in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies (ID3980): Cancer Drugs Fund Review of TA559

Produced by Kleijnen Systematic Reviews (KSR) Ltd, in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Centre (UMC+)

Authors

Mark Perry, Reviews Manager, KSR Ltd, United Kingdom (UK)
Isaac Corro Ramos, Health Economics Researcher, Institute for Medical Technology Assessment (iMTA), EUR, the Netherlands (NL)
Venetia Qendri, Health Economist, Erasmus School of Health Policy & Management (ESHPM), EUR, NL
Pim Wetzelaer, Health Economist, ESHPM, EUR, NL
Maiwenn Al, Health Economics Researcher, ESHPM, EUR, NL
Lisa Stirk, Information Specialist, KSR Ltd, UK
Kevin McDermott, Systematic Reviewer, KSR Ltd, UK
Pawel Posadzki, Reviews Manager, KSR Ltd, UK
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Nigel Armstrong, Health Economics Manager, KSR Ltd, UK
Jos Kleijnen, Founder and Owner, KSR Ltd, UK
Robert Wolff, Managing Director, KSR Ltd, UK

Correspondence to Robert Wolff, Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, YO19 6FD
United Kingdom

Date completed 17/06/2022

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme as project number NIHR135472.

Declared competing interests of the authors None.

Acknowledgements None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Perry M, Corro Ramos I, Qendri V, Wetzelaer P, Al M, Stirk L, McDermott K, Posadzki P, Ahmadu C, Armstrong N, Kleijnen J, Wolff R. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies (ID3980): Cancer Drugs Fund Review of TA559. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors
Mark Perry and Robert Wolff acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Venetia Qendri, Pim Wetzelaer, Maiwenn Al, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Kevin McDermott and Pawel Posadzki acted as systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Jos Kleijnen contributed to the writing of the report and supervised the project.

Abbreviations

ACD	Appraisal Consultation Document
AIC	Akaike information criterion
AiC	Academic in confidence
ASCT	Autologous stem cell transplant
Axi-cel	Axicabtagene ciloleucel
BIC	Bayesian information criterion
BNF	British National Formulary
BSC	Best supportive care
CAR	Chimeric antigen receptor
CDF	Cancer Drugs Fund
CEAC	Cost effectiveness acceptability curve
CES	Company evidence submission
CHASE	Cyclophosphamide, cytosine arabinoside, etoposide, dexamethasone
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CiC	Commercial in confidence
CNS	Central nervous system
CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CR	Complete response
CRF	Case report form
CRT	Chemoradiation therapy
CS	Company submission
CTG	Cancer Trials Group
DeVIC	Etoposide, dexamethasone, ifosfamide, carboplatin
DHAP	Dexamethasone, high dose cytarabine and cisplatin
DLBCL	Diffuse large B cell lymphoma
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EPOCH	Etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone
ESHAP	Etoposide, solumedrol, cytarabine, cisplatin
ESHPM	Erasmus School of Health Policy & Management
EUR	Erasmus University Rotterdam
FAD	Final appraisal determination
GCVP	Gemcitabine, cyclophosphamide, vincristine and prednisolone
GDP	Gemcitabine, cisplatin, dexamethasone
HD-MTX	High-dose methotrexate chemotherapy
HTA	Health Technology Assessment
ICE	Ifosamide, carboplatin and etoposide
ICER	Incremental cost effectiveness ratio
iMTA	Institute for Medical Technology Assessment
Inc.	Incremental
IPD	Individual participants data
IPI	International Prognostic Index
ITC	Indirect treatment comparison
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWG	International Working Group
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews
LY	Life year
LYG	Life-year gained

LYSARC	Lymphoma Academic Research Organisation
MC/IA	Mayo Clinic and University of Iowa
MCM	Mixture cure models
MDACC	MD Anderson Cancer Centre
MDSAS	Medical Data Solutions and Services
mITT	Modified intention-to-treat
N	Number of observations
N/A	Not applicable
NCIC	National Cancer Institute of Canada
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	The Netherlands
NOS	Not otherwise specified
N/R	Not reported
NR	Non-response
OCA	Osaka Cancer Registry
onekhaz	One knot hazards
oneknor	One knot normal
onekodd	One know odds
ONS	Office for National Statistics
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
PMBCL	Primary mediastinal B Cell lymphoma
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
R	Rituximab
RVP	Rituximab, vincristine and prednisolone
SACT	Systemic anti-cancer therapy
SCT	Stem cell transplant
SMR	Standardised mortality ratio
SPORE	Specialized Programs of Research Excellence
TA	Technology appraisal
thrkhaz	Three knots hazards
thrknor	Three knots normal
thrkoff	Three knots off
twokhaz	Two knots hazards
twoknor	Two knot normal
twokodd	Two knots odds
TFL	Transformed follicular lymphoma
ToE	Terms of Engagement
TSD	Technical Support Document
UK	United Kingdom
UMC+	University Medical Centre
US	United States (of America)

Table of Contents

Table of Tables

Table of Figures

1. EXECUTIVE SUMMARY

1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company evidence submission

The key committee assumptions (preferences) according to the Terms of Engagement (ToE) for the Cancer Drugs Fund (CDF) review are summarised in Table 1.1., together with brief descriptions of the opinion of the Evidence Assessment Group (EAG) on the company's level of adherence to these assumptions. These are more fully elaborated in Sections 2.2.1 to 2.2.9 of this report.

Table 1.1: Preferred assumptions from Terms of Engagement

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
Assumption 1	Population: Adults with relapsed or refractory DLBCL, PMBCL or transformed follicular lymphoma who have had two or more systemic therapies are the relevant population for the review.	Yes	Not applicable	None
Assumption 2	Comparator: The company should present clinical and cost-effective evidence for axi-cel compared with salvage chemotherapy, excluding pixantrone.	Not fully.	None	The presence or absence of pixantrone was not mentioned.
Assumption 3	Indirect Treatment Comparison: The company should fully explore the most appropriate approach for establishing the relative effectiveness of axi-cel, utilising any data that has become available during the period of managed access.	Not fully. The company did use the adjusted SCHOLAR-1 data, which is consistent with the following statement in the ToE: *"The committee recognised the limitations given the reduced sample size but concluded it would consider this adjusted SCHOLAR-1 data in its decision-making"*. However, substantial comparator data are only available from SCHOLAR-1, not the three additional comparator sources.	None	Failure to utilise the three additional sources is not properly explained, although the CES points out that only one of the three additional sources was from the UK. However, this is not a strong rationale as none of the data from ZUMA-1 were from the UK either. Search methods for new comparator data involved a 'targeted PubMed search' that is unlikely to have been sufficiently

