proposed NHS Revised Tariff as the true cost of treatment? (See further questions under **Evidence** below.)

6. Why has a Patient Level Information and Costing System (PLICS) level analysis of patient costings not been carried out, to provide an evidence-based NHS England CAR-T tariff?

7. We understand that the Revised NHS Tariff applies to all CAR-T treatments, and leukapheresis. Leukapheresis is a standard practice for many treatments such as autologous stem cell transplant and we would like to know how the costs applied to CAR-T differ to that used in ASCT for Leukapheresis?

8. How does the Revised NHS Tariff reflect that some patients will reside within a standard patient pathway, and others a complex pathway? The comments in the calculation suggest that the estimates used are based on highly complex patients.

9. What is the basis for the increase of the original £92,000 (for 2019/2020) to £97,598 for 2022/2023? It is not clear how the formula revealed in the calculation reflects inflation.

Evidence

1. What evidence is available to support the cost estimates provided by the six Trusts, on which the Revised NHS Tariff is ultimately based? Did each Trust take a consistent approach in allocating their cost? How has this been derived? Is it based on estimates or actual costs?

2. Is it possible to validate the Revised NHS Tariff, with reference to specific activities and time spent by NHS staff?

3. In determining the cost of treatment to be included in a NICE appraisal, is it sufficient to rely on estimates, or should the cost be calculated by (for example) each provider following a number of patients, and costing each patient across the pathway to arrive at the allocations?

4. In the calculation of the Revised NHS Tariff, it appears that the gross cost of £97,598 has been reduced to £75,076 and then allocated across 105 different cost fields. What evidence supports the cost distribution differentially applied into each field?

   This evidence should be reviewed in order to identify any potential issues of double counting, the relevance of the cost in practice and patient care, as well as its relevance to the NICE appraisal.

Would NICE accept this method of allocation in a manufacturer's submission?

5. How does the calculation of the Revised NHS Tariff reflect significant variations in practice, experience and capacity between provider in the delivery of CAR-T? For example:

   a. **Location of patient in 28 days post-infusion**

   Under the Gilead/Kite CAR-T marketing authorisations, patients are required to remain within proximity of a qualified clinical facility for four weeks. In practice, some London hospitals will discharge patients after 10 days to a local hotel whereas hospitals without this social care arrangement may retain patients in hospital at greater cost. In other instances, the patient's home may be within proximity of the hospital.

   What assumptions have been incorporated in the Revised NHS Tariff about where a patient will stay after infusion, and what evidence supports that this reflects current practice?

   We note that the calculation of the Revised NHS Tariff includes a 33% reduction to in-patient admission costs, and a 171% increase in the costs associated with hotel stays near the hospital resulting from reduced hospital length of stay. What evidence is available to support this level of adjustment? What are the base and revised number of days (i) in hospital and (ii) in a hotel that are reflected in the NHS Revised Tariff?

   b. **Variation**

   There is significant variation between the costs estimated by the six Trusts in the 2019 exercise.

   For example:

   - Trusts A, B and D estimated no cost for radiographers, while Trust E estimated £2,447.
   - For radiologists, the estimated costs spanned from £2,876 (Trust D) to £0 (Trust B)
   - On pathology laboratories, Trust E estimated £1,409, Trust A £11,250 and Trust D £28,497

Where there is such divergence, is it appropriate for the cost of treatment applied by NICE to apply a figure based on a simple average of these estimates?

This variety highlights the need for more evidence-based assessment.

6. How has the thirty percent (30%) reduction in the original NHS tariff, intended to remove overhead costs, been calculated? What is the rationale or evidence for this level of reduction? Were figures other than 30% modelled?

Costs included that may not be relevant

To the extent that it is available, the information provided suggests that the Revised NHS Tariff includes costs that are not relevant to a NICE appraisal:

1. The calculation of the Revised NHS tariff includes £6,514 under the heading of "Identification and work up". It is not clear what this cost represents. To the extent that it reflects the failure of prior treatments (for example biopsy to assess progression) and is not relevant to the decision to prescribe CAR-T, it is not relevant to a NICE appraisal.

   To the extent that it reflects the cost of a second biopsy, it should not be considered in the cost of treatment used in the cost effectiveness model. This is because a second biopsy is not required by clinical practice nor by our marketing authorisations. We note that the second biopsy is not required in other countries and is only a requirement of NHS England.

2. Therapists and counsellors are not routinely considered in the costing of other treatments, for example in the recent appraisal for Trodelvy, despite their services often being provided to patients.

