NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Kite, a Gilead (company)
   - Bloodwise
   - Lymphoma Action
   - NHS England

   Department of Health & Social Care – submitted a 'no comment' response

3. **Comments on the Appraisal Consultation Document from experts:**
   - Peter Clark - NHS England Cancer Drugs Fund Clinical Lead

   Comments on the Appraisal Consultation Document received through the NICE website
   - None

4. **Company appendix of new evidence** –submitted by Kite, a Gilead company (company)

5. **Evidence Review Group critique of company ACD comments** – prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York

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 diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies

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	Company	Kite Pharma, a Gilead company	**Section 3.8** We do not agree with the committee's conclusion that the lack of comparator data means the size of the benefit compared with salvage chemotherapy is unknown. We believe that in the absence of a comparator arm in ZUMA-1, the SCHOLAR-1 dataset provides a robust and relevant historic comparison. In order to reflect the committee's comments we have made several adjustments to the SCHOLAR-1 dataset which are presented in our ACD response Appendix	Comment noted. The committee agreed that the updated approach for adjusting the SCHOLAR-1 dataset was acceptable for decision making. Please see section 3.12 of the FAD.
2	Company	Kite Pharma, a Gilead company	**Section 3.10** In addition to the adjustments made to SCHOLAR-1 which take into account the committee's comments on the applicability of the data source to the UK, we have also presented data from two additional sources to validate the relevance of SCHOLAR-1 as an appropriate data source for comparison to axi-cel. These are presented in our ACD response Appendix	Comment noted. The committee considered this data and concluded that there were limitations to all of the potential data sources for the comparator arm but that using patient-level data from the updated adjustments to the SCHOLAR-1 data was most appropriate. Please see section 3.13 of the FAD.
3	Company	Kite Pharma, a Gilead company	**Section 3.11 and 3.12** In order to reflect the committee's views around SCHOLAR-1, we have made several adjustments to the dataset which are presented in our ACD response Appendix	Comment noted. The committee agreed that the updated approach for adjusting the SCHOLAR-1 dataset was acceptable for decision making. Please see section 3.12 of the FAD.
4	Company	Kite Pharma, a Gilead company	**Section 3.13** We have presented data from two additional sources in our ACD response Appendix.	Comment noted. The committee considered this data and concluded that there were limitations to all of the potential data sources for the comparator arm but that using patient-level data from the updated adjustments to the SCHOLAR-1 data was most appropriate. Please see section 3.13 of the FAD.
5	Company	Kite Pharma, a Gilead company	**Section 3.15** We do not agree with the committee's view that the need for intravenous immunoglobulins treatment after axi-cel is unknown. As stated in our Technical Engagement Response based the current ZUMA-1 data and the National Cancer Institute (NCI) study of axi-cel, intravenous	Comment noted. The committee considered this data. The committee also noted concerns from NHS England's clinical lead for the Cancer Drugs Fund that B-cell ablation is a likely consequence of successful treatment with axicabtagene

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			immunoglobulins (IVIG) was rarely used and not expected to be required over a prolonged period of time. In the ZUMA-1 trial, a total of 8.3% patients received IVIG.	ciloleucel and that longitudinal data on the infection risks associated with CAR-T cell associated agammaglobulinaemia was not yet available. Please see sections 3.15 of the FAD. The committee noted that the company provided scenario analyses in response to technical engagement where it explored the duration of IVIG treatment for people experiencing B-cell aplasia. The committee acknowledged that these changes had little effect on the overall cost-effectiveness results. Please see sections 3.22 of the FAD. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as it was considered an innovative treatment, with plausible potential to be cost-effective if the clinical uncertainty associated with its use could be addressed through collecting more data. Data is expected to be collected on the use of IVIG in NHS practise. Please see sections 1 and 3.31 of the FAD.
6	Company	Kite Pharma, a Gilead company	**Section 3.17** The extrapolation of axi-cel overall survival performed in the original company base case is deemed the most plausible approach and more accurately represents the long-term survival data for axi-cel compared with the ERG base case. We believe the approach adopted by the ERG is not appropriate and represents an unrealistic extrapolation of overall survival in the axi-cel treatment arm. We have presented further data in in our ACD response Appendix to support our overall survival extrapolation method.	Comment noted. The committee noted the further data presented by the company remained confidential and concluded that without seeing these data, the uncertainty in the cure fraction remained. The committee noted that future data-cuts are planned for ZUMA-1 and that these may provide more certainty in the survival extrapolation modelling but based on the available evidence the overall survival gain for axicabtagene ciloleucel was between the company's and the ERG's estimates. Please see section 3.18 of the FAD.
7	Company	Kite Pharma, a Gilead company	**Section 3.18** The full explanation of the impact of retreated patients awaits full release of the two year data follow up.10 patients were retreated with axi-cel, as per trial protocol. Patients that showed a complete or partial response,	Comment noted. The committee was reassured that the effect of retreatment with axicabtagene ciloleucel on overall survival was based on only 2 patients. However, the committee concluded that

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			who relapsed within 90 days of initial infusion were given the option of retreatment where possible, either from a second bag from the first lot of cells produced, or from frozen PBMC. Of the 10 patients, 6 have died at the 12 month stage, 2 patients were given a stem cell transplant (which is possible in clinical practice in the NHS and reflected in the SCT rate in the comparator group) and two patients have been retreated and are potentially contributing to overall survival. We will provide full details on these patients when the 2 year data reporting is finalised.	retreatment adds to the uncertainty around the long-term survival for people having axicabtagene ciloleucel. Please see section 3.19 of the FAD.
8	Company	Kite Pharma, a Gilead company	**Section 3.19** We have presented additional data to show the impact of using higher mortality risks than the general population – these are presented in our ACD response Appendix.	Comment noted. The committee considered this data. The committee acknowledged that the preferred assumption of excess mortality risk for functionally cured patients was not included in the company's revised base case. However, in the scenario analysis presented by the company the change showed little effect on the overall cost-effectiveness results. Please see section 3.20 of the FAD.
9	Company	Kite Pharma, a Gilead company	**Section 3.26** Given the extremely short life expectancy of the majority of patients on standard of care and the gain in overall survival with axi-cel which far exceeds the required 3 month extension, we agree with the committee's decision that axi-cel meets NICE's criteria to be considered a life-extending treatment at the end of life. To further support this decision, we have provided data from additional sources which can be seen in our ACD response Appendix.	Comment noted. The committee considered this data and concluded that using the revised base-case comparator data and its preferred extrapolation for overall survival the predicted mean was around 24 months (the exact value is commercial in confidence). The committee also considered clinical expert opinion and agreed axicabtagene ciloleucel met both of NICE's criteria to be considered a life-extending treatment at the end of life. Please see section 3.29 of the FAD.
10	Company	Kite Pharma, a Gilead company	**Section 3.29** Please note Kite/Gilead have made a formal application to the Cancer Drugs Fund details of which can be seen in our ACD response Appendix.	Comment noted. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as it was considered an innovative treatment, with plausible potential to be cost-effective if the clinical uncertainty associated with its use could be addressed through collecting more data. Please see sections 1 and 3.31 of the FAD.
11	Consultee	Bloodwise	Although all of the relevant clinical evidence has been considered, we feel that it is important to recognise the significant impact of Yescarta on small numbers of people that have participated in clinical trials and the	Comments noted. The committee noted that patient groups and NHS England consider axicabtagene ciloleucel an innovative treatment,

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
			qualitative evidence that is available. As highlighted by Bloodwise in the appraisal committee, for example, we are aware of patients that are alive today that would not have survived had they not received Yescarta. The person we spoke to, to inform our submission explained that he had an extremely positive experience, going from being “riddled with cancer” to being free of transformed follicular lymphoma thanks to CAR-T which enabled him to receive a transplant. He emphasised that although the risk of side-effects was significant, he felt well prepared for them and was comfortable about the risks given that he would otherwise not have survived. In our view, the transformative impact of CAR-T on the small group of people, for whom no other treatments had been successful, should therefore be given further consideration by the committee.	and agreed it represented a step-change in management of refractory or relapsed disease in an area where there is unmet need for more effective treatment options. However, the committee was not presented any additional evidence of benefits that were not captured in the measurement of QALYs. Please see section 3.1 and 3.27 of the FAD. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as it has plausible potential to be cost-effective if the clinical uncertainty associated with its use could be addressed through collecting more data. Please see sections 1 and 3.31 of the FAD.
12	Consultee	Bloodwise	Yes, the interpretations made of the clinical and cost effectiveness are reasonable interpretations of the evidence. We recognise the lack of direct comparative data with salvage chemotherapy and the challenges this poses for the committee in establishing Yescarta’s true cost-effectiveness. However, it is clear that Yescarta is significantly more clinically effective than chemotherapy and we hope that the manufacturer will be able to provide further evidence to demonstrate this.	Comments noted. The committee agreed that axicabtagene ciloleucel was clinically effective [see section 3.8 of the FAD] and considered the updated approach for adjusting the SCHOLAR-1 dataset (submitted by the company after consultation) as acceptable for decision making. Please see section 3.12 and 3.13 of the FAD.
13	Consultee	Bloodwise	No, we disagree with the recommendation that Yescarta is not made available on the NHS at the present time. Although we recognise that much of the data is very early stage and that clear comparative data is lacking, we also emphasise the fact that the committee acknowledges Yescarta’s clinical effectiveness from the data that is available. Given that the challenge is now to establish the degree of this effectiveness, we feel that recommending Yescarta be placed in the Cancer Drugs Fund (CDF) would be a more appropriate decision. In our view, entering Yescarta into the CDF could help to provide crucial	Comments noted. The committee agreed that axicabtagene ciloleucel was clinically effective. Please see section 3.8 of the FAD. The company’s application to the Cancer Drugs Fund (submitted after consultation) was considered by the committee when making its decision. Please see section 3.24 of the FAD. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as it was considered an innovative treatment, with plausible potential to be cost-effective if the

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			real-world data to contextualise the ZUMA-1 trial and address issues of population heterogeneity between ZUMA-1 and SCHOLAR-1. The admission of Yescarta into the CDF could also enable the committee to review the upcoming cut of ZUMA-1 data at the end of the CDF agreement, instead of waiting three years when the final appraisal decision would most likely next be reviewed.	clinical uncertainty associated with its use could be addressed through collecting more data. Please see sections 1 and 3.31 of the FAD.
14	Consultee	Lymphoma Action	We are concerned that this recommendation is not taking into account the specific needs of patients who are refractory to chemotherapy. These patients are unable to have an autologous stem cell transplant. This treatment offers a lifeline to those patients, who otherwise have exhausted comparator therapies, and whose only other option may be a clinical trial or palliative care.	Comment noted. The committee noted that patient groups and NHS England consider axicabtagene ciloleucel an innovative treatment, and agreed it represented a step-change in management of refractory or relapsed disease in an area where there is unmet need for more effective treatment options. However, the committee was not presented any additional evidence of benefits that were not captured in the measurement of QALYs. Please see section 3.1 and 3.27 of the FAD. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as it has plausible potential to be cost-effective if the clinical uncertainty associated with its use could be addressed through collecting more data. Please see sections 1.and 3.31 of the FAD.
15	Consultee	Lymphoma Action	This recommendation seems to be assessing a potentially durable and even curative response with the new technology against a short-lived response with comparators. There is no true comparator as the comparators do not meet the needs of the patients. The lack of a suitable comparator should not therefore restrict access to this treatment.	Comment noted. The committee considered this and recalled that NICE's guide to the methods of technology appraisal states that the committee will normally be guided by established practice in the NHS when identifying appropriate comparators. As salvage chemotherapy is established practice in the NHS, the committee concluded that salvage chemotherapy (excluding pixantrone) was the appropriate comparator. Please see section 3.7 of the FAD.
16	Consultee	Lymphoma Action	With regards to long-term data, this can only come if the treatment is used. The durability of the treatment looks better than any alternatives. This treatment and similar treatments are being used in other parts of the world and for other indications. Could treatment centres in the US give	Comment noted. The committee recognised that more long-term survival data for axicabtagene ciloleucel and further data on post-progression survival would allow for a more robust cost-

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			further advice?	effectiveness estimate. The committee concluded that axicabtagene ciloleucel met the criteria to be included in the Cancer Drugs Fund. Please see section 3.31 of the FAD. Axicabtagene ciloleucel is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies. Please see section 1 of the FAD.
17	Consultee	Lymphoma Action	The patients who might benefit from this technology need treatment urgently. We heard from patients who are being told about this type of treatment and how it would be their best option after failing other treatments, only to learn that they cannot access it via a clinical trial as there is great demand for places and NICE propose not to recommend it. This puts tremendous strain on patients and carers.	Comment noted. The committee noted that axicabtagene represents a step-change in management of refractory or relapsed disease in an area where there is unmet need for more effective treatment options. Please see section 3.1 and 3.27 of the FAD.
18	Consultee	Lymphoma Action	Limiting treatment to specialist centres and to patients most likely to benefit from it (e.g. low ECOG score, refractory to chemotherapy) would enable more information about the treatment to be gathered whilst offering a lifeline to those patients who are most likely to benefit.	Comment noted. The committee recognised that more long-term survival data for axicabtagene ciloleucel and further data on post-progression survival would allow for a more robust cost-effectiveness estimate. The committee concluded that axicabtagene ciloleucel met the criteria to be included in the Cancer Drugs Fund. Please see sections 1 and 3.31 of the FAD. Because of the novelty of the treatment and the logistical considerations, NHS England stated that a phased implementation will be needed. Please see sections 3.33 and 4.1 of the FAD.
19	Consultee l	Lymphoma Action	The main barrier to this recommendation appears to be cost. We hope an agreement can be reached with the pharmaceutical company to allow this treatment to be accessed on the NHS even if only on a limited basis while more robust data are collected.	Comment noted. The committee considered the company's new evidence and updated commercial access arrangement in its decision making. Please see section 3.24 of the FAD. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund

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				as it was considered an innovative treatment, with plausible potential to be cost-effective if the clinical uncertainty associated with its use could be addressed through collecting more data. Please see sections 1 and 3.31 of the FAD.
20	Consultee	NHS England	Axicabtagene ciloleucel is an innovative new treatment which represents a step-change in the treatment of relapsed or refractory diffuse large B-cell lymphoma; a patient population has limited curative options. NHS England would welcome a positive recommendation from NICE, which would give patients access to this ground-breaking new technology and the associated benefits. However, NHS England is supportive of NICE's decision based on the information on clinical and cost effectiveness and modelling available to the committee for consideration based on the available evidence.	Comment noted. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as it was considered an innovative treatment, with plausible potential to be cost-effective if the clinical uncertainty associated with its use could be addressed through collecting more data. Please see sections 1 and 3.31 of the FAD.
21	Consultee	NHS England	A number of issues are highlighted in the Appraisal Consultation Document (ACD) for Kite/Gilead to address and NHS England hopes that these will be addressed to enable NICE to consider these points further.	Comment noted. No changes to the FAD required.
22	Consultee	NHS England	NHS England and Kite/Gilead are continuing to work together to ensure a number of sites across England are ready to deliver a safe and high quality service for patients by the end of autumn 2018. Working jointly with Kite/Gilead and the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE), NHS England aims to introduce new services in a phased manner, ramping up provision to deliver a safe and effective service covering the anticipated patient population by the end of March 2020.	Comment noted. Please see sections 3.33 and 4.1 of the FAD.
23	Consultee	NHS England	While promising patients great clinical benefits, axicabtagene ciloleucel is an ideal candidate for the Cancer Drugs Funds (CDF) due to the uncertainty around longer term clinical outcomes, including overall survival. Allowing more time for clinical trial data to mature during a CDF managed access period and using real world data as an additional source of data could help to address the uncertainties highlighted by NICE.	Comment noted. The company's application to the Cancer Drugs Fund (submitted after consultation) was considered by the committee when making its decision. Please see section 3.24 of the FAD. The committee recommended axicabtagene ciloleucel for use within the Cancer Drugs Fund as it was considered an innovative treatment, with plausible potential to be cost-effective if the clinical uncertainty associated with its use could be addressed through collecting more data. Please see sections 1 and 3.31 of the FAD.