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
		For the OS data, the treatment effects from axi-cel and salvage chemotherapy are not compared in any formal analysis. The data from axi-cel and salvage chemotherapy are plotted together on a single graph, but without any measure of uncertainty, making useful interpretation difficult. The same graph also compares PFS data between axi-cel and salvage chemotherapy, but the source of the PFS data is unclear as there is no mention in the primary SCHOLAR-1 data-source that PFS data were collected. Also, inadequate search methods were used to source new data. In addition, new data were not utilised in the new analysis (see below)		sensitive to ensure all relevant evidence was found.
Assumption 4	Sources of comparator data: The Committee *[sic!]* should use SCHOLAR-1 and any additional data that has become available during the period of managed access to inform the comparator arm.	Not fully – see above	None	See above
Assumption 5	Subsequent treatments: The company should use more mature data from ZUMA-1, any data that has become available during the period of managed access, and data	Not fully. The company used the same proportion receiving IVIG as in the original submission.	Blueteq data were not used because it was unavailable at the time of submission.	The company seem to have not used more mature ZUMA-1 data or acquire or adequately utilise further data during the period of managed access.

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
	collected through Blueteq to inform the proportion of people who subsequently have IVIG, and the length of time this is required.		However, the data has been made available to the EAG	Note that NHS England has highlighted that the initial lack of IVIG data is not the company's fault
Assumption 6	Extrapolation of OS and PFS. The company should use the latest data cut from ZUMA-1 to inform the survival outcomes and SACT dataset to validate the trial outputs.	Not fully	None	Not effectively validated, as follow up in the SACT database only continued to 36 months. Analysis and presentation of the SCHOLAR-1 data in relation to the ZUMA-1 data was unclear, and so it is uncertain how much of the survival benefit is related to axi-cel.
Assumption 7	Cure assumption: The company should fully explore assumptions of cure using the more mature ZUMA-1 data and other updated data that has become available during the period of managed access.	Not fully	None	ZUMA-1 data on OS partially supported assumption of cure in approx. [redacted]% of patients, with a continuation of a plateau for OS (albeit somewhat reduced) to 60 months. This was not accompanied by new comparator evidence.
Assumption 8	Most plausible ICER: The committee agreed that axi-cel demonstrated plausible potential to be cost-effective.	Not fully	None	The updated company's base-case ICER was £49,159 per QALY gained. The EAG's preferred ICER was £50,480 per QALY gained. The model results are still sensitive to changes in OS for the salvage chemotherapy arm and to changes in PFS for the axi-cel arm.
Assumption 9	Axi-cel meets the end-of-life criteria.	The company did not fulfil the remit of verifying the assumptions underlying assumption 9.	None	To verify the assumptions underlying assumption 9, the company needed to have demonstrated axi-cel's efficacy,

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
				which has not been done to a satisfactory extent because there has not been enough integration of comparator evidence (see above).

Based on Table of key committee assumptions reported in the ToE for CDF review and the CES

Axi-cel = axicabtagene ciloleucel; CDF = Cancer Drugs Fund; CES = company evidence submission; DLBCL = diffuse large B cell lymphoma; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; IVIG = intravenous immunoglobulins; NHS = National Health Service; OS = overall survival; PFS = progression-free survival; PMBCL = primary mediastinal B Cell lymphoma; QALY = quality-adjusted life year; SACT = systemic anti-cancer therapy; ToE = Terms of Engagement; UK = United Kingdom

1.2 Summary of key issues in the clinical effectiveness evidence

There are two key issues related to the clinical effectiveness evidence.

1) The company evidence submission (CES) provided a clear description of the one-arm ZUMA-1 and systemic anti-cancer therapy (SACT) results. However, the ToE state that *"the company should present clinical and cost-effective evidence for axicabtagene ciloleucel compared to salvage chemotherapy, excluding pixantrone"*. Therefore, the EAG is particularly interested in the results of the indirect analyses performed in conjunction with patient-level data from the SCHOLAR-1 studies (used as the comparator cohort), which are neither presented clearly nor fully. The company has been asked to present combined ZUMA-1/SACT and SCHOLAR-1 results in a clear way, with appropriate statistical adjustments, to facilitate a more meaningful interpretation of clinical effectiveness, but unfortunately the company was unable to provide this.

2) The ToE states that in addition to using SCHOLAR-1 data, the CES should use *"any additional data that has become available during the period of managed access to inform the comparator arm"*. The CES discusses a *"targeted PubMed search"* that yielded three sources, only one of which was from the United Kingdom (UK; and which was an abstract). The company has confirmed that this search only used one database. This means that important sources may have been missed.

1.3 Summary of the key issues in the cost effectiveness evidence

There are two further key issues related to the cost effectiveness evidence.

3) As explained in key issue 2, the EAG considers that the company did not sufficiently explore alternative options to appropriately model long-term overall survival (OS) for salvage chemotherapy using more up-to-date evidence. Thus, despite the committee's preference of modelling OS in the salvage chemotherapy arm using a generalised gamma distribution (based on clinical plausibility), the alternative scenarios explored by the EAG indicated that the model results are still sensitive to changes in OS extrapolations for salvage chemotherapy.

4) The EAG considers that the company could have used longer follow-up data for progression-free survival (PFS) to explore the plausibility of the plateau assumption for PFS and, since this was not explored, the anticipated plateau in the PFS for axicabtagene ciloleucel (axi-cel) remains uncertain. The alternative scenarios explored by the EAG indicated that the model results are still sensitive to changes in PFS extrapolations for axi-cel.

1.4 Summary of EAG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)

The EAG made two changes to the company's base-case:

- Update the model using 2019/2020 National Health Service (NHS) Reference costs and align all the other cost inputs to the same cost year (done by the company response to request for clarification question B7).
- Proportion of patients using intravenous immunoglobulins (IVIG) treatment equal to 16% and a treatment duration at 6.5 months, as observed in the systemic anti-cancer therapy (SACT) cohort.

Table 1.2 shows the results of the EAG's deterministic base-case. The EAG's preferred ICER increased from £49,159 per quality-adjusted life year (QALY) gained to £50,480 per QALY gained.

The EAG's probabilistic sensitivity analysis (PSA) results were broadly in line with the deterministic ones. The probabilistic ICER was £49,921. [redacted]. At the threshold of £50,000 per QALY gained, the estimated probability that axi-cel is a cost effective alternative to salvage chemotherapy was [redacted].

The results of the additional scenario analyses conducted by the EAG indicated that the ICER was stable to changes in axi-cel OS extrapolations. Additionally, all mixture cure models resulted in ICERs similar to the base-case ICER, with a difference less than £200 in absolute value. The results of the scenario analysis assuming a treatment duration of 33 months (the longest treatment duration observed in the SACT cohort) suggest that the impact of IVIG treatment assumptions on cost effectiveness is minor. The model results are still sensitive to changes in OS for the salvage chemotherapy arm and to changes in PFS for the axi-cel arm.