   Would these medical professionals be likely to be allocated to these cancer patients (as a result of their disease) regardless of the decision to treat with CAR-T? If so, is it appropriate for their costs to be included in the NICE appraisal? These costs are highly unlikely to be a marginal additional cost of CAR-T.

3. There is a recognised patient drop-out rate at each stage, with survival at 12 months at approximately sixty percent (60%) [2] [1] [3] [2] [4] [3] [5][4] [6] [5]. How will you apply the tariff to the NICE assessment to accommodate for patients who drop-out at each stage?

4. In the treatment phase, the calculation shows a total of £21,573 of allocated nursing and medical staff cost. What supporting evidence has been collected to validate this number?
   This represents a significant level of care that is equivalent to ITU treatment. However, this is not required for the majority of patients treated with CAR-T, where general ward care following the first week of treatment more regularly occurs. The latest panel data [7] [6] gives us an indication of the real-world ITU admissions rate at 27.8% of all CAR-T patients, where for the majority this was limited to observation/inotropes only.

5. In the treatment phase the calculation includes £9,586 of clinical supplies and pathology costs. It is not clear what this significant sum relates to. Is there evidence to support this cost? For example, there is significant disparity in the costs allocated to clinical supplies and pathology costs by different Trusts (e.g. Trust C: £35,264 v Trust E: £1,409 [See *Car-T NHSE national costing original tariff by provider*]).

6. At the recent review meeting [ID1494], the patient expert described their experience of minimal hospital care after discharge. The calculation of the NHS Revised Tariff allocates a significant cost to the period from Day 28 to Day 100, of £5,351, including a pathology laboratory allocation of £1,144. What activities does this relate to? What proportion of patients require this care?

Technical query

1. Does the figure in C33 of the excel sheet (£75,076) relate to Z33 (£65,415) through a translation of changes? We have analysed these changes, showing of a net reduction of £9,597, however there is a small discrepancy (£64) that is unaccounted for.

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[6] G. A. O. O. L. A. B. N. C. R. e. a. Shah BD, "KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study.," *Lancet,* p. 398(10299):491–502, 2021.

[7] R. C. K. A. e. a. Kuhnl A, "A national service for delivering CD19 CAR-Tin large B-cell lymphoma - The UK real-world experience," *Br J Haematol,* pp. 198(3):492-502, 2022 Aug.

Appendix A – ID3980

In response to the request for ID3980 (Yescarta 3L DLBCL CDF exit), Table 1 presents the deterministic cost effectiveness results with the tariff applied. Compared to the company and ERG base case ICER of £50,480, presented in the public committee slides on 6 September, the use of the NHS England tariff results in an increase to the ICER of ~£9,000.

Table 1: Base-case results (with NHS tariff for CAR T) - ID3980

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59,253

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHSE, National Health Service England; QALYs, quality-adjusted life years.

Notes: [redacted] PAS applied

Appendix B – ID1684

In response to the request for ID1684 (Yescarta 2L DLBCL),

Table ***2*** presents the deterministic cost effectiveness results of ID1684 with the tariff applied. Compared to the company base case ICER of £51,154, the use of the NHS England tariff results in an increase to the ICER of ~£10,000, to £60,289 per QALY gained.

Table 2: Base-case results (with NHS tariff for CAR T) - ID1684

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,289

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

Appendix C – ID1685

In response to the request for ID1685 (Yescarta 4L FL), Table 3 presents the deterministic cost effectiveness results with the tariff applied. Compared to the company base case ICER of £40,584, presented in the public committee slides on 6 September, the use of the NHS England tariff results in an increase to the ICER of ~£11,000.

Table 3: Base-case results (with NHS tariff for CAR T) - ID1685

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Current 4L+ care	[redacted]	[redacted]	[redacted]	–	–	–	–
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,297

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHSE, National Health Service England; QALYs, quality-adjusted life years.

Notes: [redacted] PAS applied

Appendix D – ID1494

In response to the request for ID1494 (Tecartus ALL), Table 4 -Table 6 presents the deterministic cost-effectiveness results with the tariff applied.