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 18 September 2018 **email:** tacommc@nice.org.uk / NICE DOCS

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]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Section 3.8** We do not agree with the committee's conclusion that the lack of comparator data means the size of the benefit compared with salvage chemotherapy is unknown. We believe that in the absence of a comparator arm in ZUMA-1, the SCHOLAR-1 dataset provides a robust and relevant historic comparison. In order to reflect the committee's comments we have made several adjustments to the SCHOLAR-1 dataset which are presented in our ACD response Appendix
2	**Section 3.10** In addition to the adjustments made to SCHOLAR-1 which take into account the committee's comments on the applicability of the data source to the UK, we have also presented data from two additional sources to validate the relevance of SCHOLAR-1 as an appropriate data source for comparison to axi-cel. These are presented in our ACD response Appendix
3	**Section 3.11 and 3.12** In order to reflect the committee's views around SCHOLAR-1, we have made several adjustments to the dataset which are presented in our ACD response Appendix
4	**Section 3.13** We have presented data from two additional sources in our ACD response Appendix.
5	**Section 3.15** We do not agree with the committee's view that the need for intravenous immunoglobulins treatment after axi-cel is unknown. As stated in our Technical Engagement Response based the current ZUMA-1 data and the National Cancer Institute (NCI) study of axi-cel, intravenous

	immunoglobulins (IVIG) was rarely used and not expected to be required over a prolonged period of time. In the ZUMA-1 trial, a total of 8.3% patients received IVIG.
6	**Section 3.17** The extrapolation of axi-cel overall survival performed in the original company base case is deemed the most plausible approach and more accurately represents the long-term survival data for axi-cel compared with the ERG base case. We believe the approach adopted by the ERG is not appropriate and represents an unrealistic extrapolation of overall survival in the axi-cel treatment arm. We have presented further data in in our ACD response Appendix to support our overall survival extrapolation method.
7	**Section 3.18** The full explanation of the impact of retreated patients awaits full release of the two year data follow up.10 patients were retreated with axi-cel, as per trial protocol. Patients that showed a complete or partial response, who relapsed within 90 days of initial infusion were given the option of retreatment where possible, either from a second bag from the first lot of cells produced, or from frozen PBMC. Of the 10 patients, 6 have died at the 12 month stage, 2 patients were given a stem cell transplant (which is possible in clinical practice in the NHS and reflected in the SCT rate in the comparator group) and two patients have been retreated and are potentially contributing to overall survival. We will provide full details on these patients when the 2 year data reporting is finalised.
8	**Section 3.19** We have presented additional data to show the impact of using higher mortality risks than the general population – these are presented in our ACD response Appendix.
9	**Section 3.26** Given the extremely short life expectancy of the majority of patients on standard of care and the gain in overall survival with axi-cel which far exceeds the required 3 month extension, we agree with the committee's decision that axi-cel meets NICE's criteria to be considered a life-extending treatment at the end of life. To further support this decision, we have provided data from additional sources which can be seen in our ACD response Appendix.
10	**Section 3.29** Please note Kite/Gilead have made a formal application to the Cancer Drugs Fund details of which can be seen in our ACD response Appendix.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bloodwise
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Although all of the relevant clinical evidence has been considered, we feel that it is important to recognise the significant impact of Yescarta on small numbers of people that have participated in clinical trials and the qualitative evidence that is available. As highlighted by Bloodwise in the appraisal committee, for example, we are aware of patients that are alive today that would not have survived had they not received Yescarta. The person we spoke to, to inform our submission explained that he had an extremely positive experience, going from being "riddled with cancer" to being free of transformed follicular lymphoma thanks to CAR-T which enabled him to receive a transplant. He emphasised that although the risk of side-effects was significant, he felt well prepared for them and was comfortable about the risks given that he would otherwise not have survived. In our view, the transformative impact of CAR-T on the small group of people, for whom no other treatments had been successful, should therefore be given further consideration by the committee.
2	Yes, the interpretations made of the clinical and cost effectiveness are reasonable interpretations of the evidence. We recognise the lack of direct comparative data with salvage chemotherapy and the

	challenges this poses for the committee in establishing Yescarta's true cost-effectiveness. However, it is clear that Yescarta is significantly more clinically effective than chemotherapy and we hope that the manufacturer will be able to provide further evidence to demonstrate this.
3	No, we disagree with the recommendation that Yescarta is not made available on the NHS at the present time. Although we recognise that much of the data is very early stage and that clear comparative data is lacking, we also emphasise the fact that the committee acknowledges Yescarta's clinical effectiveness from the data that is available. Given that the challenge is now to establish the degree of this effectiveness, we feel that recommending Yescarta be placed in the Cancer Drugs Fund (CDF) would be a more appropriate decision. In our view, entering Yescarta into the CDF could help to provide crucial real-world data to contextualise the ZUMA-1 trial and address issues of population heterogeneity between ZUMA-1 and SCHOLAR-1. The admission of Yescarta into the CDF could also enable the committee to review the upcoming cut of ZUMA-1 data at the end of the CDF agreement, instead of waiting three years when the final appraisal decision would most likely next be reviewed.

Insert extra rows as needed

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Consultation on the appraisal consultation document – deadline for comments 5pm on 18 September 2018 **email:** tacommc@nice.org.uk / NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lymphoma Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We are concerned that this recommendation denies patients' access to the only type of treatment that may offer a potential cure. There is urgent unmet need for patients who have failed several courses of treatment and whose options are now mainly palliative or a clinical trial. This technology appears to be the only option that offers a potential cure to patients who have failed other therapies.
2	This recommendation does not seem to take sufficient account of the rarity of the indication. Clinical trials in this indication are small because the patient population fit enough for this type of treatment is small.
3	We are concerned that this recommendation is not taking into account the specific needs of patients who are refractory to chemotherapy. These patients are unable to have an autologous stem cell transplant. This treatment offers a lifeline to those patients, who otherwise have exhausted comparator therapies, and whose only other option may be a clinical trial or palliative care.
4	This recommendation seems to be assessing a potentially durable and even curative response with the new technology against a short-lived response with comparators. There is no true comparator as the comparators do not meet the needs of the patients. The lack of a suitable comparator should not therefore restrict access to this treatment.
5	With regards to long-term data, this can only come if the treatment is used. The durability of the treatment looks better than any alternatives. This treatment and similar treatments are being used in other parts of the world and for other indications. Could treatment centres in the US give further advice?
6	The patients who might benefit from this technology need treatment urgently. We heard from patients who are being told about this type of treatment and how it would be their best option after failing other treatments, only to learn that they cannot access it via a clinical trial as there is great demand for

	places and NICE propose not to recommend it. This puts tremendous strain on patients and carers.
7	Limiting treatment to specialist centres and to patients most likely to benefit from it (e.g. low ECOG score, refractory to chemotherapy) would enable more information about the treatment to be gathered whilst offering a lifeline to those patients who are most likely to benefit.
8	The main barrier to this recommendation appears to be cost. We hope an agreement can be reached with the pharmaceutical company to allow this treatment to be accessed on the NHS even if only on a limited basis while more robust data are collected.

Insert extra rows as needed

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 18 September 2018 **email:** tacommc@nice.org.uk / NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Axicabtagene ciloleucel is an innovative new treatment which represents a step-change in the treatment of relapsed or refractory diffuse large B-cell lymphoma; a patient population has limited curative options. NHS England would welcome a positive recommendation from NICE, which would give patients access to this ground-breaking new technology and the associated benefits. However, NHS England is supportive of NICE's decision based on the information on clinical and cost effectiveness and modelling available to the committee for consideration based on the available evidence.
2	A number of issues are highlighted in the Appraisal Consultation Document (ACD) for Kite/Gilead to address and NHS England hopes that these will be addressed to enable NICE to consider these points further.
3	NHS England and Kite/Gilead are continuing to work together to ensure a number of sites across England are ready to deliver a safe and high quality service for patients by the end of autumn 2018. Working jointly with Kite/Gilead and the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE), NHS England aims to

	introduce new services in a phased manner, ramping up provision to deliver a safe and effective service covering the anticipated patient population by the end of March 2020.
4	While promising patients great clinical benefits, axicabtagene ciloleucel is an ideal candidate for the Cancer Drugs Funds (CDF) due to the uncertainty around longer term clinical outcomes, including overall survival. Allowing more time for clinical trial data to mature during a CDF managed access period and using real world data as an additional source of data could help to address the uncertainties highlighted by NICE.

Insert extra rows as needed

NHS England submission for the 2nd meeting of the NICE appraisal of axicabtagene ciloleucel for the treatment of patients with relapsed/refractory diffuse large B cell lymphoma and primary mediastinal B cell lymphoma after 2 lines of systemic therapy

1. NHS England welcomes the improved reimbursement arrangement offered by Gilead for the use of axicabtagene ciloleucel in the Cancer Drugs Fund for this lymphoma indication. [redacted]. NHS England confirms that the structure of the reimbursement offered by Gilead can be transacted by NHS England in the CDF.
2. NHS England also welcomes the confirmation from Gilead that payment for axi-cel will be triggered only when a patient receives infusion of axi-cel. NHS England's authorisation system for the use of axi-cel will play its part in minimising the loss of patients between leucapheresis and infusion.
3. NHS England confirms that it considers it reasonable for the company to use a 10% figure for the rate of stem cell transplantation in the comparator arm. This figure is within the range previously submitted by NHS England to NICE for consideration at the 1st appraisal meeting. NHS England notes that the company has assumed that all of these stem cell transplants are allogeneic in nature. NHS England considers that some will be autologous although the majority is likely to be allogeneic.
4. NHS England notes that the long term overall survival rate in the company's economic model for the comparator arm is 10%. If there is a 10% stem cell transplant rate, then the likely long term rate of survival is likely to be less than 10% as there will be extremely few other long term survivors without high dose chemotherapy and stem cell transplantation. NHS England's experts therefore would put the long term survival rate at about 6%. The company's long term overall survival modelling for the comparator arm could therefore be regarded as being a too optimistic.
5. [redacted]
6.

[redacted]

7. NHS England considers that axicabtagene ciloleucel is a highly promising treatment for a group of patients with a very poor prognosis as a consequence of having failed at least 2 lines of systemic therapy. The median duration of follow up is only 15.4 months which is short for a potentially curative treatment. The short duration of follow-up and its resultant uncertainties on clinical effectiveness translate into modelling assumptions which are key to the determination of cost effectiveness. Both issues would be answered by further follow-up. NHS England is also capable of monitoring the degree and duration of use of immunoglobulin if this is important to the Appraisal Committee. For all of the above reasons, NHS England strongly supports the company proposal for the entry of axicabtagene ciloleucel into the Cancer Drugs Fund in order to provide much greater certainty as to the determination of clinical and cost effectiveness. [redacted]

Prof Peter Clark
NHS England Chemotherapy Clinical Reference Group chair and clinical lead for the Cancer Drugs Fund

September 2018

18 September 2018

Dr Frances Sutcliffe
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RE: Kite/Gilead response to appraisal consultation document (ACD): Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

Dear Frances,

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) on axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115].

Kite/Gilead believe axi-cel represents a paradigm shift in the treatment of selected haematological malignancies and is committed to working with all relevant stakeholders to make axi-cel available to patients in England and Wales.

Based on the issues raised in the ACD, Kite/Gilead have updated the company base case cost-effectiveness analysis to reflect the committee's position and address key concerns and uncertainties. In addition, a revised [redacted] scheme has also been incorporated into the updated base case scenario for the committee's consideration.

We have also been in discussion with the Cancer Drug Fund, and as the maturity of our survival data is a critical uncertainty in the clinical and cost effectiveness of Yescarta®, we have indicated that we would like to be considered a candidate for the CDF.

Please contact me if you have any further queries.

Yours sincerely

Gordon Lundie

Director, Market Access and Reimbursement

Executive Summary

In response to the NICE ACD Kite/Gilead have revised the SCHOLAR-1 dataset as requested and provided an updated [redacted] scheme in addition to providing further UK patient data to support End of Life for axi-cel. With the revised [redacted] the ICER for axi-cel is [redacted] which we hope the committee will view as a cost-effective use of NHS resources.

The Kite/Gilead response to the ACD focusses on four key aspects:

1. **Company revised base case**

Based on the issues raised in the ACD, Kite/Gilead have updated the company base case cost-effectiveness analysis to reflect the committee's position and address key concerns and uncertainties. This includes the following:

- Adjustment of the SCHOLAR-1 cohort for comparative effectiveness results
- Validation of the axi-cel Overall Survival (OS) extrapolation data
- Adjustment to resource use and costs incorporated into the cost-effectiveness model

Table 1 presents the updated company base case results when incorporating the above scenarios and using the axi-cel **list price**:

Table 1: Model results of the updated company base case at list price

	BSC	Axicabtagene ciloleucel	Incremental
Total costs at list price	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER at list price	[redacted]	[redacted]	[redacted]

2. **Updated [redacted] pricing analysis**

The company has an updated [redacted] scheme which includes a [redacted]. This equates to an overall discount of [redacted] off the axi-cel list price. The overall discount and ICER are based on [redacted] (i.e. [redacted]) in the model base case and have also accounted for the discount rate of 3.5% [redacted].

Table *2* shows the results of the updated company base case when this updated [redacted] taken into account.

Table 2: Results of the updated company model base case [redacted] scheme

	BSC	Axicabtagene ciloleucel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

The results show that when the updated [redacted] incorporated into the updated base case analysis axi-cel represents a cost-effective treatment option when applying a willingness to pay threshold of £50K per QALY gained.

3. Validation of BSC OS with additional data sources

Two sources were used to validate the appropriateness of the SCHOLAR-1 dataset for the purposes of decision-making in the axi-cel appraisal:

- A Real-World Evidence (RWE) cohort taken from an audit of patients with DLBCL from an Oxford University Hospitals database
- A subset of the international CORAL study as used by the Evidence Review Group (ERG) in the NICE tisagenlecleucel-T DLBCL ongoing appraisal (ID1166).

As can be seen in Section 3, when comparing the Kaplan–Meier (KM) curves from the Oxford RWE dataset and from the CORAL subset with the adjusted KM curves from the SCHOLAR-1 study (excluding primary refractory and 0% SCT) there is substantial overlap suggesting that the adjusted SCHOLAR-1 dataset reflects real world outcomes and outcomes observed in other relevant clinical trials.

4. Validation of the applicability of End of Life criteria

Kite/Gilead note the comment from the committee that it “acknowledged that axicabtagene ciloleucel did not unequivocally meet the criterion for short life expectancy”. To further support the case for axi-cel to be considered a life-extending treatment at the end of life, data from the Oxford RWE dataset and CORAL subset are presented below in Table 3. Both datasets show a very poor prognosis for the vast majority of patients and that at the 24 month time period approximately 80% of patients had died with very few patients surviving past this period.

Table 3: OS at different time points for different BSC sources – SCHOLAR-1, CORAL and Oxford RWE dataset

	SCHOLAR-1: 0% SCT	**SCHOLAR-1: 10% SCT**	**SCHOLAR-1: 100% SCT**	**CORAL: 0% SCT**	**CORAL: 100% SCT**	**Oxford RWE dataset (excl. ECOG 2-3)**	**Oxford RWE dataset (all ECOG)**
Median OS (months)	4.0	4.5	9.7	3.3	11.1	10.1	5.3
Survival at:							
6 months	34.8%	41.9%	70.1%	29.8%	69.80%	64.3%	48.8%
12 months	16.7%	25.2%	42.5%	16.2%	40.90%	40.1%	27.1%
18 months	15.2%	18.6%	34.6%	13.6%	36.10%	26.7%	18.1%
24 months	10.4%	15.5%	33.0%	13.6%	33.50%	21.4%	14.5%

1. Company revised base case

Adjustment of SCHOLAR-1 cohort for comparative effectiveness results

To account for the uncertainty surrounding the overall survival (OS) data used for the best-supportive care (BSC) arm that axi-cel is compared against, further scenarios were tested. The original company base case (in the original company submission and evidence review group [ERG] report) used the SCHOLAR-1 data, excluding for ECOG 2-4 patients (but still includes patients with unknown ECOG status), which results in [redacted] of patients receiving stem cell transplant (SCT). The inclusion of ECOG unknown status patients was criticised by the ERG as being potentially biased. The ERG preferred base case therefore excluded both ECOG 2-4 and patients with an unknown ECOG status. Although this better matched the ZUMA-1 trial in terms of baseline ECOG status, it resulted in an unrealistically high proportion of patients (41%) receiving SCT. Based on clinical opinion (Cancer Drug Fund discussions and tisagenlecleucel appraisal meeting), approximately 10% of patients would receive SCT in clinical practice after undergoing 2 or more lines of systemic treatment; in this updated analysis, the SCHOLAR-1 data has therefore been revised and adjusted to reflect this more clinically plausible SCT proportion for the BSC arm.