Assuming a Gompertz, a log-logistic and a lognormal OS extrapolation for salvage chemotherapy resulted in an ICER of £55,787, £46,048 and £46,977 per QALY gained, respectively. The EAG considers that the company did not sufficiently explore alternative options to appropriately model long-term OS for salvage chemotherapy using more up-to-date evidence. More recent data should be used to confirm what scenario is more clinically plausible for modelling OS in the salvage chemotherapy arm.

Likewise, assuming a generalised Gamma (the second-best single parametric fit) PFS extrapolation for axi-cel resulted in an ICER of £67,765 per QALY gained. When a lognormal mixture cure model (best fit) was assumed for axi-cel PFS, the ICER was £51,096 per QALY gained. Given the plateau-like shape of the standard Gompertz distribution (used in the base-case), assuming PFS mixture cure models for axi-cel resulted in ICERs similar to the base-case ICER, as expected. In particular, ICERs based on PFS mixture cure models for axi-cel differed less than £1,000 in absolute value compared to the base-case (results not shown). Assuming a two-knots normal spline model (best fit) resulted in an ICER of £55,257 per QALY gained. All ICERs based on the other possible spline models were above £55,000 per QALY gained (results not shown). The EAG considers that the company could have used longer follow-up data for PFS to explore the plausibility of the plateau assumption for PFS and, since this was not explored, the anticipated plateau in the PFS for axi-cel remains uncertain.

Table 1.2: EAG preferred base-case deterministic cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Change in ICER (£)*
BSC	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,480	+1,321

Based on economic model submitted with the response to the request for clarification.
* Change in ICER with respect to the base-case ICER in the CES
Axi-cel = axicabtagene ciloleucel; BSC = best supportive care (salvage chemotherapy); CES = company evidence submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

2. INTRODUCTION AND BACKGROUND

2.1 Background

The Terms of Engagement (ToE) states that *"axicabtagene ciloleucel is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after two or more systemic therapies, only if the conditions in the managed access agreement are followed"*.[1]

Incremental cost effectiveness ratios (ICERs) presented to the committee included a [redacted]. This equates to an overall discount of [redacted].[2]

The committee's preferred ICER was between the company's base-case of [redacted] per quality-adjusted life year (QALY) gained and the Evidence Assessment Group (EAG) upper-bound base-case of [redacted] per QALY gained versus salvage chemotherapy. The EAG ICER used the EAG's alternative analysis and the combined costing approach (considering the use of higher proportion of post-treatment autologous stem cell transplants, a cure assumption at 5 rather than 2 years, intravenous immunoglobulins (IVIG) use for 3 years and the use of the intention-to-treat population) with a generalised gamma distribution for overall survival (OS) for salvage chemotherapy.[2]

The committee agreed that axicabtagene ciloleucel (axi-cel) met end-of-life criteria and therefore is plausibly cost effective. The committee accepted that, although there was significant uncertainty in the cost effectiveness estimates, many of the assumptions in the company's base-case appear plausible and might be verified through further data collection.[2]

The committee's key uncertainties were the OS estimates for axi-cel, the convergence of OS and progression-free survival (PFS), and post-treatment IVIG use. The committee agreed that more mature trial data would reduce uncertainty in these factors. It was anticipated at the start of data collection that Medical Data Solutions and Services (MDSAS) would provide data for IVIG use in the National Health Service (NHS). Subsequently, it was established that IVIG use in the NHS would be provided by the NHS Blueteq System.[2]

2.2 Critique of company's adherence to committees preferred assumptions from the ToE

Table 2.1 summarises the key committee assumptions (preferences) according to the ToE.[1] It also summarises the extent to which the company evidence submission (CES) has adhered to the committee preferences.[2] Sections 2.2.1 to 2.2.9 elaborate the EAG comments further.

Table 2.1: Preferred assumptions from Terms of Engagement

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
Assumption 1	Population: Adults with relapsed or refractory DLBCL, PMBCL or transformed follicular lymphoma who have had two or more systemic therapies are the relevant population for the review.	Yes	Not applicable	None
Assumption 2	Comparator: The company should present clinical and cost-effective evidence for axi-cel compared with salvage chemotherapy, excluding pixantrone.	Not fully.	None	The presence or absence of pixantrone was not mentioned.
Assumption 3	Indirect Treatment Comparison: The company should fully explore the most appropriate approach for establishing the relative effectiveness of axi-cel, utilising any data that has become available during the period of managed access.	Not fully. The company did use the adjusted SCHOLAR-1 data, which is consistent with the following statement in the ToE: *"The committee recognised the limitations given the reduced sample size but concluded it would consider this adjusted SCHOLAR-1 data in its decision-making"*. However, substantial comparator data are only available from SCHOLAR-1, not the three additional comparator sources. For the OS data, the treatment effects are not compared in any formal analysis. The data from axi-cel and salvage chemotherapy are plotted together on a single graph, but without any measure of uncertainty, making useful interpretation difficult. The same graph also compares PFS	None	Failure to utilise the three additional sources is not properly explained, although the CES points out that only one of the three additional sources was from the UK. However, this is not a strong rationale as none of the data from ZUMA-1 were from the UK either. Search methods for new comparator data involved a 'targeted PubMed search' that is unlikely to have been sufficiently sensitive to ensure all relevant evidence was found. See above for further details.

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
		data between axi-cel and salvage chemotherapy, but the source of the PFS data is unclear as there is no mention in the primary SCHOLAR-1 data-source that PFS data were collected. Also, inadequate search methods were used to source new data. In addition, new data were not utilised in the new analysis (see above)		
Assumption 4	Sources of comparator data: The Committee *[sic!]* should use SCHOLAR-1 and any additional data that has become available during the period of managed access to inform the comparator arm.	Not fully – see above	None	See above
Assumption 5	Subsequent treatments: The company should use more mature data from ZUMA-1, any data that has become available during the period of managed access, and data collected through Blueteq to inform the proportion of people who subsequently have IVIG, and the length of time this is required.	Not fully. The company used the same proportion receiving IVIG as in the original submission.	Blueteq data were not used because it was unavailable at the time of submission. However, the data has been made available to the EAG	The company seem to have not used more mature ZUMA-1 data or acquire or adequately utilise further data during the period of managed access. Note that NHS England has highlighted that the initial lack of IVIG data is not the company's fault
Assumption 6	Extrapolation of OS and PFS. The company should use the latest data cut from ZUMA-1 to inform the survival outcomes and SACT dataset to validate the trial outputs.	Not fully	None	Not effectively validated, as follow up in the SACT database only continued to 36 months. Analysis and presentation of the SCHOLAR-1 data in relation to the ZUMA-1 data was unclear, and so it is uncertain