Table 4: Base-case results (with NHS tariff for CAR T) - ID1494 Overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
KTE-X19	[redacted]	13.686	[redacted]	[redacted]	-	[redacted]	-
INOTUZUMAB	[redacted]	6.752	[redacted]	[redacted]	6.934	[redacted]	£27,748
FLAG-IDA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,855

Table 5: Base-case results (with NHS tariff for CAR T) - ID1494 Ph- population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
KTE-X19	[redacted]	12.641	[redacted]	[redacted]	-	[redacted]	-
BLINATUMOMAB	[redacted]	4.582	[redacted]	[redacted]	8.059	[redacted]	£38,951
FLAG-IDA	[redacted]	3.222	[redacted]	[redacted]	9.419	[redacted]	£46,773
INOTUZUMAB	[redacted]	6.752	[redacted]	[redacted]	5.889	[redacted]	£31,236

Table 6: Base-case results (with NHS tariff for CAR T) - ID1494 Ph+ population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
KTE-X19	[redacted]	13.614	[redacted]	[redacted]	-	[redacted]	-
PONATINIB	[redacted]	5.388	[redacted]	[redacted]	8.226	[redacted]	£45,321
FLAG-IDA	[redacted]	3.222	[redacted]	[redacted]	10.392	[redacted]	£42,474
INOTUZUMAB	[redacted]	6.752	[redacted]	[redacted]	6.862	[redacted]	£27,042

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

ERG critique of the revised CAR-T therapy Tariff provided by NHS England

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Date completed: **21 October 2022**

Contains: [redacted]

Comment on revised tariff price provided by NHS England

NHS England have provided some further details on the figures underpinning their CAR-T tariff. There is a lack of detail on the actual methods used. From the information provide, the ERG has the following understanding.

The starting point is a set of per patient expenditures, as estimated by 6 NHS trusts, required to establish and deliver a CAR-T service. The cost per patient appears to have been estimated based on treating 24 patients per centre per year.

These expenditures were reported by trusts against direct staff, indirect staff, and consumables. This exercise seems to have originally taken place in 2019/20, with the expenditures on each line averaged across trusts and totalled to provide the basis for the tariff. The tariff has been uplifted for inflation each year, equating to a total £97,598 in 2022/23 prices.

NHS England have provided some further details on how they have now revised/adjusted the current tariff. They state that they have removed overheads which were fully absorbed in the original lines of expenditure (adding 30% to directly incurred salary and consumable costs). The effect of this is to reduce the total expenditure (and tariff) by approximately 23% (i.e. from £97,598 to £75,076). NHS England note that the revised tariff now represents the marginal cost of treating a patient.

NHS England note further adjustments to account for changes in assumptions around: 1) length of stay and acuity of care; 2) the proportion of patients able to receive pre-conditioning in an ambulatory setting; and 3) the percentage of patients who are well enough to spend some of the first 28 days post-infusion outside of hospital (often in a local hotel instead). These adjustments translate into a 20% reduction in preconditioning costs (-1734), a 33% reduction in inpatient admission costs (-9,749), but a corresponding 171% increase in hotel costs (+1,867). The net impact on the tariff is a further reduction of £9,616 (75,076 – 9,616 = 65,415). A further breakdown is provided which apportions the £65,415 across different components of the patient's treatment pathway (to 100 days post-infusion). This is show in Table 1 below, alongside what the company have costed for each component in their model.

The ERG finds it difficult to comment on the validity of the overall Tariff figure for the following reasons:

- *We are not party to the assumptions and methods originally used by trusts to estimate their expenditures against the different elements of resource, or how these equate with the actual quantities of resource use that are currently required to deliver of CAR-T therapy.*
- *The expenditure figures do not reveal the quantities of resource assumed or the corresponding costing assumptions, or exactly what the costs incorporate. For example, the guidance in the original summary spreadsheet suggests trust were instructed to exclude lymphodepletion from reported expenditures but then the tariff breakdown apportions a proportion of overall expenditure to pre-conditioning (Table 1).*
- *It is not clear if the original expenditure estimates provided by trusts are based on actual data/experience, or projections of what they thought they would need to treat a given number of patients. There is a note in the summary worksheet suggesting that costs were to be based on PLICs, which may suggest they were based on experience of treating patients.*

- *The throughput for calculating expenditure per patient, and potential for economies of scale is not clear. If the calculations account for fixed investment costs for setting up a new service, economies of scale may be realised as provision/throughput increases. Alternatively, per patient costs may reduce if new infrastructure is shared across other specialties and indications.*
- *NHS England state that as part of their revisions, overheads have been removed from the original costs, but this would seem inappropriate. It is recognised that costs included in an economic evaluation should reflect the value of all resources used: staffing, capital, consumables, and an appropriate allocation of shared overheads. So, to remove overheads does not seem well justified.*
- *The stated adjustments to costs for pre-conditioning care, length of stay (for infusion), and acuity of care are not transparently described or justified, and the original assumptions are not clear on this either; i.e. what has been assumed originally with respect to length of stay and acuity of care for estimating expenditures?*

The CAR-T tariff obviously accounts for higher staffing ratios than those accounted for in more general malignant lymphoma admission costs that the company use to estimate their admission costs. It also includes hotel costs, to allow patients to stay within the locality of the treatment centre, which are not included in the company model. However, the tariff breakdown seems to suggest that any scenario that its application in the company's model will double count leukapheresis and preconditioning costs which are included separately, and it may also double count specific adverse events.