To ensure SCHOLAR-1 is more comparable to the ZUMA-1 population, the updated analysis based on patient level data for SCHOLAR-1, patients with an ECOG 2-4 and an unknown ECOG status were excluded, in line with the ERG preferred approach. This reduced the SCHOLAR-1 sample size from 562 (overall evaluable patients for OS) to 188 (excluding ECOG 2-4 and unknown). Furthermore, to be in line with the axi-cel EMA label, primary refractory patients were also excluded. This further reduces the sample size from 188 to 133 (excluding primary refractory patients). Among the 133 remaining patients, 67 (50.4%) underwent SCT. To adjust the SCT proportion in this population for OS, the ERG approach outlined in the NICE ACD slides for Tisagenlecleucel-T diffuse large B-cell lymphoma (DLBCL) appraisal (ID1166) was used.[1] For this, firstly OS for the SCHOLAR-1 population who underwent SCT (n=67) (i.e. the SCT population) was obtained and survival parametric curves were fitted to the OS Kaplan Meiers (KM) for this SCT population. Then, the same was done but with patients who did not receive SCT (i.e. non-SCT population), the remainder of the population, representing 66 patients (49.6%). This therefore gave the lower and upper bound OS in terms of the proportion of patients receiving SCT. From these two OS curves, in line with the method adopted by the ERG for the ID1166 appraisal, a weighted average OS can be obtained to represent OS for a specified proportion of patients receiving SCT. For example, in the updated company base case where 10% SCT is assumed, the OS

was estimated by using a weighted average: (0.9 * OS for the non-SCT population) + (0.1 * OS for the SCT population).

Figure 1 presents the KMs and best fitting parametric curves (Gompertz) for the no SCT and SCT populations (SCHOLAR-1 with ECOG 2-4 and unknowns and primary refractory patients excluded) and the derived curve fit for the base case 10% SCT population.

Figure 1: Overall survival of BSC: SCHOLAR-1 (ECOG 0-1 only and excluding primary refractory) with 10% SCT

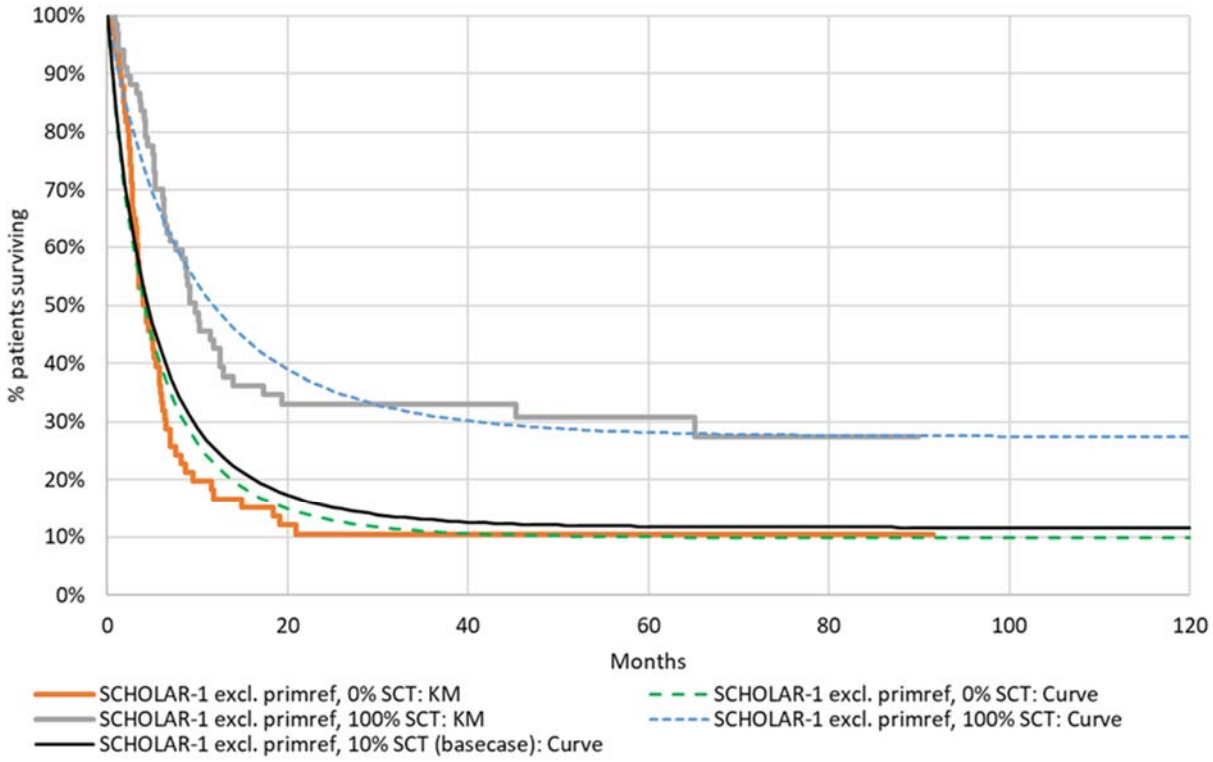


Table 4 presents the OS at different time points for the three SCHOLAR-1 scenarios presented in Figure 1. For the 100% ST and the 0% SCT scenarios, the OS based on the KM was reported; for the 10% SCT (model base case), the OS based on the curve fit (Gompertz) data was reported.

Table 4: OS at different time points for different SCHOLAR-1 scenarios

	100% SCT (based on KM)	10% SCT (base case, based on model result)	0% SCT (based on KM)
6 months	70.1%	41.9%	34.8%
12 months	42.5%	25.2%	16.7%
18 months	34.6%	18.6%	15.2%
24 months	33.0%	15.5%	10.4%
40 months	33.0%	12.6%	10.4%
60 months	30.8%	11.8%	10.4%
80 months	27.3%	11.6%	10.4%

The model results with the updated SCHOLAR-1 data (ECOG 0-1 only and removing primary refractory patients) with 0% SCTs and 10% SCTs are presented in Table 5 alongside the original company base case.

The 10% SCT scenario resulted in an ICER of [redacted], a decrease of 2.7% compared to the original company base case. Note, apart from the change of SCT proportion, the revised 10% SCT base case also removed ECOG unknown and primary refractory patients compared with the original company base case. The ICER impact is smaller compared to QALY impact when the SCT proportions are changed, this is because the lower SCT proportion decreases both the QALYs and SCT cost for the BSC arm.

Table 5: SCHOLAR-1 population with ECOG 2-4 and unknowns and primary refractory patients excluded and varied SCT %: vs original company base case at list price.

Scenario	Incremental costs at list price	Incremental QALYs	ICER at list price	% change from base-case ICER
Original company base case	[redacted]	[redacted]	[redacted]	
10% SCT	[redacted]	[redacted]	[redacted]	-2.7%
0% SCT	[redacted]	[redacted]	[redacted]	-4.7%

Axi-cel OS extrapolation

The extrapolation of axi-cel OS performed in the original company base case is deemed the most plausible approach and more accurately represents the long-term survival data for axi-cel compared with the ERG base case. Whilst the company base case used a mixture cure model for OS, with around 50% long-term survivors the ERG base case used a single parametric curve for OS which converges to progression-free survival [PFS] at around 2 years then follows PFS, resulting around 40% long-term survivors

The company base case and ERG base case predicted 50.6% and 41.0% OS at 2 years, respectively. The company base case appears to fit the tail of the ZUMA-1 KM well which shows 52% of patients alive at 2 years (11 August 2017 cut-off date, with median follow-up of 15.4 months), although it is acknowledged that there are very small numbers at risk at the tail of the KM.[2]

Section 5.2.2 of the ERG report stated “The differences in the cure fraction estimated for axi-cel PFS and OS may result from the survival follow-up not being sufficient to capture the mortality of patients experiencing a late progression, and with longer follow-up it is plausible that the cure fraction for OS for axi-cel might converge towards the cure fraction for PFS.” As a response to this consideration, the ERG used an alternative scenario where OS and PFS converge at around 24 months.

[redacted]

One additional scenario analysis was performed to address the uncertainty of excess mortality for long-term survivors. In this scenario analysis, similar to the approach used by the ERG in the NICE Tisagenlecleucel-T DLBCL on-going appraisal (ID1166), a standard mortality ratio (SMR) of 1.09 was used for alive patients after 60 months for both the axi-cel and BSC arm. The impact on the original company base case ICER of this scenario analysis are presented in Table 6. The use of excess mortality results in an ICER increase of 1.6%

Table 6: Updated excess mortality assumptions at list price.

Scenario	**Incremental costs**	**Incremental QALYs**	**ICER**	**% change from base-case ICER**
Original company base case	[redacted]	[redacted]	[redacted]	N/A
Excess mortality for long-term survivors (SMR=1.09, after 60 months)	[redacted]	[redacted]	[redacted]	1.6%

Resource use and costs

To be in line with the committee's preference to use the same costing assumptions as the ERG, the resource use and costs modifications that the ERG performed were used in the updated company base case. The only exception is the costing of SCT. In the ACD, it was noted that clinical experts did not consider the use of autologous SCT costs (as used in the ERG base case) to be reflective of clinical practice and preferred to use allogeneic SCT costs (as used in the company base case). Therefore, in the company updated base case, the SCT costs were kept as allogeneic. In summary, the following resource use and cost updates were made to be consistent with the assumptions use by the ERG:

- SCT costs were discounted (previously these were assigned as a one-off cost at the start of the model)
- BSC costs for administration are assumed to be monthly costs for an outpatient visit as opposed to a one-off inpatient admission cost
- Cytokine release syndrome (CRS) management involves the cost of 4 ICU days as opposed to 1

The impact on the original company base case ICER of these updated resource use and costing assumptions are presented in Table 7. Applying all three ERG costing assumptions results in an ICER increase of 1.6%, when using the ACD preferred assumptions on SCT (all BSC patients receive autologous SCT).

For completeness, an additional scenario analysis is performed whereby the proportion of BSC patients having autologous and allogeneic SCT is assumed a 50:50 split; this results in an ICER increase of 3.5% (see Table 7).

Table 7: Updated resource use and cost assumptions at list price.

Scenario	Incremental costs	Incremental QALYs	ICER at list price	% change from base-case ICER
Original company base case	[redacted]	[redacted]	[redacted]	N/A
ERG resource use and cost assumption (100% Allo SCT for BSC)	[redacted]	[redacted]	[redacted]	1.6%
ERG resource use and cost assumption (50% Allo SCT for BSC)	[redacted]	[redacted]	[redacted]	3.5%

Updated company base case

Table 8 presents the results of the updated company base case using the list price of axi-cel. This considers the following scenarios:

- SCHOLAR-1 comparative data: ECOG 0-1 only patients and primary refractory patients removed, adjusted OS representing 10% SCT
- Axi-cel OS extrapolation using the company base case approach using mixture cure model for OS
- Resource used and costs following ERG base case, with the exception of SCT costs

Table 8: Model results of the updated company base case at list price.

	BSC	**Axicabtagene ciloleucel**	**Incremental**
Total costs at list price	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER at list price	[redacted]	[redacted]	[redacted]

2. [redacted] pricing analysis

The company has an updated [redacted] scheme which includes [redacted].

[redacted], which has been accepted as implementable by the Cancer Drug Fund and NHS England, delivers a total discount of [redacted]

Table 9: Results of the updated company model base case with [redacted]

	BSC	Axicabtagene ciloleucel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

The overall discount and ICER are based on the estimated [redacted] (i.e. [redacted]) in the model base case and have also accounted for the discount rate of 3.5% [redacted].

3. Validation of best supportive care OS with external data sources

To further support the approach taken to adjust SCHOLAR-1 data used to represent the BSC arm OS in the cost-effectiveness analysis, two additional studies relevant to the BSC arm were explored. The cohort was from an Oxford RWE dataset t(not yet published) which reported OS and PFS of 41 patients with relapsed or refractory DLBCL, PMBCL and TFL who are ineligible for autologous SCT. The company has been working for several months to obtain a UK patient-level dataset but this was not available at the time of submission In February 2018. Compared to SCHOLAR, the Oxford RWE dataset is from a small sample size, although it is a UK-only evidence base. The second data et is a subset of an international CORAL study which was preferred and analysed by the ERG in the NICE Tisagenlecleucel-T DLBCL on-going appraisal (ID1166).[1] Note the overall CORAL study is also one of the four trials included within SCHOLAR-1. This subset of CORAL study assessed survival in relapsed DLBCL patients after failing second-line salvage therapy (n=203) and the key results are published by Van Den Neste.[3] Note, though the company has access to SCHOLAR-1 patient level data, and hence CORAL patient level data, it is not possible to match the CORAL patients in the SCHOLAR-1 study with the subset of CORAL study (n=203) after failing second-line salvage therapy (as reported in by Van Den Neste). Therefore, OS and baseline patient characteristics for the subset of CORAL study reported in this document are based on published literature.[3]

The baseline patient characteristics of the Oxford RWE dataset and the subset of CORAL study compared to SCHOLAR-1 and ZUMA-1 are presented in Table 10.

Table 10: Study baseline characteristics

		SCHOLAR-1		Oxford audit		CORAL[3]
	ZUMA-1 mITT (N = 108)	**All patients (N = 593)**	**ECOG 0-1 (N = 188)**	**All patients (N = 41)**	**ECOG 0-1 (N = 28)**	**All patients (N = 203)**
Age (years)						
Median (Min, Max)	59 (23, 76)	56 (20, 83)	54 (20, 69)	[redacted]	[redacted]	55 (19, 65)
<65 Years, n (%)	81 (75)	509 (86)	181 (96)	[redacted]	[redacted]	203 (100)
≥65 Years, n (%)	27 (25)	84 (14)	7 (4)	[redacted]	[redacted]	0
IPI Score						
0 – 1, n (%)	27 (25)	69 (12)	69 (37)	[redacted]	[redacted]	35 (30)
2, n (%)	33 (31)	61 (10)	54 (29)	[redacted]	[redacted]	N/A
≥3, n (%)	48 (44)	80 (13)	54 (29)	[redacted]	[redacted]	N/A
2-3, n (%)	N/A	N/A	N/A	[redacted]	[redacted]	60 (52)
4-5, n (%)	N/A	N/A	N/A	[redacted]	[redacted]	20 (17)
Not Assessed, n (%)	0	383 (65)	11 (6)	[redacted]	[redacted]	0
Disease Stage						
I-II, n (%)	18 (17)	69 (12)	62 (33)	[redacted]	[redacted]	NR
III-IV, n (%)	90 (83)	149 (25)	119 (63)	[redacted]	[redacted]	NR
IIIS, n (%)	0	0	0	[redacted]	[redacted]	NR
IE, n (%)	0	0	0	[redacted]	[redacted]	NR
Not Assessed, n (%)	0	375 (63)	7 (4)	[redacted]	[redacted]	NR
Total Number of Lines of Chemotherapy & ASCT Received						
1, n (%)	2 (2)	89 (15)	44 (23)	[redacted]	[redacted]	0

2-3, n (%)	65 (60)	464 (78)	143 (76)	[redacted]	[redacted]	203 (100)
≥4, n (%)	**35 (33)**	**37 (7)**	1 (1)	[redacted]	[redacted]	0
*Note: age was not reported in one patient record, hence the values not summing to 100%						

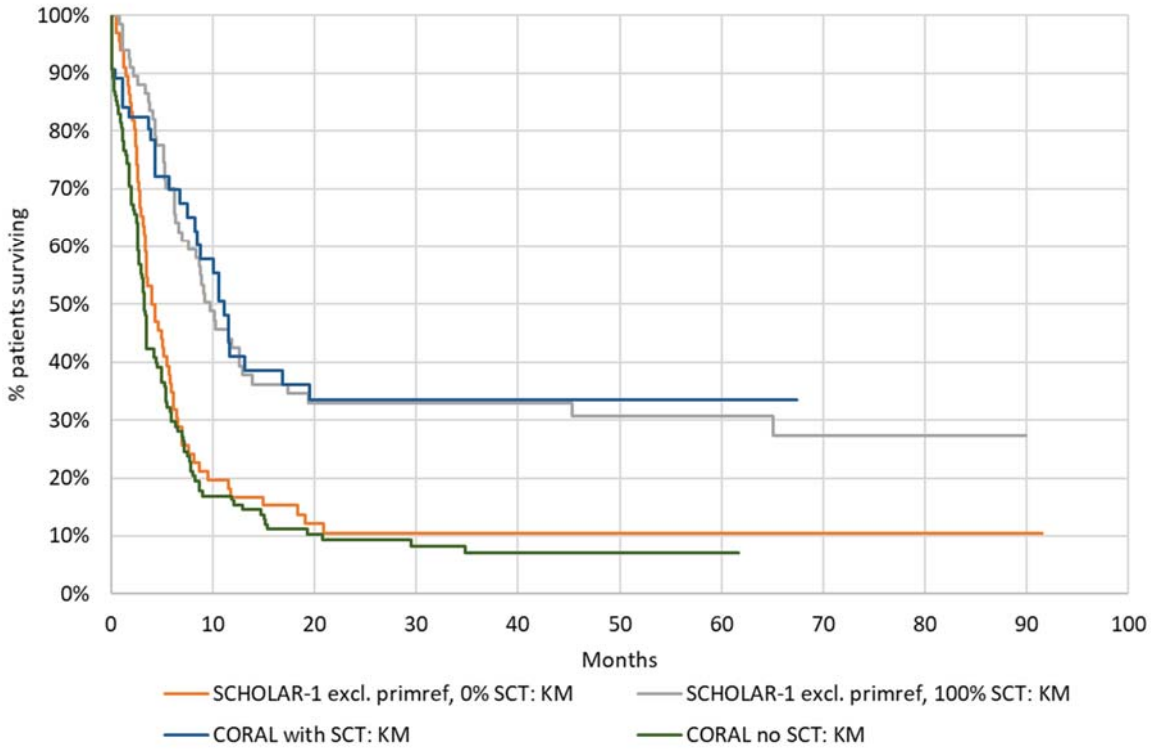
Comparison of SCHOLAR-1 survival compared with CORAL from tisagenlecleucel-T review

The KMs reported in the CORAL publication were split into two populations: patients who have a SCT and patients who do not. These are comparable to the SCHOLAR-1 OS KMs with and without SCT, and the comparison shows that both sub-populations have similar survival between the two sources which is expected as the company expect significant overlap of patients between the two sources.