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	EAG comment
				how much of the survival benefit is related to axi-cel.
Assumption 7	Cure assumption: The company should fully explore assumptions of cure using the more mature ZUMA-1 data and other updated data that has become available during the period of managed access.	Not fully	None	ZUMA-1 data on OS partially supported assumption of cure in approx. [redacted]% of patients, with a continuation of a plateau for OS (albeit somewhat reduced) to 60 months. This was not accompanied by new comparator evidence.
Assumption 8	Most plausible ICER: The committee agreed that axi-cel demonstrated plausible potential to be cost-effective.	Not fully	None	The updated company's base-case ICER was £49,159 per QALY gained. The EAG's preferred ICER was £50,480 per QALY gained. The model results are still sensitive to changes in OS for the salvage chemotherapy arm and to changes in PFS for the axi-cel arm.
Assumption 9	Axi-cel meets the end-of-life criteria.	The company did not fulfil the remit of verifying the assumptions underlying assumption 9.	None	To verify the assumptions underlying assumption 9, the company needed to have demonstrated axi-cel's efficacy, which has not been done to a satisfactory extent because there has not been enough integration of comparator evidence (see above).

Based on Table of key committee assumptions reported in the ToE for CDF review and the CES

Axi-cel = axicabtagene ciloleucel; CDF = Cancer Drugs Fund; CES = company evidence submission; DLBCL = diffuse large B cell lymphoma; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; IVIG = intravenous immunoglobulins; NHS = National Health Service; OS = overall survival; PFS = progression-free survival; PMBCL = primary mediastinal B Cell lymphoma; QALY = quality-adjusted life year; SACT = systemic anti-cancer therapy; ToE = Terms of Engagement; UK = United Kingdom

2.2.1 Assumption 1: Population

Adults with relapsed or refractory diffuse large B cell lymphoma (DLBCL), primary mediastinal B cell lymphoma (PMBCL) or transformed follicular lymphoma who have had two or more systemic therapies are the relevant population for the CDF review.

The EAG can confirm that data presented from the ZUMA-1 trial are for the specified population.

2.2.2 Assumption 2: Comparator

The company should present clinical and cost effective evidence for axicabtagene ciloleucel compared with salvage chemotherapy, excluding pixantrone.

The EAG does not agree that this fully was adhered to in the CS.[2] A formal comparison with salvage chemotherapy was not adequately made, as described in the section below.

2.2.3 Assumption 3: Indirect treatment comparison

The company should fully explore the most appropriate approach for establishing the relative effectiveness of axicabtagene ciloleucel, utilising any data that has become available during the period of managed access.

The EAG considers that this assumption was not adequately adhered to in the CES.[2]

- Firstly, data from comparators are inadequately analysed and presented, and cannot be described as an indirect treatment comparison, because a formal quantitative comparison is not adequately made.
- Secondly, the company did not appear to make sufficiently thorough attempts to seek new data during the period of managed access. For example, the company describes a '*targeted PubMed search*' which was conducted to obtain newly available comparator data; such a search strategy would be likely to miss important sources because 'PubMed' is only one of several databases that would be appropriate.

With regard to the first issue, although OS and PFS data from the SCHOLAR-1 studies are presented alongside the ZUMA-1 data, this is carried out without any measures of uncertainty, making it difficult to properly interpret the effects of the intervention against the comparator. Although direct OS data were collected by both the ZUMA-1 and SCHOLAR-1 studies, there is no evidence from the SCHOLAR-1 primary source{Crump, 2017 #94} that PFS data were collected. Therefore, it is unclear how PFS data ostensibly relating to salvage chemotherapy were presented alongside axi-cel PFS data in the submission. If these were simulated values modelled from other outcome data this has not been made adequately clear in the submission and further clarification is needed. Data from the three additional studies found from further searching were also not included, apart from one data point relating to salvage chemotherapy: a median OS of 195 days (6.4 months).{Radford, 2019 #87} However this was not integrated with the SCHOLAR-1 data in the comparison with ZUMA-1 data.

In response to a request to provide more detail of the integrated analysis[3, 4] the company provided a summary of adjustments that had been previously made to the SCHOLAR-1 database, which were aimed at permitting better congruence with the ZUMA-1 data. However, no evidence has been provided to support the notion that these adjustments make the datasets more comparable, and it is therefore unclear that the SCHOLAR-1 database provides useful comparator data. Table 2.2 summarises these adjustments.

Table 2.2:Summary of SCHOLAR-1 adjustments

SCHOLAR-1 adjustments	Justification for adjustment	Resulting population size
No adjustments	N/A	636
Refractory subgroup classified as "last refractory categorisation"	This was based on the refractory status at the last time in the treatment course the subject was determined to be refractory and is most consistent with how analyses in ZUMA-1 were conducted.	593
Patients evaluable for survival only	Not reported	562
Patients with an ECOG score of 2-4 and unknown removed	Consistent with the EAG-preferred approach for the original submission.	188
Primary refractory patients removed	Consistent with the axi-cel EMA label.	133
Weighted to reflect an expected subsequent SCT rate of 10%	Based on clinical opinion.	Undergoing SCT: 67 Not under-going SCT: 66

Based on Table 1 of the response to the request for clarification[3]
Axi-cel = axicabtagene ciloleucel; EAG = Evidence Assessment Group; ECOG = Eastern Cooperative Oncology Group; EMA = European Medicines Agency; N/A = not applicable; SCT = stem cell transplant

The EAG acknowledges that the company did make an attempt to make the SCHOLAR-1 dataset more comparable to ZUMA-1, although the EAG considers that more sophisticated methods to adjust for confounding as described in NICE TSD 17, could have been employed.[5] However, the EAG also acknowledges that, according to the ToE, this was considered suitable for decision-making.

The second issue has been pursued in the clarification letter, with the company being asked to provide full details of the search strategy used.[4] The company response was that *"a basic literature search (via PubMed) was undertaken to review any additional data pertaining the use of conventional chemotherapy within the 3L DLBCL setting which may further inform our assumptions around the comparator arm. This was based on suitable keyword MeSH term searches, for example, related to "DLBCL" OR "diffuse large B cell lymphoma" AND "chemotherapy" AND "relapsed/refractory", and search criteria were further refined to datasets published since 2018 (following the last appraisal of axi-cel in this setting). Whilst acknowledging the absence of high rigour that one would typically expect of a conventional SLR approach, this search revealed a very limited number of datasets, which we have referred to and commented on in Section A.7 of the company evidence submission (CES). The outcome of this search is not unexpected since the establishment of CAR T-cell therapy for DLBCL after two or more prior therapies in the last few years has meant that a counterfactual 'world' without CAR-T is expected to have significantly limited the use of chemotherapy for patients treated with curative intent in this setting. Therefore, nothing of any further scientific rigour than the original SCHOLAR-1 dataset has been identified in which to inform the comparator arm in this appraisal. This conclusion was deemed very reasonable by UK clinical expert validation when reviewing the economic modelling and clinical assumptions part of this resubmission".*[3]

The EAG notes that the confirmation that only one dataset was used implies a probable lack of sensitivity in the search. In turn, this means that important sources may have been missed.