Given these uncertainties, the ERG has provided the following scenarios for consideration:

1) *Application of the revised CAR-T Tariff with the company's leukapheresis, preconditioning, infusion/monitoring, and health state costs for the first 112 days (4 cycles) removed from the model.*
2) *Application of the revised CAR-T Tariff with the company leukapheresis, preconditioning, infusion/monitoring, health state costs for the first 112 days, and specific adverse event costs removed from the model (this does not include adverse events assumed to result in ICU admission and high cost drugs, which are explicitly excluded from the tariff).*

Given the uncertainties related to the resource use assumptions underpinning the NHS England tariff, the ERG suggests further scenarios that a) inflate the company's infusion/monitoring admission costs to account for the higher levels of staffing required to deliver and monitor CAR-T therapy compared to other malignant lymphoma admissions, and b) account for hotel costs to allow patients to stay local to the treating centre up to day 28 following discharge from hospital.

The challenge here is determining and justifying an appropriate inflation factor for the admission costs. Assuming the base HRG for lymphoma reflects admissions to general haematology wards with nurse to patient ratios of 1:6, and that CAR-T therapy admissions on balance require a nursing ratio more in line with high dependency (level 2) care (1:2), then nursing costs can be expected to be approximately 3 times higher for CAR-T admissions. Assuming medical time and other resources are also increased by this factor, we assess a scenario (3) that inflates the company's infusion admission cost estimate by 3, but otherwise retains the company's cost assumptions. Note, this is a rough calculation which has not been clinically validated but is provided for discussion.

With respect to hotel costs, we assess a scenario (4) that multiplies the average number of days between discharge from hospital and day 28 by a going rate for hotel accommodation (£150 per night).

Finally, scenario (5) applies the combined changes in (3) and (4). Results of these scenarios are provided in Tables 2 and 3, showing the impact of changes around the company and ERG base cases from appraisal committee meeting two, respectively. A separate confidential appendix provides a set of results with confidential discounts applied to comparator and subsequent treatments.

Table 1 Comparison of costs to 100 days based on the NHS England revised Tariff and the company's modelling assumptions

	Pre-infusion phase			Treatment phase (infusion + 28 days)			Post infusion (+28 to 100)	Total
Estimates	Identification and work up	Leukapheresis	Pre-conditioning	Straightforward inpatient admission	Early follow up close to treatment centre	Adverse Events	Follow up post discharge to home	
Company	0	[redacted]	£2,881	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tariff	£6,514	£2,459	£6,935	£19,499	£11,588	£13,070	£5,351	£65,415

Notes: [a] Health state health care resource use costs incurred during the first 28 day model cycle; [b] AE costs incurred up to 112 days in the model (includes tocelizumab and ICU admissions for a percentage with CRS, which are excluded from the tariff); [b] Incudes health state health care resource use costs from 28 days up to 112 days in the model.

Table 2 Scenario analysis on company base case, around the CAR-T therapy infusion and monitoring costs

Setting	Company revised base case (ACM 2)	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Company base case			[redacted]	[redacted]	£40,584	N/A
CAR-T delivery costs	Leukapheresis: [redacted] Preconditioning: £2,881 Infusion/monitoring: [redacted] Adverse events [redacted] Health state costs [redacted]	1) Apply NHS England Tariff: £65,415, remove company Leukapheresis, Preconditioning, Infusion/monitoring, and Health state costs (first 112 days).	[redacted]	[redacted]	£50,718	£10,134
		2) Apply NHS England Tariff: £65,415, remove company Leukapheresis, Preconditioning, Infusion/monitoring, Health state costs (first 112 days), and AE costs.	[redacted]	[redacted]	£49,972	£9,388
		3) Company costing, but with inflation of infusion admission costs by a factor of 3 (to account for increased acuity).	[redacted]	[redacted]	£46,360	£5,776
		4) Company costing, but with hotel costs applied for: 28 - [redacted] = [redacted] days ([redacted])	[redacted]	[redacted]	£41,018	£434
		5) 3 and 4 combined	[redacted]	[redacted]	£46,794	£6,210

Notes: [a] AE costs incurred in the model up to 112 days, at least some of which are accounted for in the tariff; [b] Follow-up health state costs incurred to 112 days in the model, which will be accounted for in the tariff.