For the subset of CORAL study, no patient level data was available, thus baseline characteristics were derived from the publication.[3] Information on disease stage was not reported and so this cannot be compared. Table 10 shows that age in the subset of CORAL study is similar to the SCHOLAR-1 population, IPI score appears to be slightly higher and number of treatment lines is restricted to two.

Figure 2 presents the OS KM from SCHOLAR-1 vs CORAL. Two KMs from the publication were digitised to create the curve.

Figure 2: Overall survival of SCHOLAR-1 vs CORAL

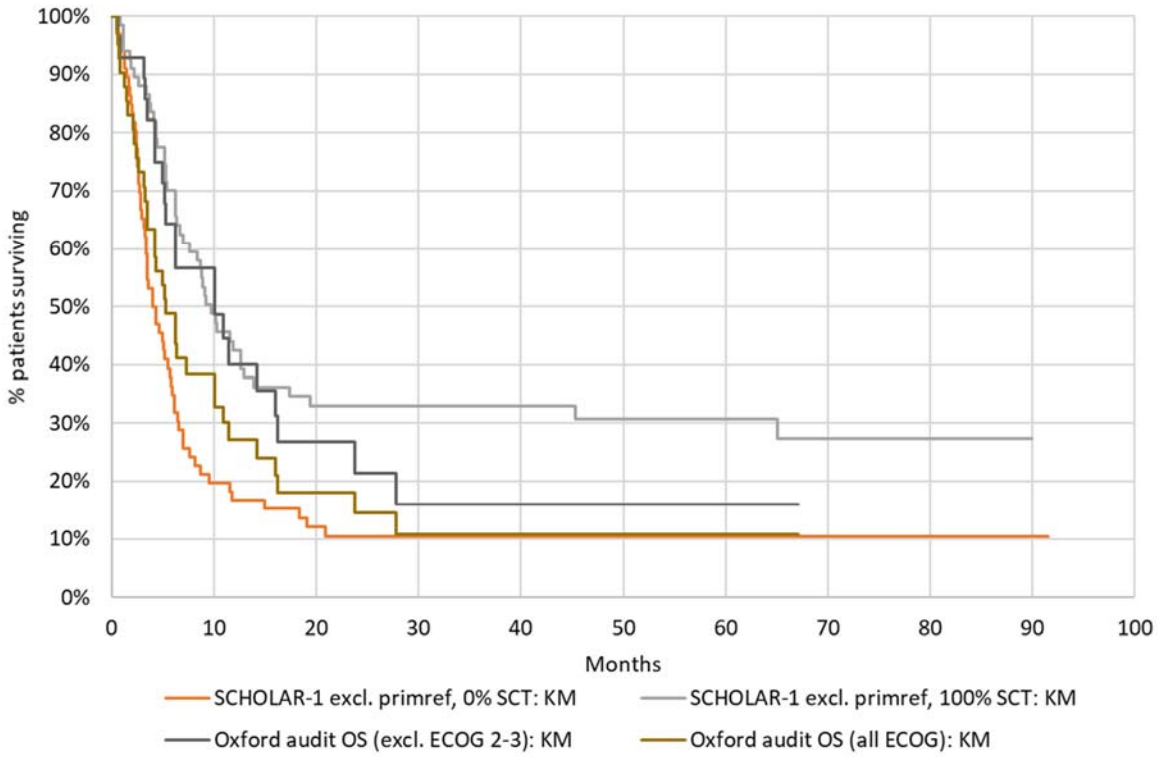


Comparison of the Oxford RWE dataset and SCHOLAR-1

Two OS KMs were also plotted for the Oxford RWE dataset for comparison: one for all patients and for ECOG 0-1 only patients (i.e. excluding ECOG 2-3 patients). Both KMs show better survival compared to the no SCT groups from SCHOLAR-1 and CORAL study. Overall survival is better in the Oxford RWE dataset ECOG 0-1 population, although it should be noted that the baseline patient characteristics of Oxford RWE dataset are different from SCHOLAR-1 and CORAL and the population is very small (N = 28) and thus associated with great uncertainty.

Figure 3 shows that the Oxford RWE dataset KM curve (all ECOG) and the SCHOLAR-1 KM (excluding primary refractory, 0% SCT) largely overlap, supporting the case that the adjusted SCHOLAR-1dataset reflect real world outcomes. When the SCHOLAR-1 data is adjusted for 10% SCT, as in figure 1, it would sit between the two Oxford RWE KM curves in Figure 3, further supporting the fit for the adjusted SCHOLAR-1 population in comparison with real world outcomes

Figure 3: Overall survival of SCHOLAR-1 vs Oxford RWE dataset



4. End of Life

We note the ACD's comments on End of Life criteria in 3.26. The Oxford and CORAL datasets are presented as further supporting evidence for the application of End Of Life criteria for axi-cel. Consistent with input by the clinical experts at the appraisal committee all the data sources show that for the vast majority of patients the outcome is dismal, with survival generally measured in months. The median is short and less than 6 months. 80% or more have died within two years. A small proportion do have longer term survival increasing the mean vs the median but the fact remains that the vast majority of patients have a very poor prognosis and will die within months with current treatment options.

The Oxford RWE dataset shows that median survival is [redacted] months, although at the time of data cut off, [redacted] patients were still alive, one at [redacted] years following BEAM ASCT, [redacted] in complete response (at [redacted] years without follow on therapy) and [redacted] with an average survival of [redacted] years (but all with progressive disease). In total, [redacted] of patients [redacted] had died, only [redacted] survived beyond [redacted] years.

In the CORAL cohort over 80% of patients had died before the 2 year stage, consistent with the Oxford RWE dataset.

Table 11 presents the observed median OS and the OS at different time points for the different BSC scenarios (SCHOAR-1, CORAL and Oxford RWE dataset) that are presented in Figure 2 and Figure 3**Error! Reference source not found.**. These were derived directly from the KM data.

Table 11: OS at different time points for different BSC sources – SCHOLAR-1, CORAL and Oxford RWE dataset

	SCHOLAR-1: 0% SCT	**SCHOLAR-1: 100% SCT**	**CORAL: 0% SCT**	**CORAL: 100% SCT**	**Oxford RWE dataset (excl. ECOG 2-3)**	**Oxford RWE dataset (all ECOG)**
Median OS (months)	4.0	9.7	3.3	11.1	10.1	5.3
Survival at:						
6 months	34.8%	70.1%	29.8%	69.80%	64.3%	48.8%
12 months	16.7%	42.5%	16.2%	40.90%	40.1%	27.1%
18 months	15.2%	34.6%	13.6%	36.10%	26.7%	18.1%
24 months	10.4%	33.0%	13.6%	33.50%	21.4%	14.5%
40 months	10.4%	30.8%	13.6%	33.50%	16.0%	10.8%
60 months	10.4%	27.3%	13.6%	33.50%	16.0%	10.8%

References

1. National Institute for Health and Care Excellence (NICE). Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma ID1166. 2018. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10269.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *NEJM*. 2017.
3. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant*. 2016; 51(1):51-7.

Single Technology Appraisal (STA)

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

ERG commentary on the response submitted by the company to the ACD

Produced by: CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

Date 24/09/2018 (Final version)

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

1 Overview

The company's response to the Appraisal Consultation Document (ACD) included:

1 Cost-effectiveness results from an updated model including a revised company base-case.

2 A proposed confidential [redacted] agreement [redacted].

3 Additional evidence to validate the overall survival estimates and approaches used for best-supportive care (BSC) and axi-cel and to demonstrate the applicability of the End of Life criteria.

The Evidence Review Group (ERG) was requested by NICE to provide commentary and validity checks on the additional analyses submitted by the company in response to the ACD and to identify any areas of remaining uncertainty.

Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. However, the ERG checked the implementation of the proposed changes and successfully replicated the main results presented by the company. The ERG also undertook a series of exploratory analyses to address any areas of remaining uncertainty.

2 ERG commentary on the revised company analysis

2.1 Company revisions in response to the ACD

The company proposed several amendments to reflect the committee's stated preferences and to address other key uncertainties raised in the ACD for axi-cel. The company also provided additional evidence to support these amendments and to reinforce key assumptions and approaches. The company's response covered:

- Adjustment of the SCHOLAR-1 cohort for comparative effectiveness results.
- Validation of the overall survival (OS) extrapolation for BSC.
- Validation of the OS extrapolation for axi-cel.
- Adjustment to resource use and costs incorporated into the cost-effectiveness model.
- Further supportive evidence for the application of the End of Life criteria for axi-cel.

The amendments made by the company to reflect the committee's preferred assumptions and to address areas of uncertainty raised in the ACD are discussed below.

2.2 Adjustments of the SCHOLAR-1 cohort for comparative effectiveness results

Because ZUMA-1 was a single-arm study with no direct comparator data, the company used results from SCHOLAR-1 for the comparator (salvage chemotherapy) in their original submission. SCHOLAR-1 is a retrospective study with pooled data from 4 separate datasets.

The ACD stated that that the committee considered that there was considerable heterogeneity between the ZUMA-1 and SCHOLAR-1 populations and that the proposed adjustments to the SCHOLAR-1 dataset did not adequately account for the differences. The committee also concluded that SCHOLAR-1 was not representative of the population for which axi-cel would be an option in the NHS and that alternative comparator data were needed using alternative data sources (e.g. ORCHARRD subgroups and the Haematological Malignancy Research Network).

In response to the ACD comments, the company provided an updated analysis intended to make the SCHOLAR-1 cohort more comparable to the ZUMA-1 population. This analysis excluded patients with ECOG 2-4 and unknown ECOG status. The company also excluded primary refractory patients to more closely align with the European Medicines Agency (EMA) label. Combining these exclusions reduced the SCHOLAR-1 sample size from 562 patients to 133 patients.

Of these 133 patients, 67 (50.4%) subsequently underwent a stem cell transplant (SCT). This is higher than the transplant rate of 41% assumed in the ERG's original exploratory analysis (excluding ECOG and unknown ECOG status but including primary refractory patients). To address the committee's concern that the rate of SCT in the ERG's exploratory analysis was not reflective of the population for

which axi-cel would be an option in the NHS, the company proposed a further adjustment to the SCHOLAR-1 subgroup data.

The company's adjustment used a similar approach to that proposed by the ERG for the ongoing appraisal of Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies (ID1166). In ID1166, the ERG proposed using separate survival curves conditioned on whether patients were eventually transplanted or not. These conditional survival curves were then used to generate a weighted survival estimate according to different rates of SCT. In ID1166, the ERG considered that this approach provided a way to more explicitly address the uncertainties surrounding the likely SCT rate in routine clinical practice.

Employing a similar methodology to ID1166, the company fitted separate parametric survival curves to the Kaplan-Meier (KM) data for OS for patients who received SCT (n=67) and those who did not (n=66), using the cohort of 133 patients from SCHOLAR-1. The company then generated a weighted OS estimate assuming a 10% SCT rate in routine clinical practice; where the weighted OS estimate = 0.9 * OS for the non-SCT population + 0.1 * OS for the SCT population. The company reported that the gompertz were the best fitting parametric curves for both the SCT and no SCT groups.

Figure 1 summarises the KM data and the parametric gompertz curves for the SCT and no SCT groups, together with the weighted survival function assuming a 10% rate of SCT.

Figure 1: Overall survival of BSC: SCHOLAR-1 (ECOG 0-1 only and excluding primary refractory) with 10% SCT (*Replication of Figure 1 in company response document (p7)*)

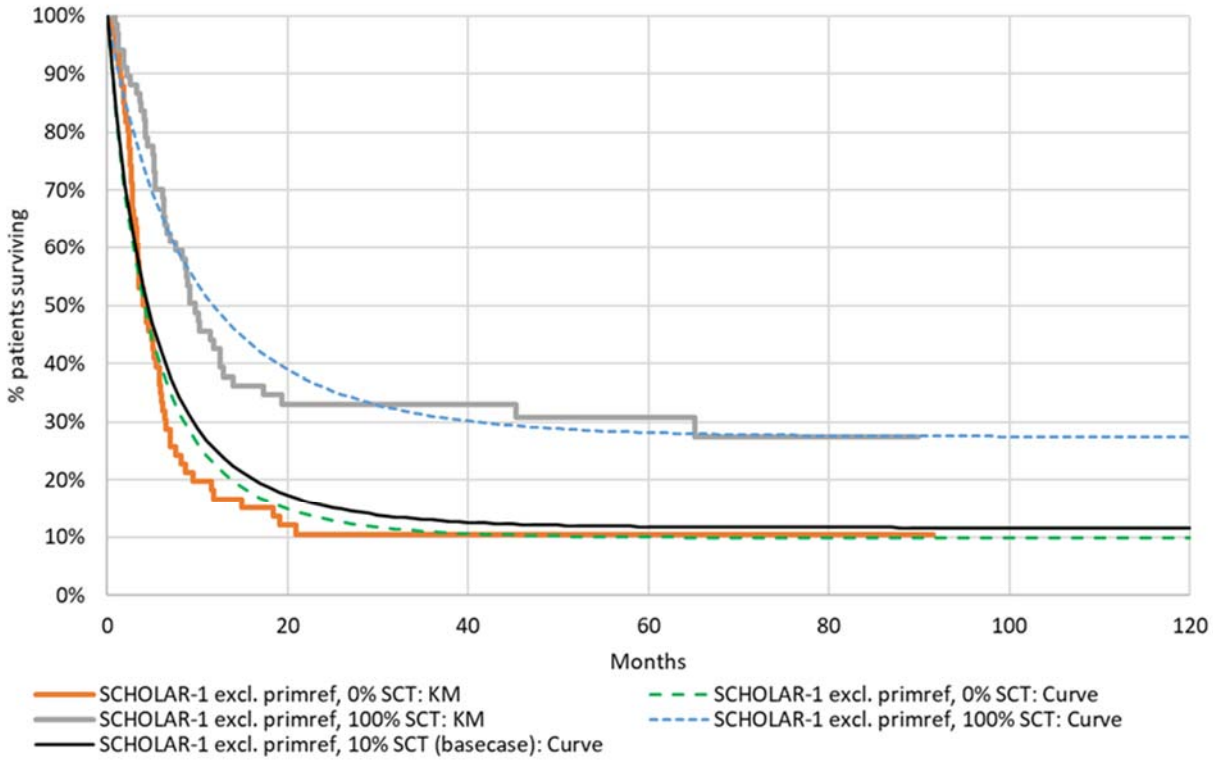


Table 1 summarises the ICER results from the company's original base and scenarios based on the revised SCHOLAR-1 population (i.e. excluding ECOG2-4, unknown ECOG status and primary refractory patients) and assuming either a 0% SCT rate or a 10% SCT rate.