2.2.4 Assumption 4: Sources of comparator data

The Committee should use SCHOLAR-1 and any additional data that has become available during the period of managed access to inform the comparator arm.

The EAG considers that this assumption was not adequately adhered to in the CES.[2] SCHOLAR-1 as well as the three additional data sources found have not been utilised effectively in the CES. Please see comments in Sections 2.2.2 and 2.2.3 for further details.

The company argued that SCHOLAR-1 remained the most suitable data source given: *"1) the strengths of the SCHOLAR-1 study; 2) the Committee consensus previously on the study being the most appropriate source, and the approach used to analyse the data from the source and; 3) that, via the CDF, use of CAR T-cell therapies for DLBCL after two or more treatment lines has become so established that trying to find a newer data source to model the counterfactual of a 'world' without these therapies being available is unfeasible"* (page 28). What those strengths are was not explicitly stated, although the EAG believes that this might refer to the availability of individual participants data (IPD), which permitted adjustment to improve comparability. The EAG have already commented on the committee view of SCHOLAR-1. As for the use of CAR T-cell therapies, this highlights two issues, one of which being that what is standard of care for the index population and thus should be a comparator might have changed during the managed access period. Of course, the ToE precludes this. The other issue is whether the company is referring to the use of CAR-T at later lines of therapy than the index population i.e., as subsequent therapy: if this is the case then the EAG considers that these data sources could have been included. As referred to in Section 2.2.3, the company did retrieve three other studies, although no outcome from these studies were used for comparison with axicabtagene ciloleucel. The reasons given for not using them was that only one of them was from the UK and this was only available as an abstract. A median OS was reported from it, but, no equivalent was presented from SCHOLAR-1.

2.2.5 Assumption 5: Subsequent treatments

The company should use more mature data from ZUMA-1, any data that has become available during the period of managed access, and data collected through Blueteq to inform the proportion of people who subsequently have IVIG, and the length of time this is required.

Although initially unavailable for reasons beyond the control of the company, Blueteq data were subsequently made available to the EAG in the Systemic Anti-Cancer Therapy (SACT) report.[6] Notwithstanding this, the EAG considers that this assumption was not adhered to because of the apparent failure to utilise more mature ZUMA-1 data. However, as detailed in Section 2.2.8, any assumption on IVIG data (proportion of patients receiving treatment and treatment duration) has almost no impact on the incremental cost effectiveness ratio (ICER).

2.2.6 Assumption 6: Extrapolation of overall survival (OS) and progression-free survival (PFS)

The company should use the latest data cut from ZUMA-1 to inform the survival outcomes and SACT dataset to validate the trial outputs.

The longer term 60-month OS data from ZUMA-1 were reported by the company to support the hypothesis that around [redacted]% of patients receiving axi-cel will experience long-term remission.[2] The EAG agrees that there is a plateau with about [redacted]% survival in the first 12 months, followed by over [redacted]% in the next 12 months and then over [redacted]% in each of the next 12 months up to 60 months. This was partly validated, as follow up in the SACT database only continued to 36 months. Comparator data from

SCHOLAR-1 was provided for overall survival but no formal ITC was provided, notwithstanding the committee consideration of the adjusted SCHOLAR-1 data being appropriate for decision making (see Section 2.2). As highlighted elsewhere, the analysis and presentation of the SCHOLAR-1 data in relation to the ZUMA-1 data were unclear: in particular, there was no equivalent landmark analysis and so it is uncertain how much of the survival benefit is related to axi-cel.

PFS data from ZUMA-1 are available up to 35 months follow-up, and again demonstrates a prolonged plateau.[2] However, this is not validated by SACT data and there are no SCHOLAR-1 data to provide comparator data. As detailed in Section 4.6.3, the EAG suggests that the company should have used longer-term data (e.g. also 60 months) to support the plateau assumption.

Overall, therefore, the EAG believes that this assumption has not been fully adhered to.

2.2.7 Assumption 7: Cure assumption

The company should fully explore assumptions of cure using the more mature ZUMA-1 data and other updated data that has become available during the period of managed access.

The ZUMA-1 data on OS partially supported the assumption of cure in a proportion (approximately [redacted]%) of patients, with a continuation of a plateau for OS (albeit somewhat reduced) to 60 months.[2] However, this was not accompanied by new comparator evidence.

2.2.8 Assumption 8: Most plausible ICER

The Committee agreed that axicabtagene ciloleucel demonstrated plausible potential to be cost effective.

The committee agreed that the most plausible ICER is between the company's base-case ICER of [redacted] per QALY and the EAG's revised (upper-bound) base-case of [redacted] per QALY gained versus salvage chemotherapy.[1] The ICERs in all company's scenario analyses were lower than £50,000 per QALY gained, whereas of the EAG's scenario and exploratory analyses, all but one scenario led to an ICER above £50,000 per QALY gained.[1] Therefore, the committee agreed that the most plausible ICER is between the company's and the EAG's revised base-case estimates.[1]

In the CES, the updated company's base-case ICER was £49,159 per QALY gained.[2] The updated ICER used the log-logistic mixture cure model for OS of axi-cel based on the 60-month ZUMA-1 data cut, a generalised gamma distribution for OS for salvage chemotherapy, applied a standardised mortality ratio (SMR) of 1.09 to patients in both treatment arms who were alive after 60 months, PFS for axi-cel modelled based on ZUMA-1 24-month data cut, updated population life tables using 2021 Office for National Statistics (ONS) data, and assumed a [redacted], instead of a simple discount of [redacted] to the axi-cel list price combined with [redacted] for patients who do not survive 12 months after infusion that was used in the original submission. These changes also included a correction of an error found in the application of the SMR, which is now applied to the mortality rate rather than to the probability of death, as in the previous version of the model.

The EAG made two changes to the company's base-case:

- Update the model using 2019/2020 NHS Reference costs and align all the other cost inputs to the same cost year (done by the company response to clarification question B7).[3]
- Proportion of patients using IVIG treatment equal to 16% and a treatment duration at 6.5 months, as observed in the SACT cohort.[6]

The EAG's preferred ICER increased from £49,159 per QALY gained to £50,480 per QALY gained. The results of the additional scenario analyses conducted by the EAG indicated that the ICER was stable to changes in axi-cel OS extrapolations and in IVIG treatment assumptions. The model results are still sensitive to changes in OS for the salvage chemotherapy arm and to changes in PFS for the axi-cel arm.