Table 3 Scenario analysis on company base case, around the CAR-T therapy infusion and monitoring costs

Setting	Company revised base case (ACM 2)	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
ERG base case (as per company but with PF utility retained for long-term surivors)			[redacted]	[redacted]	£41,178	NA
CAR-T delivery costs	Leukapheresis: [redacted] Preconditioning: £2,881 Infusion/monitoring: [redacted] Adverse events [redacted] Health state costs [redacted]	1) Apply NHS England Tariff: £65,415, remove company Leukapheresis, Preconditioning, Infusion/monitoring, and Health state costs (first 112 days).	[redacted]	[redacted]	£51,460	£10,282
		2) Apply NHS England Tariff: £65,415, remove company Leukapheresis, Preconditioning, Infusion/monitoring, Health state costs (first 112 days), and AE costs.	[redacted]	[redacted]	£50,704	£9,525
		3) Company costing, but with inflation of infusion admission costs by a factor of 3 (to account for increased acuity).	[redacted]	[redacted]	£47,039	£5,861
		4) Company costing, but with hotel costs applied for: 28 - [redacted] = [redacted] days ([redacted])	[redacted]	[redacted]	£41,619	£440
		5) 3 and 4 combined	[redacted]	[redacted]	£47,480	£6,301

Notes: [a] AE costs incurred in the model up to 112 days, at least some of which are accounted for in the tariff; [b] Follow-up health state costs incurred to 112 days in the model, which will be accounted for in the tariff.

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

Confidential comparator PAS appendix – Revised following the third Appraisal Committee Meeting

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Contains: [redacted] and [redacted] **price information**

In the updated Tables that follow, the NHSE CAR-T tariff is applied at £41,101 per patient rather than the £65,415 originally applied.

Tables 1 and 2 provide the results around the company and ERG base case, respectively, when the axi-cel PAS is a [redacted] and comparator list prices are applied.

Table 1 Scenario analysis on company base case, around the CAR-T therapy infusion and monitoring costs – using NHS England Tariff at £41,101 and new axi-cel PAS ([redacted]) but no comparator/subsequent treatment discounts

Setting	Company revised base case (ACM 2)	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Company base case			[redacted]	[redacted]	£35,337	NA
CAR-T delivery costs	Leukapheresis: [redacted] Preconditioning: £2,881 Infusion/monitoring: [redacted] Adverse events [redacted] Health state costs [redacted]	1) Apply NHS England Tariff: £41,101, remove company Leukapheresis, Preconditioning, Infusion/monitoring, and Health state costs (first 112 days).	[redacted]	[redacted]	£40,182	£4,845
		2) Apply NHS England Tariff: £41,101, remove company Leukapheresis, Preconditioning, Infusion/monitoring, Health state costs (first 112 days), and AE costs.	[redacted]	[redacted]	£39,436	£4,099

Setting	Company revised base case (ACM 2)	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case

Notes: [a] AE costs incurred in the model up to 112 days, at least some of which are accounted for in the tariff; [b] Follow-up health state costs incurred to 112 days in the model, which will be accounted for in the tariff.

Table 2 Scenario analysis on ERG base case, around the CAR-T therapy infusion and monitoring costs – using NHS England Tariff at £41,101 and new axi-cel PAS ([redacted]) but no comparator/subsequent treatment discounts

Setting	Company revised base case (ACM 2)	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
ERG base case (as per company but with PF utility retained for long-term surivors)			[redacted]	[redacted]	£35,855	NA
CAR-T delivery costs	Leukapheresis: [redacted] Preconditioning: £2,881 Infusion/monitoring: [redacted] Adverse events [redacted] Health state costs [redacted]	1) Apply NHS England Tariff: £41,101, remove company Leukapheresis, Preconditioning, Infusion/monitoring, and Health state costs (first 112 days).	[redacted]	[redacted]	£40,771	£4,916
		2) Apply NHS England Tariff: £41,101, remove company Leukapheresis, Preconditioning, Infusion/monitoring, Health state costs (first 112 days), and AE costs.	[redacted]	[redacted]	£40,014	£4,159

Setting	Company revised base case (ACM 2)	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case

Notes: [a] AE costs incurred in the model up to 112 days, at least some of which are accounted for in the tariff; [b] Follow-up health state costs incurred to 112 days in the model, which will be accounted for in the tariff