Table 1: **SCHOLAR-1 population with ECOG 2-4 and unknowns and primary refractory patients excluded and varied SCT %: vs original company base case at list price.**

Scenario	Incremental costs at list price	Incremental QALYs	ICER at list price	% change from base-case ICER
Original company base case	[redacted]	[redacted]	[redacted]	
10% SCT	[redacted]	[redacted]	[redacted]	-2.7%
0% SCT	[redacted]	[redacted]	[redacted]	-4.7%

(Replication of Table 5 in company response document, p8)

ERG commentary

The adjustments proposed by the company employ a similar methodology to the approach proposed by the (same) ERG in the ongoing NICE appraisal of Tisagenlecleucel (ID1166). Although the company used a different source to generate the conditional survival curves (SCT, no SCT), they also presented additional data which showed that the data from the separate sources (SCHOLAR-1 and CORAL extension study) appeared comparable (see Section 2.3 below for further details). The ERG also compared predictions (undiscounted life years) using the separate sources and can confirm that the weighted predictions using the revised SCHOLAR-1 cohort and the CORAL extension study are very similar when the same SCT rate is used.

Only limited data were reported by the company on the parametric curves fitted to the SCHOLAR-1 data. Although the gompertz was reported to be the best fitting parametric curve for both the SCT and no SCT groups, no goodness of fit statistics or visual comparisons were presented for other survival functions. The ERG notes that the choice of the gompertz function is consistent with the best fitting survival distribution reported by the ERG in ID1166 based on the CORAL extension data. However, the ERG also highlights that their additional exploratory analysis (reported in later sections) clearly shows that distributional assumptions applied to the OS data for BSC are a key driver of cost-effectiveness, with important implications for the End of Life criteria. Further details are reported in Section 5 of this report.

Despite the limited details reported by the company, the assumptions and data used to model the OS extrapolation for BSC appear broadly consistent with the approach reported by the ERG in ID116. The ACD for ID1166 stated that "*the committee concluded that a single parametric survival model applying a Gompertz curve to overall survival data from the first CORAL extension study is appropriate to model salvage chemotherapy*" (Paragraph 3.14 ACD document for ID1166).

Although the company's revised approach for BSC draws extensively from the approach for the ongoing NICE appraisal of Tisagenlecleucel (ID1166), the ERG notes that the company's assumption that 10% of patients would receive SCT in clinical practice is lower than the 12.5% rate used by the ERG in their alternative base case and accepted by the committee for ID1166.

The company stated that the 10% rate was based on clinical opinion obtained as part of Cancer Drug Fund discussions and the Tisagenlecleucel appraisal meeting. However, a rate of 12.5% appears more consistent with the committee's preferences reported in the ACD for ID1166, where the committee "*concluded that there was uncertainty around the use of stem cell transplant in clinical practice but using data from the first CORAL extension study and assuming that 12.5% of patients have subsequent stem cell transplant was appropriate to model the salvage chemotherapy comparator arm*" (ACD for ID1166, paragraph 3.13).

The ERG concludes that company's approach appears consistent in approach (and in terms of the associated survival predictions) with ID1166, the main difference being the use of a lower SCT rate (10% vs 12.5%). The ERG also notes that while the gompertz was reported to be the best fitting distribution, the company did not provide any measures of statistical goodness of fit or assessment of external validity to support this choice. As highlighted in the End of Life section of this report, the distributional choice is a key driver of cost-effectiveness and an important area of remaining uncertainty.

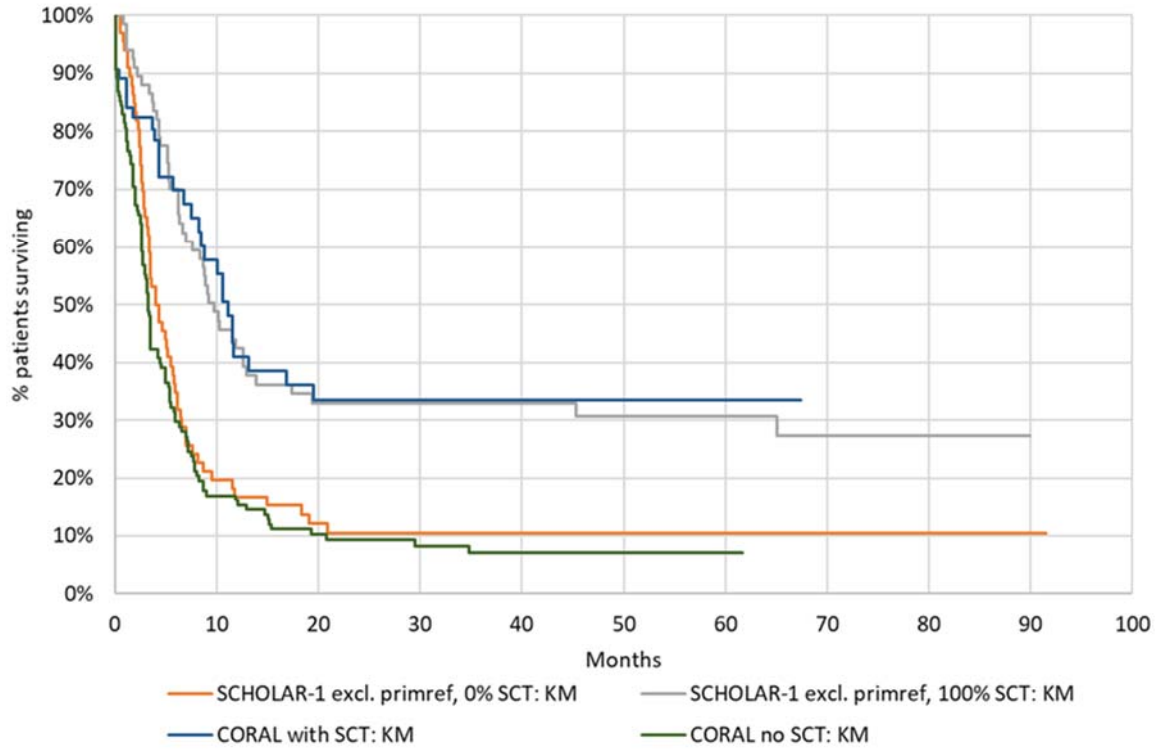
2.3 Validation of the overall survival (OS) extrapolation for BSC

The company explored two additional studies to further support and validate their revised OS extrapolation for BSC. These studies included the CORAL extension study used by the ERG in ID1166 and also results from an unpublished UK audit study (Oxford RWE dataset).

The company compared baseline characteristics between the SCHOLAR-1 population and the CORAL extension study population (reported in Table 10 in the company response document – for all patients in SCHOLAR-1 and the subgroups of patients with ECOG 0-1). The company reported that the age was similar in both studies, although it was noted that in the CORAL study the IPI score appeared slightly higher and the number of treatment lines was also restricted to two.

The company also presented a comparison of the KM OS data from the SCHOLAR-1 population used in their revised base case (i.e. excluding ECOG 2-4, unknown ECOG and primary refractory patients). This is summarised in Figure 2. The company concluded that the KM data from SCHOLAR-1 and the CORAL extension study, for patients with and without SCT, were comparable. The ERG concurs with this conclusion and confirms that the survival predictions are very similar using the separate cohorts.

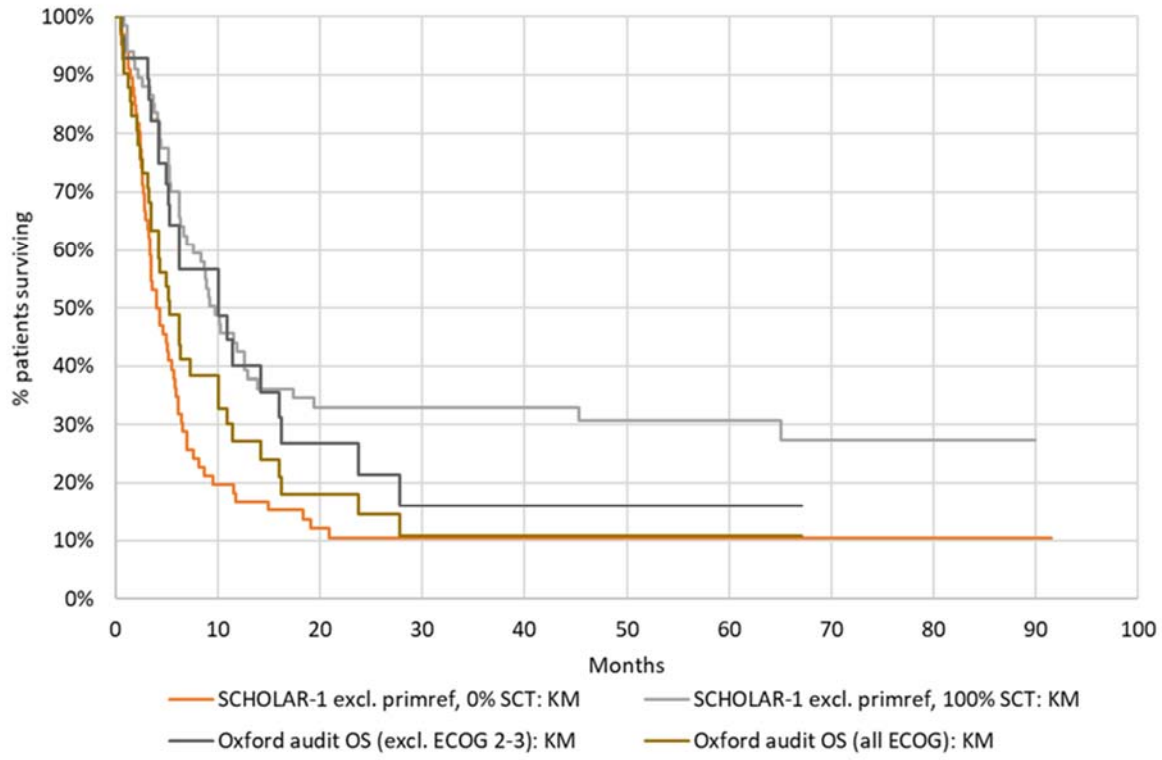
Figure 2: Overall survival of SCHOLAR-1 vs CORAL (Replication of Figure 2 in company response document, p18)



The company response also included reference to an audit study referred to as the Oxford RWE dataset. This dataset included OS and PFS data for 41 patients (including 28 patients with ECOG 0-1) with relapsed or refractory DLBCL, PMBCL and TFL who were ineligible for autologous SCT. The company noted that they had attempted to obtain a UK patient-level dataset for their original submission but this was not available at the time of submission. However, the company response document reported limited details on the audit data (i.e. baseline characteristics and KM curves only).

The company compared baseline characteristics with the SCHOLAR-1 population (reported in Table 10 in the company response document - all patients and ECOG 0-1). The company noted that the baseline patient characteristics of Oxford RWE dataset were different from SCHOLAR-1 and CORAL and the audit population was very small (N = 28). However, the company considered that the audit data provided further evidence supporting the use of the adjusted SCHOLAR-1 population.

Figure 3: Overall survival of SCHOLAR-1 vs Oxford RWE dataset



2.4 Validation of the OS extrapolation for axi-cel.

Background

The company's base case approach within their original submission used a mixture cure model for OS, which assumed a cure fraction of 50% of patients receiving axi-cel. The approach also assumed that cured patients were immediately restored to the age- and gender-matched mortality of the general UK population after axi-cel infusion.

In their original report, the ERG highlighted the difference in the cure fractions across the alternative mixture cure models (between 1% and 53%). This suggested to the ERG that the OS data for ZUMA-1 was not sufficiently mature to be able to estimate a robust cure fraction. The ERG also noted that the differences in the cure fractions estimated for PFS and OS had not been fully addressed by the company. The ERG concluded that the company employed the most optimistic assumptions for the OS estimates for axi-cel.

In their original report, the ERG suggested that the differences in the PFS and OS cure fractions estimated for axi-cel may result from the survival follow-up not being sufficient to capture the mortality of patients experiencing a late progression. With longer follow-up, the ERG considered that

it was plausible that the cure fraction for OS for axi-cel might converge towards the (lower) cure fraction for PFS. To address these concerns, the ERG proposed an alternative 'hybrid' modelling approach using the best fitting single parametric OS curve for axi-cel (log logistic) and, at the point of convergence with the axi-cel PFS curve, OS estimates were subsequently switched to the mortality risk of the general population (age and gender matched). Hence, the ERG's approach resulted in a cure fraction for OS that was the same as the cure fraction for PFS.

The ACD reported that the committee concluded that neither the company's nor the ERG's approaches to extrapolating long-term survival for people having axi-cel were appropriate. Specifically the committee noted uncertainties surrounding the cure fraction for OS based on the company's exploratory analysis which varied between 1% and 53%. The committee also concluded that the ERG's approach of adjusting the axi-cell OS curve was not appropriate because its analysis did not consider the possibility of patients having subsequent salvage chemotherapy after disease relapse with axicabtagene ciloleucel. The committee concluded that the use of the PFS cure fraction could be a conservative extrapolation of overall survival in the axi-cel treatment arm. The committee considered that future data-cuts for ZUMA-1 may provide more certainty but was aware that these would not be available during the appraisal.

Company response to ACD

The company's response to the ACD provided additional arguments and evidence to support their original approach and to demonstrate that this provided a more plausible and accurate representation of the long-term survival data for axi-cel than the ERG's alternative 'hybrid' approach.

The company noted that their base case and the ERG alternative base case predicted 50.6% and 41.0% OS at 2 years, respectively. The company stated that their approach more appropriately captured the tail of the ZUMA-1 KM which shows 52% of patients alive at 2 years (11 August 2017 cut-off date, with median follow-up of 15.4 months). However, the company also acknowledged that there are very small numbers at risk at the tail of the KM.

Although the final point of convergence between OS and PFS in the ERG's alternative approach happened at 52 months, the company noted that by 24 months the curves were already close to convergence. To further support their original approach, the company also reported preliminary results from the updated ZUMA-1 trial. The company stated that these data are confidential and undergoing review. [redacted]

[redacted]

ERG commentary

Due to the confidential nature of the updated ZUMA-1 trial data, the ERG is unable to either confirm or refute the company's findings. Instead, the ERG provides further commentary and additional evidence to reinforce their views that the company's approach is overly optimistic for the extrapolation of OS for axi-cel and to further support the plausibility of the potential longer term convergence of OS and PFS.

In their original report, the ERG concluded that the differences in the estimate cure fractions for PFS and OS suggested either: (i) that there were a significant number of patients who become cured following progression (i.e. due to subsequent therapies) or (ii) the OS data was not sufficiently mature to robustly estimate the cure fraction for OS. In relation to the first issue, the ERG noted that there were ten patients in ZUMA-1 who underwent retreatment with axi-cel after disease progression. The ERG concluded that this may lead to a potentially positive bias in the subsequent OS data for axi-cel, compared to that which would be expected in routine practice. This is because retreatment is not permitted according to the marketing authorisation of axi-cel. As previously stated, in relation to the second issue, the ERG considered that a plausible explanation for the differences could be the more limited time at risk for mortality.

The committee considered that "*the ERG's approach of adjusting the overall survival curve was not appropriate, because its analysis did not consider the possibility of patients having subsequent salvage chemotherapy after disease relapse*" (paragraph 3.17, ACD). As a result, the committee concluded that "*the use of the progression free survival cure fraction could be a conservative extrapolation of overall survival in the axicabtagene ciloleucel treatment arm*" (paragraph 3.17, ACD).