2.2.9 Assumption 9: Axicabtagene ciloleucel meets the end-of-life criteria

The committee agreed that axi-cel met end-of-life criteria and therefore is plausibly cost effective.[2] The committee accepted that, although there was significant uncertainty in the cost effectiveness estimates, many of the assumptions in the company's base-case appear plausible and might be verified through further data collection.[2] Unfortunately, the quality of the further data collection, please see points above, has not been sufficient to verify the assumptions underlying the assumption that axi-cel meets end-of-life criteria.

3. CLINICAL EFFECTIVENESS

3.1 Overview of the new clinical evidence

3.1.1 Sources of evidence

The clinical efficacy of axi-cel for the treatment of relapsed or refractory DLBCL and PMBCL in adult patients after two or more systemic therapies, is reported by the CES as having been investigated by ZUMA-1.[2]

ZUMA-1 is a phase 1/2, single-arm, multi-centre, open-label study of the intervention axi-cel in 108 patients with aggressive B-cell Non-Hodgkin's Lymphoma (DLBCL, PMBCL, and transformed follicular lymphoma (TFL)) that is either refractory to treatment or has relapsed ≤12 months after autologous stem cell transplant (ASCT). Included patients had prior therapy with an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen; no central nervous system (CNS) lymphoma; no history of allogeneic stem cell therapy (SCT); and no prior anti-CD19, chimeric antigen receptor (CAR), or other genetically modified T-cell therapy.

The latest data cut of the ZUMA-1 study (11 August 2021) includes 60 months' minimum follow-up, referred to as the 60-month data cut. All survival analyses for axi-cel were conducted using the modified intention-to-treat (mITT) population from combined phases I and II of ZUMA-1 (N=108), i.e. those patients who received at least 1 x 10^6 anti-CD19 CAR T-cells/kg body weight. From the 60-month data cut, in the phase I (N=7) and phase II (N=101) populations, the median potential follow-up duration from axi-cel infusion was [redacted] months and [redacted] months, respectively. The median actual follow-up, defined as the time from axi-cel infusion to the date of death or the last date known alive, was [redacted] months in phase I and [redacted] months in phase II. OS and OS by objective responses were collected to address key uncertainties raised in the original submission.

The other source of evidence cited by the CES for axi-cel is the SACT dataset.[2] This provides single-arm evidence on OS and, in the final report, IVIG usage, for a real-world cohort of patients treated with axi-cel for the same indications.[6] The patient characteristics are generally similar to ZUMA-1.

One finding highlighted by the company is the level of missing data from SACT on the Eastern Cooperative Oncology Group (ECOG) performance status. In the ZUMA-1 population, 58% of patients had an ECOG performance status of >0; in the SACT cohort, this was 39%, but 37% had missing outcomes. The company states that missing outcomes from SACT make a comparison to ZUMA-1 difficult. The company also perceives a further limitation of the SACT data: in the initial period of SACT data-collection, when axi-cel first became available, general management was less effective and so SACT outcomes may not be truly representative of the overall current situation in today's United Kingdom (UK) clinical practice.[2]

As mentioned, both the ZUMA-1 and SACT datasets were single-arm. Therefore, additional comparator evidence has been derived. The committee previously identified SCHOLAR-1 as the most relevant source of comparator data for decision-making. Given the heterogeneity between the patient populations for relevant comparator treatments (where the majority of patients have received only one prior line of therapy), as outlined in the original submission, the availability of patient-level data to account for differences between patient characteristics and key prognostic factors was considered more rigorous and allowed a more appropriate comparison. The SCHOLAR-1 study was conducted using data from four sources for which patient-level data were available:

1. MD Anderson Cancer Centre (MDACC) database,

2. Mayo Clinic and University of Iowa (MC/IA) Specialized Programs of Research Excellence (SPORE) database,
3. The National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) randomised Phase III study LY.12, and
4. The French Lymphoma Academic Research Organisation (LYSARC) randomised Phase III Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study.

The availability of patient-level data allowed for patients to be included that more closely matched the patient population of ZUMA-1 and for adjustments to be made to account for any differences.

The ToE requested that any new sources of evidence akin to SCHOLAR-1 should also be included as comparator evidence.[1] A targeted PubMed search using keyword searches was conducted to identify additional sources of comparative data published since September 2018. The search identified three publications that provided outcomes of salvage chemotherapy in the relapsed or refractory setting.

Table 3.1 summarises the methodology of the included studies.

EAG comment: The EAG accepts that the company's reservations about the quality of the SACT cohort are justified. The missing data, particularly in terms of 'disease type' and ECOG performance status, do reduce the usefulness of the SACT database as a reference point.

The CES discusses a 'targeted PubMed search' for additional comparator data that yielded three sources, only one of which was from the UK (and which was an abstract). The company was asked to describe more formal searches undertaken, using a fuller selection of databases, that are more likely to have yielded more comprehensive data.[4] In its response to the request for clarification, the company stated that a basic PubMed search was conducted using 'suitable keyword MeSH' search terms, and results limited to studies published after 2018.[3] They acknowledge the *"absence of high rigour that one would typically expect of a conventional SLR approach"*, but claim that the low number of records found was not unexpected, *"since the establishment of CAR T-cell therapy for DLBCL after two or more prior therapies in the last few years has meant that a counterfactual 'world' without CAR T is expected to have significantly limited the use of chemotherapy for patients treated with curative intent in this setting"*.[3]

The EAG believes that more rigorous searches, including searches for conference proceedings and other relevant completed and ongoing studies using resources other than PubMed (e.g. EMBASE) may have retrieved additional useful references. Unfortunately, the EAG was unable to undertake independent searches and review the results, as this would be outside of the EAG remit. It is therefore not possible to assess to what extent the company searches missed any potentially relevant studies.

The CES provides no evidence that any of the data from the three additional sources were used in the indirect treatment comparison analyses.[2] Only one outcome was used from the SCHOLAR-1 data in the indirect treatment comparison analyses, and this was not adequately integrated with the ZUMA-1 data.

3.1.2 Patient characteristics in the ZUMA-1 trial, SACT cohort study, SCHOLAR-1 data and the three new sources

Baseline characteristics of the ZUMA-1, SACT cohort, SCHOLAR-1 data,[7] and data from the three new sources, namely Radford et al. 2019,[8] Fuji et al. 2021,[9] and Nakaya et al. 2019[10] are summarised in Table 3.2. Most of the information about the comparators is derived from the primary sources.