The ERG respectfully disagrees with the committee's conclusions and the company's assertion that the ERG's proposed approach should not be considered. The ERG was presented with no evidence to support the 'curative' potential of salvage chemotherapy after axi-cel and/or any evidence from the company which attempted to address the potential confounding due to subsequent retreatment with axi-cel. The ERG also notes that in the ongoing appraisal of Tisagenlecleucel (ID1166), there appeared to be consistency in the cure fractions reported for OS and PFS (Committee papers, ERG report p83), suggesting that patients were not 'cured' with subsequent salvage chemotherapies following treatment with Tisagencleucel. The ERG highlights that retreatment with Tisagencleucel

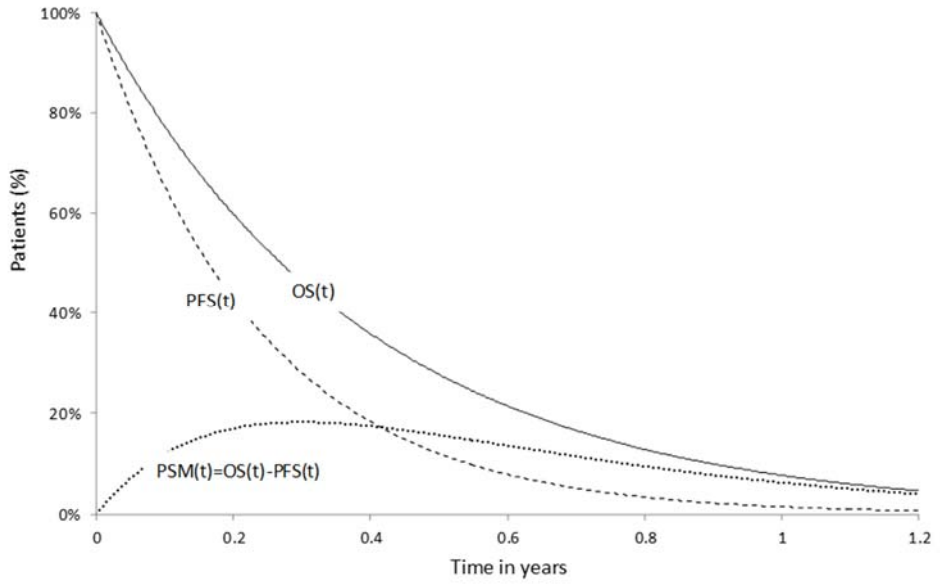
was not permitted in the trials informing ID1166. The ERG also notes that while the company stated that they would provide additional evidence in response to the ACD to demonstrate the impact on axicel retreatment, no evidence was subsequently reported in the company's response.

The ERG would like to highlight that the company did include additional evidence examining post-progression survival within their revised Excel model. However, the data and associated analyses included in the revised Excel model were not reported or discussed in the company's response document. Neither were these data used in the company's revised base-case analysis. Despite the limited data and information included in the Excel model, the ERG considers that these data and analyses may provide important supportive information that should be considered by the appraisal committee.

The modelling approach used in the company's original submission (and their revised base-case) uses a partitioned survival analysis approach. This means that the PFS and OS survival curves are modelled independently and directly inform state membership of the 'Pre-progression' and 'Death' states over time, respectively. The proportion of patients in the 'Post-progression' state during each model cycle is then determined by the difference between the modelled OS and PFS survival curves. The process of determining state membership using a partitioned survival analysis approach is illustrated in Figure 4.

Figure 4: Determining state membership using partitioned survival analysis approach

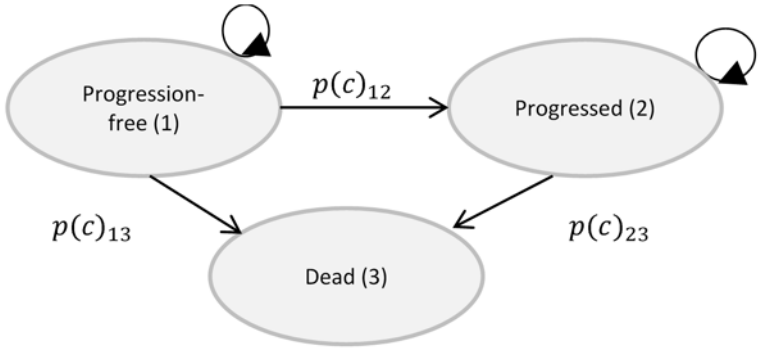
PSM(t) denotes progressed state membership (PSM) as a function of time (t).



The ERG highlights that an alternative modelling approach for axi-cel was included in the revised Excel model but was not discussed or reported in the company's response document. This alternative approach was based on a state-transition modelling approach for axi-cel, informed using multi-state survival analysis. In contrast to the partitioned survival analysis approach (which models OS and PFS independently), the state-transition modelling approach uses explicit structural links between health states (pre-progression, post-progression and death) and uses multi-state survival analysis to jointly estimate transitions based on the OS and PFS data. Importantly, the multi-state survival analysis directly utilises information on both pre- and post-progression survival.

The process of determining state membership using a state-transition modelling approach is summarised in Figure 5.

Figure 5: Determining state membership using partitioned survival analysis approach



Arrows indicate allowed transitions including the possibility that individuals will remain in the same state, arrow labels denote the probability of transitioning from state i to j (pij) in a given cycle, c.

The state transition approach requires three transition probabilities to be estimated: (i) the probability of disease progression, i.e. *p(c)12*; (ii) the probability of death conditional on being in the progression-free state, i.e. *p(c)13* and (iii) the probability of death conditional on being in the progressed state i.e. *p(c)23*. The associated KM data and parametric curves fitted by the company to inform these transitions are summarised in Figures 6-8.

Figure 6 : Transition 1 – Progression-free to progressed state ($p(c)_{12}$)

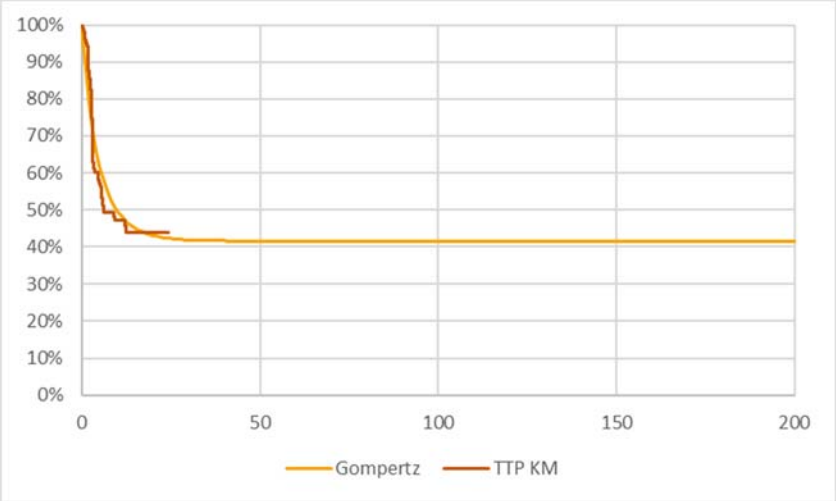


Figure 7: Transition 2 – Progression-free to dead ($p(c)_{13}$)

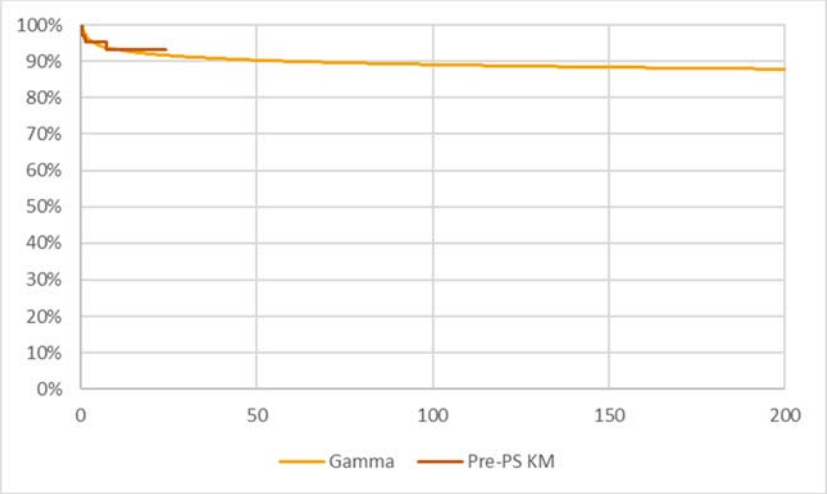
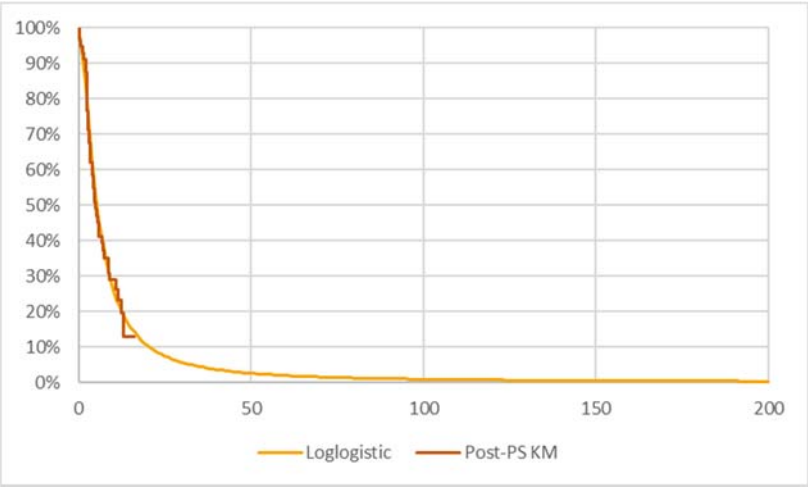


Figure 8: Transition 3 – Progressed to dead ($p(c)_{23}$)



The ERG highlights that Figure 8 is based on an analysis of post-progression survival (Transition 3). Importantly, this figure does not appear to support the 'curative' assumption of subsequent post-progression treatments. This is important because this assumption underpins the validity of the company's OS extrapolation approach for axi-cel. Instead, the ERG considers that this data lends more support to the ERG's approach which assumed that the OS and PFS curves would eventually converge over time.

Figures 9-11 summarise the KM data and the OS extrapolations based on 3 alternative approaches:

(i) The company's revised base-case approach using a partitioned survival modelling.
(ii) The company's state transition modelling approach (included in the company's Excel model but not reported in the company response document).
(iii) The ERG's alternative 'hybrid' modelling approach.

Importantly, all 3 approaches use the same patient cohort and survival data for axi-cel. However, approach (ii) also makes use of post-progression survival data which is not used in either approaches (i) or (iii). Also, approach (iii) includes an additional assumption originally proposed by the ERG to reflect uncertainty in the underlying OS data.

The ERG highlights that the approach which makes greatest use of data (i.e. including pre-progression and post-progression survival from the ZUMA-1 trial), appears to be more similar to the ERG's original proposed 'hybrid' approach than to the company's base case approach.

Figure 9: Company – partitioned survival approach (revised base case approach)

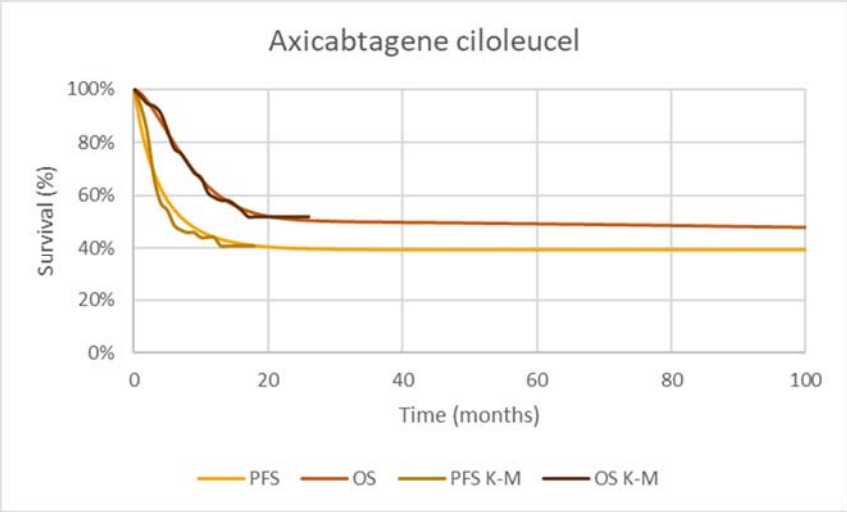


Figure 10: Company – state transition approach (included in Excel model)

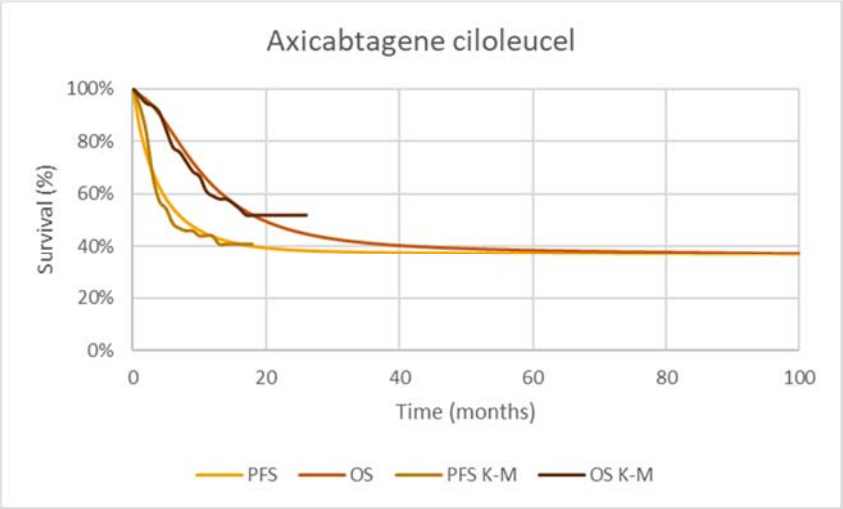
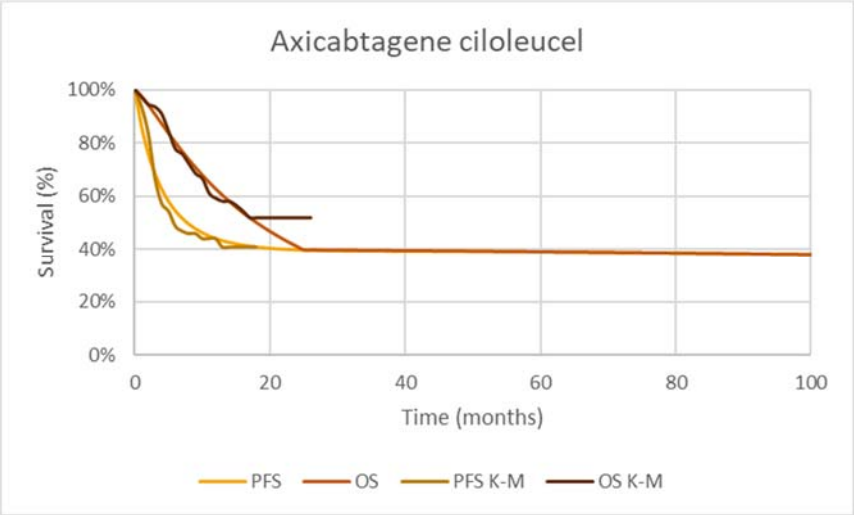


Figure 11: ERG alternative base-case - partitioned survival approach (with ERG assumption of convergence of OS and PFS)



While the ERG acknowledges that there exists considerable uncertainty surrounding the OS extrapolations, the state-transition modelling approach reinforces the ERG's original conclusion that the company's base case approach appears overly optimistic for the extrapolation of OS for axi-cel. Furthermore, the ERG notes that the additional state-transition approach does not support the company's conclusions that the ERG's proposed approach is not plausible and should not be considered further.

Although the state-transition modelling approach also suggests that the OS curve for axi-cel may converge to the PFS curve, the explicit use of the post-progression data indicates that this convergence may happen after a longer time period than the ERG's original hybrid approach. Hence, while it is difficult to conclude that the ERG's approach is conservative based on the assumption that the OS and PFS curves will converge, it can be argued that the ERG's approach maybe conservative in forcing this convergence at an earlier point than suggested by the multi-state survival analysis.

Despite the similarity of approaches (ii) and (iii), the ERG does not consider that it is appropriate to conclude that the company's base-case approach is clinically implausible and hence unsuitable for consideration by the committee in their deliberations. Inevitably, given the immaturity of the OS evidence for axi-cel, significant uncertainties remain concerning how the longer term survival estimates will evolve over longer follow up periods. While the current data appears to lend greater support to approaches (ii) and (iii), it would be unwise to select any single approach as the 'optimal' approach. The ERG also acknowledges that limited information was provided by the company on approach (ii). As a result, the ERG was unable to assess and/or validate the statistical approach used. Given the significant uncertainties surrounding the extrapolation of OS for axi-cel, the ERG's exploratory analyses reports results using all 3 extrapollation approaches.

Finally, the ERG notes that the company also included an additional scenario analysis, where a standard mortality ratio (SMR) of 1.09 was used for alive patients after 60 months for both the axi-cel and BSC arm. This was similar to the approach used by the ERG in the on-going appraisal of Tisagencleucel (ID1166), The inclusion of a longer term excess mortality assumption resulted in a 1.6% increase in the company's original base case ICER. However, this assumption was not subsequently included in the updated company base case.

2.5 Company amendments to resource use and cost

As part of their updated base case, the company also proposed a series of amendments to several resource use and cost assumptions. These amendments were undertaken to align with the committee's preference to use the same costing assumptions as the ERG. The company noted that the only exception to the ERG's proposed amendments concerned the costing of SCT. The ACD reported that the clinical experts did not consider the use of autologous SCT costs (as used in the ERG base case) to

be reflective of clinical practice and preferred to use allogeneic SCT costs (as used in the company base case). Therefore, in the company updated base case, the SCT costs were kept as allogeneic.

In summary, the following resource use and cost updates were made by the company to be consistent with the assumptions used by the ERG and the committee's stated preferences:

- SCT costs were discounted (previously these were assigned as a one-off cost at the start of the model).
- BSC costs for administration were assumed to be monthly costs for an outpatient visit as opposed to a one-off inpatient admission cost.
- Cytokine release syndrome (CRS) management involves the cost of 4 ICU days as opposed to 1.

ERG commentary

The model changes were checked by the ERG and were found to be correctly implemented. The only change proposed by the ERG which was not included related to the ERG's assumption that subsequent SCT would be 100% autologous (compared to 100% allogeneic in the company's original base-case). However, the ERG acknowledges that the company's revision is consistent with the clinical advice expressed during the committee meeting and reflected in the ACD:

"*However, the clinical experts noted the cost of autologous stem cell transplant used in the ERG's base case were not reflective of clinical practice. They explained that autologous stem cell transplants are considered a second-line therapy, so patients with relapsed or refractory disease after 2 previous systemic therapies would have more expensive allogeneic stem cell transplants at this point in the treatment pathway*." (ACD, paragraph 3.21, p20)

Although the company's approach to the cost of subsequent SCT is consistent with the clinical views expressed for this specific appraisal, it should also be noted that in the ongoing appraisal of Tisagencleucel (ID116), the ERG used data on the relative rates of autologous versus allogeneic transplants reported in the CORAL extension study. This study reported that 87.5% of patients receiving SCT in a 3rd line setting received an autologous transplant and 12.5% received an allogeneic transplant (Committee papers, ERG report p135).

The ERG concludes that there is uncertainty both in the absolute rate of SCT in UK clinical practice and the relative use of autologous versus allogeneic transplant. However, the ERG notes that the evidence used from the CORAL extension study reported that autologous transplants were given more often than allogeneic transplants to patients treated in a 3rd line setting. The potential impact of alternative assumptions are further explored by the ERG within their set of exploratory analyses.

The ACD for axi-cel also raised uncertainties concerning the need for intravenous immunoglobulins (IVIG) treatment. In particular, the committee expressed concern that the company had underestimated the effect of this with axi-cel (*ACD, paragraph 3.15, p15*). The ERG highlights that no changes were proposed by the company to their original base-case assumptions. The ERG also notes that in ID1166, the committee accepted the ERG's assumption that B-cell aplasia may persist for up to 3 years (compared to the company's assumption of 1 year). To aid consistency in decision making across the separate appraisals, the ERG's exploratory analysis explores the impact of assuming treatment with IVIG for 3 years.

3 Results from the company's updated base case

Deterministic results from the company's updated base case are summarised in Table 2 (based on axi-cel list price) and Table 3 (based on proposed [redacted] for axi-cel).

As previously discussed, the company's updated base case includes the following changes:

- SCHOLAR-1 comparative data: ECOG 0-1 only patients and primary refractory patients removed, adjusted OS representing 10% SCT.
- Axi-cel OS extrapolation using the company base case approach using mixture cure model for OS.
- Resource used and costs following ERG base case, with the exception of SCT costs.

The combined impact of these changes resulted in a minor improvement in the ICER results (list price analysis) compared to the original company base case [redacted] per QALY). This improvement is due to the larger incremental QALYs predicted with the updated results ([redacted] QALYs) compared to the original base case ([redacted]). The increase in the incremental QALYs is due to the reduction in the QALYs estimated for BSC using the new approach [redacted]

Despite the increase in the incremental QALYs estimated using the company's updated approach, the impact on the ICER is small compared to the company's original base case. This is because there is also an increase in the incremental costs in the updated analysis due to the revised resource use and cost assumptions.

The updated [redacted] results in an ICER of £[redacted] per QALY using the company's updated base case.

Table 2: Updated company deterministic results (list price)

	BSC	Axicabtagene ciloleucel	Incremental
Total costs at list price	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER at list price	[redacted]	[redacted]	[redacted]

Table 3: Updated company deterministic results (including [redacted])

	BSC	Axicabtagene ciloleucel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER with [redacted]	-	-	[redacted]

4 ERG exploratory analyses

The ERG's critique noted that the use of a 12.5% SCT rate for BSC/salvage chemotherapy is more consistent with the ACD recommendations for ID1166. The critique also highlighted that several uncertainties remain, particularly regarding the OS extrapolation for axi-cel. In Section 2.4, the ERG compared 3 alternative extrapolation approaches:

(i) The company's revised base-case approach using a partitioned survival modelling.

(ii) The company's state transition modelling approach (included in the company's Excel model but not reported in the company response document).

(iii) The ERG's alternative 'hybrid' modelling approach.

Given these uncertainties, the ERG exploratory analyses presents results using all 3 extrapolation approaches, assuming a 12.5% SCT rate for BSC. Following these analyses, the ERG also explores the impact of several remaining areas of uncertainty.

The ERG's exploratory analyses are all based on the company's updated [redacted]. Furthermore, given the limited time provided to the ERG to critique the company's response and to undertake additional analyses, all of the ERG's exploratory analyses are based on deterministic results.

Table 4 shows the impact of updating the company's base case using a 12.5% SCT rate for BSC. Increasing the SCT rate BSC from 10% (company's base assumption) to 12.5%, results in a minor increase in the deterministic ICER (increasing from [redacted] per QALY).

Table 4: Updated company deterministic base case results with 12.5% SCT rate for BSC (extrapolation approach [i])

	BSC	**Axicabtagene ciloleucel**	**Incremental**
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER at [redacted] price	[redacted]	[redacted]	[redacted]

Tables 5 and 6 summarise the ICER results using the alternative extrapolation approaches. The ICER of axi-cel increases to £[redacted] and £[redacted] per QALY using the company's state-transition modelling approach and the ERG's original 'hybrid' approach, respectively. The ICER results for these alternative extrapolation approaches are very similar.

Table 5: Deterministic results using the company's state-transition modelling approach for axi-cel OS with 12.5% SCT rate for BSC (extrapolation approach [ii])

	BSC	Axicabtagene ciloleucel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER at [redacted] price	[redacted]	[redacted]	[redacted]

Table 6: Deterministic results using the ERG's 'hybrid' for axi-cel OS with 12.5% SCT rate for BSC (extrapolation approach [iii])

	BSC	Axicabtagene ciloleucel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER at [redacted] price	[redacted]	[redacted]	[redacted]

At first glance, it might appear counter-intuitive that the ERG's 'hybrid' approach results in slightly more favourable ICER's compared to the state-transition modelling approach, given that the ERG's hybrid approach appears to lead to faster convergence of the OS and PFS curves. However, the ERG highlights that the multi-state survival analysis involves simultaneous and joint estimation of the 3 transition probabilities (*1. Pre-progression to death; 2. Pre-progression to progressive disease; and 3. Progressive disease to death*). The joint estimation of these separate transitions results in different predicted survival estimates for both PFS and OS. Although difficult to see from the previous figures

(Figures 9-11), the flattening of the PFS curve using the multi-state survival analysis occurs at a slightly lower survival estimate than when PFS is extrapolated independently. Hence, the reduction in QALY gains resulting from faster convergence (extrapolation approach [ii]) is offset by the additional QALY gains due to the higher survival estimates arising from the flattening of the PFS curve occurring at a higher survival estimate (compared with extrapolation approach [ii]). However, the final ICER results are very similar, despite the differences in the alternative extrapolation approaches (ii) and (iii),

The ERG critique of the company response also raised several additional areas of uncertainty. Firstly, concerning the relative rate of allogeneic versus autologous SCT for BSC. The ERG identified additional evidence used in ID1166 which reported that 87.5% of those patients who subsequently received an SCT received an autologous transplant in a 3rd line setting. Secondly, the ERG noted that the company proposed no additional amendments to address the committee's concerns regarding the impact of B-cell aplasia and the associated use of IVIG. Again, the ERG noted that in ID1166, the committee considered that a scenario assuming a 3-year treatment period with IVIG (as opposed to one year) was appropriate to reflect this uncertainty for Tisagencleucel.

In addition, the ERG also highlight 2 additional areas of uncertainty that were raised in the ERG's original report that were not addressed within the company response document.

- The ERG's original report noted that the company's model assumed that those patients' who remain in the 'Pre-progression' health state for at least two years (in either treatment group), will subsequently revert to the same HRQoL as the general population and will not incur any further costs related to their previous condition. In their original report, the ERG noted that the follow-up of ZUMA-1 was too short to ascertain this and that the ERG considered that a 5-year period was more consistent with previous cost-effectiveness studies and findings from the largest study identified by the ERG reporting on long-term outcomes of DLBCL survivors.

- The ERG's original report also highlighted that OS and PFS data for axi-cel was based on the mITT population (i.e. patients who actually received axi-cel). As a result, model entry for patients receiving axi-cel occurs from the point of infusion of axi-cel, rather than from the point of the initial leukapheresis procedure. The ERG noted that the additional time between the decision to use axi-cel and subsequent axi-cel infusion (i.e. the time between the initial leukapheresis procedure and receipt of axi-cel infusion) could be significantly longer than the time between the decision to use salvage chemotherapy and the start of chemotherapy. Although the company's model includes the additional costs of leukapheresis and conditioning chemotherapy, the company base case analysis did not quantify the potential impact on survival and HRQoL outcomes of the 11 patients out of 119 enrolled to ZUMA-1 who received leukapheresis but were not subsequently

infused (e.g. due to adverse events, death or manufacturing failure). The ERG considers that this potentially biases the analysis against BSC. The ERG highlights that company subsequently included this functionality in response to the ERG's original points for clarification but did not include this in the revised base case results.

The ERG undertook 4 additional scenarios to address each of these areas of remaining uncertainty (Scenarios 1-4). An additional scenario (Scenario 5) explored the impact of combining all the alternative scenario assumptions within a single analysis. Table 7 provides a description of the ERG's additional scenarios.

Table 7 : Overview of ERG's additional scenario analyses

Description of ERG scenario	Company base case assumption	ERG scenario assumption
Scenario 1: Auto vs allo	100% allogeneic transplant for BSC	87.5% autologous transplant and 12.5% allogeneic transplant for BSC
Scenario 2: IVIG use for 3 years	1 year	3 years
Scenario 3: Cure – 5 years	Cure – 2 years	Cure – 5 years
Scenario 4: ITT analysis	MITT analysis	ITT analysis
Scenario 5: Combined impact of Scenarios 1-4	As above	All of the above changes for Scenarios 1-4 combined in a single scenario

Table 8 summarises the deterministic cost-effectiveness results for these scenarios using the 3 alternative extrapolation approaches for axi-cel OS. The results show that Scenarios 1, 2 and 4 have a relatively minor impact on the ICER results. The results of Scenario 3 shows the biggest impact, increasing the base-case ICER by approximately £3,000-£4,000. When all the scenarios were combined and ICERs presented for each of the alternative extrapolation approaches, the resulting ICERs ranged between £[redacted] (company base case extrapolation method) and £[redacted] (company state-transition extrapolation approach) per QALY.

Table 8: Deterministic cost-effectiveness results for ERG scenarios using alternative extrapolation approaches for axi-cel OS ([redacted])

	Extrapolation approach (i) *Company base case approach*			**Extrapolation approach (ii)** *Company state-transition approach*			**Extrapolation approach (iii)** *ERG 'hybrid' approach*		
ERG Scenario	**Incr. Cost**	**Incr. QALY**	**ICER**	**Incr. Cost**	**Incr. QALY**	**ICER**	**Incr. Cost**	**Incr. QALY**	**ICER**
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: *Auto vs allo*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: *IVIG 3 years*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: *Cure -5years*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: *ITT analysis*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 5: *1-4 combined*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 End of Life

The ACD concluded that axi-cel meets both criteria to be considered a life-extending treatment at the end of life. However, the ACD also noted some uncertainty the specific criteria for life-extending for people with a short life expectancy (normally less than 24 months) due to concerns that the SCHOLAR-1 data was not representative of the population for whom axi-cel would be an option. The committee recognised these uncertainties in their statement that "*axicabtagene ciloleucel did not unequivocally meet the criterion for short life expectancy but that it was plausible that the criterion could apply*" (ACD paragraph 3.26, p23).

The company response document reported that the Oxford audit data and the CORAL extension study provided further supporting evidence for the application of End Of Life criteria for axi-cel. The company provided a summary (Table 11, company response document) of the observed median OS and the OS at different time points for the different cohorts (SCHOLAR-1, CORAL and Oxford RWE dataset). The company stated that these data sources reinforced the dismal outcome for the vast majority of patients, with survival generally measured in months. The company recognised there was a small proportion that have longer term survival which leads to an important difference between the mean and median survival estimates. However, the company reiterated that the vast majority of patients have a very poor prognosis and will die within months with current treatment options. Although not reported by the company, the ERG notes that the median OS predicted in the company's base case model for BSC is less than 5 months.

Table 9 provides a summary of the undiscounted (mean) survival estimated for BSC, estimated by the ERG, based on the company's revised model and assuming a 12.5% SCT rate.

Table 9: **Undiscounted (mean) survival estimates for BSC: company's revised model (12.5% SCT rate)**

Time horizon	Undiscounted Life Years (mean)	% of patients still alive
1 year	[redacted]	[redacted]
2 years	[redacted]	[redacted]
5 years	[redacted]	[redacted]
10 years	[redacted]	[redacted]
15 years	[redacted]	[redacted]
20 years	[redacted]	[redacted]
30 years	[redacted]	[redacted]
40 years	[redacted]	[redacted]
Lifetime (44 years)	[redacted]	[redacted]

The undiscounted results highlight the marked difference between the median and mean OS estimates for BSC. The mean undiscounted life years in the company's revised model (12.5% SCT) is [redacted]

years, which is significantly greater than the 24 months conventionally used to determine eligibility for End of Life.

The ERG also highlights that the estimate of [redacted] years is very similar to that estimate predicted by the ERG for salvage chemotherapy for the ongoing appraisal of Tisagencleucel (ID1166). The ACD for Tisagencleucel reported that "*the committee agreed that tisagenlecleucel could not be considered to meet NICE's criteria to be considered a life-extending treatment at the end of life*".

It is clear from Table 9 that the difference between the median and mean OS estimates is driven by the model predictions that a small proportion of patients will experience long term survival with current treatment options. The ERG considers that the uncertainty surrounding these longer term survival estimates should also be taken into consideration. The ERG notes that the median follow-up was not reported in the SCHOLAR-1 publication. Although the longest follow-up appears to be approximately 180 months (15 years), the ERG notes that longest follow up for the subgroup of patients with ECOG 0-1 is around 120 months (10 years). Due to the lack of reporting of numbers of risk it is difficult to determine how many patients are contributing to the different time points. However, the ERG notes that there appear to be relatively small numbers of patients still being followed up beyond about 80 months.