EAG comment: The CES provides very little information about the three additional sources, and does not incorporate data from these sources into the analysis. Therefore, in addition to failing to provide a clear presentation of how axi-cel performs compared to the SCHOLAR-1 comparator data, the CES has not utilised any of the new data sources in its indirect treatment comparison analysis. The EAG considers this to represent a failure to achieve the specified ToE, which was to update the comparator evidence.[1]

Table 3.1: Summary of methodology of the ZUMA-1 trial, SACT cohort study, SCHOLAR-1, and 3 additional studies.

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
Location	The study was conducted at 24 centres (23 in the USA and 1 centre in Israel).	UK	USA, Canada, France	No details provided in the CES. The following information has been derived from the primary source: UK single centre.	No details provided in the CES. The following information has been derived from the primary source: Two sources in Japan: 1) population-based cancer registry and 2) insurance data.	No details provided in the CES. The following information has been derived from the primary source: Japan: Kansai Medical University Hospital and Kansai Medical University Medical Centre.
Design	ZUMA-1 is an ongoing Phase 1/2, single-arm, multi-centre, open-label study.	Observational study	The SCHOLAR-1 study was conducted using data from four sources for which patient-level data relating to salvage chemotherapy were available: MDACC database; MC/IA SPORE database; NCIC CTG randomised phase III study LY.12; and the French LYSARC randomised phase III CORAL	No details provided in the CES. The following information has been derived from the primary source: Retrospective analysis.	No details provided in the CES. The following information has been derived from the primary source[9]: Retrospective study.	No details provided in the CES[2]. The following information has been derived from the primary source[10]: Retrospective analysis.

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
			study. The availability of patient-level data allowed for patients to be included that more closely matched the patient population of ZUMA-1 and for adjustments to be made to account for any differences. Of the total 593 participants in the 4 studies, only data with ECOG 0-1 were included (n=188) to allow closer matching with the ZUMA-1 participants.			
Eligibility criteria for participants	**Inclusion criteria:** • Histologically confirmed DLBCL, PMBCL, or TFL • Chemotherapy-refractory disease, defined as one or more of the following:	Adults with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic	No details provided in the CES. The following information has been derived from the primary source: *"All*	No details provided in the CES. The following information has been derived from the primary source: *"Patients*	No details provided in the CES. The following information has been derived from the primary source: *"In this retrospective study,*	No details provided in the CES. The following information has been derived from the primary source: *"Among 530 patients diagnosed with DLBCL from April*

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
	– No response to first-line therapy (primary refractory disease); patients who are intolerant to first-line therapy chemotherapy were excluded – No response to second or later lines of therapy • Refractory after ASCT, defined as occurrence of disease progression or relapse ≤12 months after ASCT (must have biopsy proven recurrence in relapsed patients) or, if salvage therapy was given after ASCT, the patient must have had no response to or relapsed after the last line of therapy. • Prior therapy including anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen. • Measurable disease according to the revised IWG Response Criteria	therapy, and TFL after one or more lines of systemic therapy.	*patients from each data source who met criteria for refractory DLBCL, including TFL and PMBCL, who received subsequent therapy were considered for analysis. Refractory DLBCL (including subtypes PMBCL and TFL) was defined as progressive disease (received ≥4 cycles of first-line therapy) or stable disease (received 2 cycles of later-line therapy) as best response to chemotherapy or relapse ≤12 months after ASCT. TFL and PMBCL were included because*	*with DLBCL 2006-2017 and a R/R event 2011-2017. Additional eligibility criteria were: age ≥18 years; ≥1 prior anti-CD20 antibody-containing chemo-immunotherapy regimen; no history of high-grade transformation; and no lymphomatous CNS involvement".*	*we included adult patients registered in the OCR from 2010 to 2015 who were aged 70 years or younger and who had DLBCL, not otherwise specified (NOS), according to the International Classification of Diseases for Oncology, Third Edition morphological code 9680/3. We included patients who received CHOP or a CHOP-like regimen in combination with rituximab as first-line chemotherapy and who subsequently received salvage chemotherapy. We did not include patients with primary central nervous system lymphoma. Patients who had already received*	*2002 to November 2017, 131 relapsed and refractory patients who received salvage therapy were enrolled in this study".*

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
	for Malignant Lymphoma (hereafter referred to as IWG 2007 criteria)[11] • No evidence of CNS lymphoma • Age 18 or older • ECOG performance status of 0 or 1 • Adequate haematologic, renal, hepatic, pulmonary and cardiac function **Exclusion criteria:** • History of allogeneic SCT • Autologous stem cell transplant within 6 weeks of informed consent • Prior CD19 targeted therapy with the exception of patients who received axi-cel in this study and are eligible for retreatment • Prior CAR therapy or other genetically modified T-cell therapy • Presence of fungal, bacterial, viral, or other infection that was uncontrolled or requiring		*they are histologically similar and are clinically treated as large-cell lymphoma. Patients must have received an anti-CD20 monoclonal antibody and an anthracycline as 1 of their qualifying regimens. For IA/MC, LY.12, and CORAL, patients were included at first instance of meeting refractory criteria, whereas for MDACC, patients who first met refractory criteria from second-line therapy onward were included. Patients with primary central nervous system*		*chemotherapy in other hospitals were excluded".*	

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
	IV antimicrobials for management. • History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/haemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement.		*lymphoma were excluded".*			
Trial drugs and method of administration	Patients received a single infusion of axi-cel at a target dose of 2 x 106 anti-CD19 CAR T-cells/kg (±20%). The minimum dose to be administered was 1 x 106 anti-CD19 CAR T-cells/kg. For patients weighing >100 kg, a maximum flat dose of 2 x 108 anti-CD19 CAR T-cells was to be administered. The entire bag of axi-cel was to be infused. Axi-cel is administered after a conditioning chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 IV on the 5th, 4th, and 3rd day before infusion of axi-cel.	Axi-cel, but details unclear.	Inadequate details provided in the CES. The following information has been derived from the primary source: *"Briefly, the MDACC observational cohort included patients with DLBCL and TFL who were relapsed or refractory to initial rituximab-containing chemotherapy, had failed salvage platinum-*	Inadequate details provided in the CES. The following information has been derived from the primary source: *"Systemic 2L therapies (≥5% incidence) included R-DHAP (20.2%; n=18), R-GDP (20.2%; n=18), DHAP (10.1%; n=9), R-GCVP (7.9%; n=7), and gemcitabine (5.6%; n=5)"*	Inadequate details provided in the CES. The following information has been derived from the primary source: *"Second line drugs included the following:* • *ESHAP-based (22.2%)* • *CHASE-based (20.6%)* • *DeVIC/ICE-based (13.8%)* • *HD-MTX/AraC-based (11.6%)* • *Gemcitabine-based (9.0%)*	Inadequate details provided in the CES. The following information has been derived from the primary source: *"The most common salvage regimen was R-DeVIC (rituximab, etoposide, dexamethasone, ifosfamide, carboplatin) (42%), followed by R-ESHAP (rituximab, etoposide, solumedrol, cytarabine, cisplatin) (23%). Other aggressive regimens were administered to 12% of patients, and*