As a consequence of basing lifetime extrapolations on censored survival data, inevitably the clinical appropriateness and robustness of the subsequent predictions need to be carefully considered. The ERG highlights that while the gompertz distribution was selected by the company as the best fitting model for the OS extrapolation of BSC, this function also suggests a flattening of the OS estimates at around 60-80 months (see Figure 1). The ERG notes that the model also includes various constraints which result in the company switching to the general population mortality survival estimates if the model predictions mortality risk with either BSC or axi-cel fall below these. As a result of the flattening of the gompertz curve, patients receiving BSC are switched to general population mortality risks at around 60-80 months.

The ERG notes that the company included a separate scenario where they applied a standard mortality ratio (SMR) of 1.09 for alive patients after 60 months for both the axi-cel and BSC arm. However, this was not applied in the revised company base case. Table 10 provides a comparison of undiscounted life years, undertaken by the ERG, using a range of alternative SMR ratios applied at 60 months. The scenarios show that the undiscounted estimates fall as the SMR ratio increases. However, the undiscounted life years for BSC remain above 24 months even when an SMR ratio of 10 is assumed.

Table 10: **Undiscounted (mean) survival estimates for BSC: ERG scenarios using alternative SMR ratios**

Time Horizon	Excess mortality after 5 years (SMR)	Undiscounted Life Years (mean)
Lifetime (44 years)	1	[redacted]
Lifetime (44 years)	1.08	[redacted]
Lifetime (44 years)	2	[redacted]
Lifetime (44 years)	5	[redacted]
Lifetime (44 years)	10	[redacted]

One plausible explanation for the difference between the median and mean OS is the long term survival in patients who have a successful SCT. The ERG notes that the small percentage of long term survivors is close to the rate of SCT assumed in the model for BSC (12.5%). To further investigate these issues and to help inform the validity of the longer term predictions for BSC, the ERG undertook a series of additional exploratory analyses.

Firstly, the ERG calculated the undiscounted life years for patients who didn't receive SCT. The undiscounted life years estimated in the company's model assuming a 0% SCT rate with BSC was [redacted] years. The ERG noted that this also implied durable survival in a proportion of patients who didn't receive a SCT. The ERG questioned the clinical plausibility of these results without a curative treatment such as SCT.

Based on these findings, the ERG looked more closely at the choice of the gompertz distribution to model OS for BSC. The ERG previously highlighted that the company reported that this was the best fitting model but did not provide goodness of fit statistics or assessments of external validity to support this choice. To examine the potential impact of the distributional choice for the BSC OS function, the ERG estimated the undiscounted life years using a range of alternative distributions. These are summarised in Table 11.

Table 11: Undiscounted life-years for BSC using alternative distributions

Time Horizon	OS distribution for BSC	Undiscounted Life Years (mean)
Lifetime (44 years)	Gompertz (base case)	[redacted]
Lifetime (44 years)	Exponential	[redacted]
Lifetime (44 years)	Gamma	[redacted]
Lifetime (44 years)	Log logistic	[redacted]
Lifetime (44 years)	Lognormal	[redacted]
Lifetime (44 years)	Weibull	[redacted]

Table 11 clearly shows that the undiscounted life year estimates for BSC appear extremely sensitive to the choice of survival function, with estimates ranging from [redacted] years. The ERG notes that the gompertz used by the company in their base case predicts significantly longer mean survival compared to the other distributions. The ERG also notes that 4 of the 6 distributions result in estimates of mean life years less than 24 months.

Based on these findings it is clear that the assumptions concerning the extrapolation of BSC are critical both in terms of End of Life considerations but also in terms of the robustness of the ICER results. Given the potential importance of these additional findings undertaken to further inform the committee's deliberations concerning End of Life, the ERG also considered that it would be important to also show the impact of using alternative survival distributions in terms of the ICER results.

Table 12 summarises the ICER results assuming different survival distributions for BSC and different extrapolation approaches for axi-cel. These analyses are based on the company's revised model and assuming a 12.5% SCT rate. To explore the robustness of these results to other uncertainties raised by the ERG, Table 13 summarises the ICER results using the ERG's scenario 5 (which combined alternative inputs from Scenarios 1-4).

The ERG highlights that the ICER results are sensitive both to the method of extrapolation of OS for axi-cel and particularly to the choice of survival distribution to represent the overall survival of current treatment options.

The ERG concludes that the key uncertainties that need to be considered by the committee are:

(i) The plausibility and validity of the alternative extrapolation approaches for OS with axi-cel.
(ii) The appropriate distributional function for the extrapolation of OS for BSC.
(iii) The importance of other remaining areas of uncertainty addressed in the ERG's alternative scenarios (Scenarios 1-5).

Table 12: ICER results using alternative distribution for the overall survival with BSC: company inputs and 12.5% SCT rate ([redacted])

	Extrapolation approach (i) *Company base case approach*			**Extrapolation approach (ii)** *Company state-transition approach*			**Extrapolation approach (iii)** *ERG 'hybrid' approach*		
OS (BSC) distribution	**Incr. Cost**	**Incr. QALY**	**ICER**	**Incr. Cost**	**Incr. QALY**	**ICER**	**Incr. Cost**	**Incr. QALY**	**ICER**
Gompertz (Base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13: ICER results using alternative distribution for the overall survival with BSC: inputs based on ERG scenario 5 and 12.5% SCT rate ([redacted])

	Extrapolation approach (i) *Company base case approach*			**Extrapolation approach (ii)** *Company state-transition approach*			**Extrapolation approach (iii)** *ERG 'hybrid' approach*		
OS (BSC) distribution	**Incr. Cost**	**Incr. QALY**	**ICER**	**Incr. Cost**	**Incr. QALY**	**ICER**	**Incr. Cost**	**Incr. QALY**	**ICER**
Gompertz (Base case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6 Additional clarification responses from the company

After submitting their ACD response, the company subsequently provided further clarification responses to address questions raised by the NICE technical team. The ERG received these after they had completed the final draft of their report. Given the late stage of receipt, the ERG was unable to fully integrate these clarification responses into the main commentary sections. However, a brief summary is provided below, alongside a discussion of any implications for the ERG's previous critique.

Figures 12 and 13 provide a visual summary of the alternative fitted curves for the overall survival of BSC produced by the company.

Figure 12: Overall survival of BSC: SCHOLAR-1 (ECOG 0-1 only and excluding primary refractory) with 100% SCT, KM and fitted curves (replication of Figure 1 in company response to NICE questions)

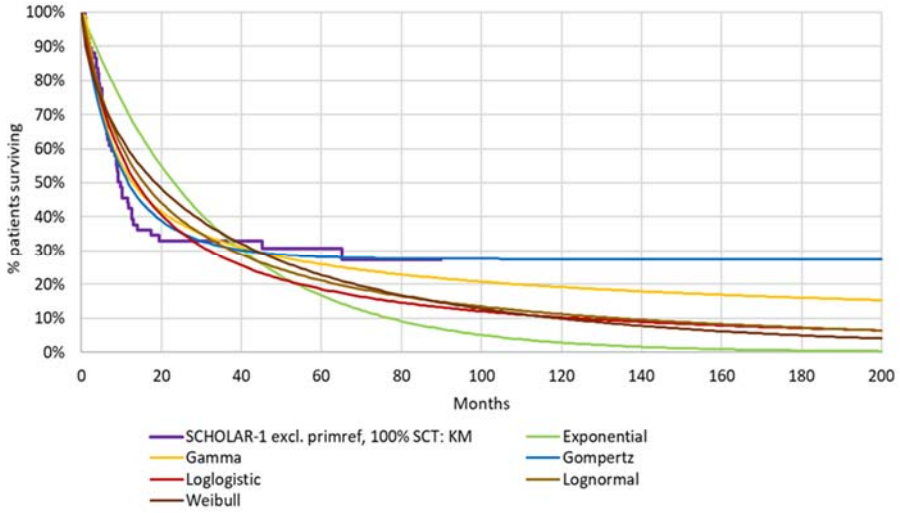


Figure 13: Overall survival of BSC: SCHOLAR-1 (ECOG 0-1 only and excluding primary refractory) with 0% SCT, KM and fitted curves (replication of Figure 2 in company response to NICE questions)

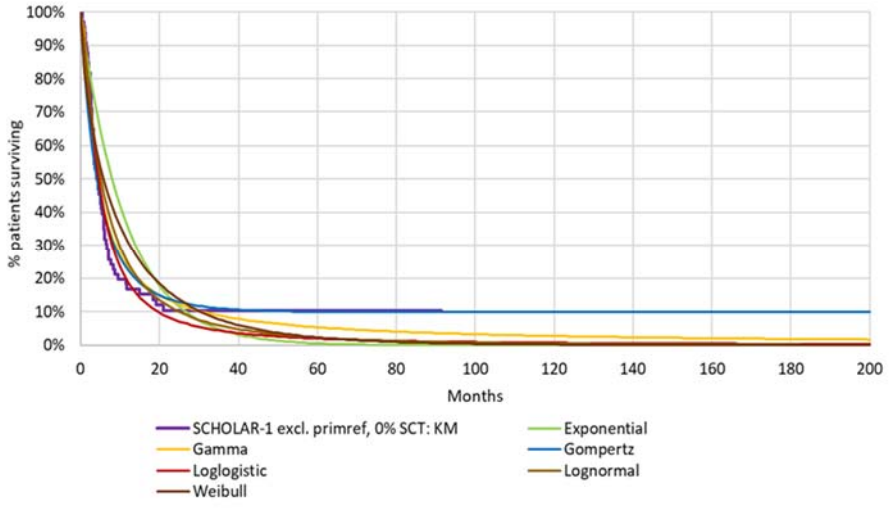


Table 14 provides a summary of the goodness of fit statistics using Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics.

Table 14 : Overall survival of BSC: SCHOLAR-1 (ECOG 0-1 only and excluding primary refractory) with 100% SCT and 0% SCT, goodness of fit statistics

	100% SCT		0% SCT	
Distribution for OS (BSC)	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	416.95	419.16	408.75	410.94
Weibull	402.61	407.02	396.66	401.04
Gompertz	378.04	**382.44**	364.03	368.41
Loglogistic	389.03	393.44	364.47	368.85
Lognormal	387.40	391.81	370.14	374.52
Generalised gamma	**376.59**	383.21	**360.82**	**367.39**

Best fitting distributions highlighted in bold based on AIC and BIC statistics

The company clarified that the gompertz curve fits were used in the response to the ACD because visually they appear to best fit the observed data and are the only curves (among other standard parametric curves) that represent the plateau of OS data. The company also stated that the gompertz results in the most conservative selection as it provides the best OS extrapolation for BSC.

The ERG highlights that the choice of parametric function should consider internal validity (i.e. visual assessment and goodness of fit statistics) and external validity (i.e. the extent to which the long term predictions align with other data sources and/or clinical experience). The ERG agrees with the company that the use of the gompertz provides the most conservative selection for the comparison versus axi-cel. However, as the choice of function has important implications both for End of Life considerations and for the most appropriate ICER results, the ERG considers that a more thorough discussion of internal and external validity should have been provided by the company.

The ERG notes that the gompertz and generalised gamma distributions appear to have the highest internal validity for the 0% and 100% SCT populations. While the company asserts that the gompertz distribution is the best fitting model, this ERG notes that there are differences based on the AIC and BIC statistics. Using the AIC statistics the generalised gamma appears the best fitting distribution for both the 0% and 100% SCT populations. However, the difference in the AIC statistics compared with the gompertz show that both models appear reasonable choices. For the 0% SCT population, the generalised gamma has the lowest AIC and BIC statistics. However, again the differences in the AIC and BIC statistics between generalised gamma and gompertz are small and do not provide clear support for one of these particular distributions.

Given that there appear to be alternative survival distributions which appear to have similar fit, one potential approach that could be used to more formally account for the uncertainty surrounding choice of survival distribution is to use a model averaging approach. This technique involves the parameterisation of uncertainty surrounding the choice of distribution, through including all plausible survival functions as part of a weighted distribution, and sampling both the parametric uncertainty associated within each distribution and the uncertainty (or weights) surrounding the choice of preferred method. Each model is assigned a weight that represents the adequacy of that distribution in predicting the lifetime survival of the modelled cohort, in comparison to all other distributions considered in the model.

There are a number of measures of model adequacy that can be considered to derive the weights including statistical adequacy measures such as AIC and BIC, or the use expert judgement. As outlined in Jackson et al (2007), the AIC values reported from each survival distribution can converted to a probability weight (w_k) using the following equations:

$$A_k = e^{(-0.5 \times AIC)}$$

$$w_k = \frac{A_k}{\sum A_k}$$

Table 15 summarises the weights for each survival distribution based on the AIC weights. The ERG highlights that the generalised gamma distribution provides the highest weights for both the 0% and 100% SCT populations.

Table 15: Summary of goodness of fit statistics and AIC weights (ERG calculations)

	100% SCT		**0% SCT**	
Distribution for OS (BSC)	**AIC**	**AIC based weight**	**AIC**	**AIC based weight**
Exponential	416.95	0%	408.75	0%
Weibull	402.61	0%	396.66	0%
Gompertz	378.04	32.49%	364.03	14.65%
Loglogistic	389.03	0.13%	364.47	11.75%
Lognormal	387.40	0.3%	370.14	0.69%
Generalised gamma	376.59	67.08%	360.82	72.91%

The ERG acknowledges that there is significant uncertainty surrounding the OS extrapolations for BSC. However, the ERG concludes that the generalised gamma may provide a more appropriate choice than the gompertz distribution. The ERG also highlights the importance of considered the

clinical plausibility of the alternative functions (external validity) as well as the internal goodness of fit statistics.

The company were also requested by the NICE technical team to provide a rationale and summary of results for the alternative modelling approach (state transition model – extrapolation approach [ii]) provided in the revised Excel model. The company responded that the state transition model and related data were undertaken for internal exploratory analyses and were not intended to be used in the final model or the ACD response. In response to NICE's question, the company provided an updated model which removed the state-transition data and functionalities.

The ERG considers the state-transition analyses may provide meaningful insights for the committee regarding the validity of the company's approach vs the ERG's hybrid approach for the extrapolation of OS for axi-cel. The ERG was disappointed that the company chose not to provide any further rationale or discussion of this approach and instead preferred to remove the data and functionality.

7 Conclusions

The ERG concludes that the key uncertainties that need to be considered by the committee are:

(i) The plausibility and validity of the alternative extrapolation approaches for OS with axi-cel.

The ERG considers that the results using extrapolation approach [ii] and [iii] report similar findings and appear more plausible than the company's base case approach. The ERG recognises the uncertainties and does not rule out any extrapolation approach, but notes a preference for the ICER results generated using extrapolations approaches based on the state-transition approach or the ERG's 'hybrid' approach over the company's base case approach.

The ERG's exploratory analyses found that the range of ICERs vary between [redacted] (company base case approach) and [redacted] (state transition approach) per QALY, across the alternative extrapolation approaches.

(ii) The appropriate distributional function for the extrapolation of OS for BSC.

The ERG acknowledges that there is significant uncertainty surrounding the OS extrapolations for BSC. However, the ERG concludes that the generalised gamma may provide a more appropriate choice than the gompertz distribution. The ERG also highlights the importance of considering the clinical plausibility of the alternative functions (external validity) as well as the internal goodness of fit statistics.

The ERG's exploratory analyses found that the range of ICERs vary between [redacted] (company base case extrapolation approach for axi-cel) and [redacted] (state transition approach for axi-cel) per QALY, using the generalised gamma distribution for the overall survival for BSC.

(iii) *The importance of other remaining areas of uncertainty addressed in the ERG's alternative scenarios (Scenarios 1-5).*

The ERG notes that there are several areas of remaining uncertainty which were explored by the ERG using separate scenarios (Scenarios 1-5). The ERG higlights that the combined scenario (scenario 5) appears most consistent with the ERG's preferred base case used for the ongoing NICE appraisal of Tisagencleucel (ID 1166).

The ERG's exploratory analyses found that the range of ICERs vary between £[redacted] (company base case extrapolation approach for axi-cel) and £[redacted] (state transition approach for axi-cel) per QALY, using the generalised gamma distribution for the overall survival for BSC and combining the ERG's alternative assumptions for other areas of remaining uncertainty.

The ERG concludes by reminding the committee that the ERG's exploratory analyses were all based the company's updated [redacted] and are based on deterministic results.

References

Jackson C, Thompson S and Sharples D. Accounting for uncertainty in health economic decision models by using model averaging. J. R Statist Soc A (2009). 172, 383-404.