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
	Paracetamol 650 mg given orally and diphenhydramine 12.5 mg IV or orally approximately 1 hour before axi-cel infusion is also recommended. 111 patients were enrolled and leukapheresed (81 with DLBCL in Cohort 1 and 30 with PMBCL/TFL in Cohort 2). 101 patients were treated with axi-cel: 77 in Cohort 1 and 24 in Cohort 2. Concomitant medication: • Corticosteroid therapy at a dose ≥5 mg/day of prednisone or equivalent doses of other corticosteroids and other immunosuppressive drugs were to be avoided for 7 days prior to leukapheresis and 5 days prior to axi-cel administration. • Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after axi-cel administration, unless used to manage axi-cel-		*containing chemotherapy, and received a second salvage therapy at MDACC. The IA/MC is a Midwest US observational cohort that enrolled unselected, newly diagnosed patients with lymphoma who then entered prospective documentation of primary and subsequent treatments and outcomes. In the international randomized LY.12 study, 619 patients (from 4 countries) were enrolled at the time of relapse after anthracycline-containing therapy and were*		• *Mitoxantrone-based (11.1%)* • *Others (10.9%)"*	*included R-CHASE (rituximab, cyclophosphamide, cytosine arabinoside, etoposide, dexamethasone) (n=5), rituximab plus methotrexate-based treatment (n=5), R-CHOP-based treatment (n=3), R-GDP (rituximab, gemcitabine, cisplatin, dexamethasone) (n=2), and R-EPOCH (rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone) (n=1). Finally, 23% of patients underwent palliative therapy such as radiation, rituximab monotherapy, oral etoposide, or oral prednisolone"*

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
	related toxicities. Other medications that might interfere with the evaluation of the investigational product were also to be avoided for the same period unless medically necessary. • Treatment for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than the investigational product in this protocol, and other investigational agents, were prohibited, except as needed for treatment of disease progression after the axi-cel infusion. • The investigator was allowed to prescribe medications deemed necessary to provide adequate supportive care. All concomitant medications used during the 3 months following infusion of axi-cel (and a limited set of selected		*randomly assigned to 1 of 2 salvage regimens with a goal of consolidative ASCT. The CORAL study enrolled 477 patients (from 11 countries) with DLBCL who were in their first relapse or whose lymphoma was refractory to first-line therapy, and patients were randomly assigned to 1 of 2 salvage regimens with a goal of consolidative ASCT. In the latter 2 studies, eligible patients with CD20+ lymphoma were randomly assigned to rituximab maintenance or observation after ASCT"*			

Trial name	ZUMA-1 NCT02348216	SACT dataset	SCHOLAR-1[7]	Radford et al. 2019[8]	Fuji et al. 2021[9]	Nakaya et al. 2019 [10]
	concomitant medications through 24 months beyond disease progression) were to be recorded in the CRF.					
Outcomes collected for the CDF review	• OS • PFS • IVIG usage	• OS • IVIG usage*	• OS • Objective response rate	• Overall response rate • OS	• PFS • OS	• PFS • OS
Subgroups	None	None	None	Stem-cell transplanted/ non-transplanted patients	Stem-cell transplanted/ non-transplanted patients	Unclear
Duration of study and follow-up	60 months minimum follow-up	Unclear	Unclear	At least 2-year follow-up	At least 3-year follow-up	Up to 75 months

Based on Table 6 of CS document B,[12] Table 3 of CES CDRF,[2]as well as primary studies[7-10]

* Real-world IVIG usage data not available at the time of CES submission, but provided in the final SACT report[6]

2L = second line; ASCT = autologous stem cell transplant, CAR = chimeric antigen receptor; CDF = Cancer Drug Funds; CES = company evidence submission; CHASE = cyclophosphamide, cytosine arabinoside, etoposide, dexamethasone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CNS = central nervous system; CORAL = Collaborative Trial in Relapsed Aggressive Lymphoma; CRF = case report form; CRT = chemoradiation therapy; CS = company submission; CTG = Cancer Trials Group; DeVIC = etoposide, dexamethasone, ifosfamide, carboplatin; DHAP = dexamethasone, high-dose cytarabine and cisplatin; DLBCL = diffuse large B cell lymphoma; ECOG = Eastern Cooperative Oncology Group; EPOCH = etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone; ESHAP = etoposide, solumedrol, cytarabine, cisplatin; GCVP = gemcitabine, cyclophosphamide, vincristine and prednisolone; GDP = gemcitabine, cisplatin, dexamethasone; HD-MTX = High-dose methotrexate chemotherapy; ICE = ifosfamide, carboplatin, and etoposide; IV = intravenous; IVIG = intravenous immunoglobin; IWG = International Working Group; LYSARC = Lymphoma Academic Research Organisation; MC/IA = Mayo Clinic and University of Iowa; MDACC = MD Anderson Cancer Centre; NCIC = National Cancer Institute of Canada; NOS = not otherwise specified; OCR = Osaka Cancer Registry; OS = overall survival; PFS = progression-free survival; PMBCL = primary mediastinal B Cell lymphoma; R = rituximab; SACT = systemic anti-cancer therapy; SCT = stem cell transplant; SPORE = Specialized Programs of Research Excellence; TFL = transformed follicular lymphoma; UK = United Kingdom; USA = United States (of America)

Table 3.2: Baseline characteristics of patients in the ZUMA-1 trial, SACT cohort study, SCHOLAR-1, and three additional studies.

Patient characteristic	SACT cohort (N=127)	ZUMA-1 mITT population (N=101)	SCHOLAR 1[7] (N=188, limited to ECOG 0-1)	Radford et al.[8] (N=89)	Fuji et al.[9] (N=189)	Nakaya et al.[10] (N=131)
Median age						
Age (range)	59.5 (N/R)	58 (23, 76)	54 (20, 69)	66 (58, 72)	63 (24, 70)	68 (35, 87)
Age category, n (%)						
< 40 40–49 50–59 60–69 70–79 80+	34 (11%) 43 (14%) 82 (26%) 124 (39%) 35 (11%) 0 (0%)	Age ≥ 65 years: 24 (24%)	Age ≥ 65 years: 7 (4%)	N/R	N/R	N/R
Sex, n (%)						
Male Female	191 (60%) 127 (40%)	68 (67%) 33 (33%)	N/R	N/R	N/R	N/R
ECOG performance status, n (%)						
0 1 2 Missing	75 (24%) 111 (35%) 13 (4%) 119 (37%)	42 (42%) 59 (58%) 0 (0%) 0 (0%)	0-1 100%	N/R	N/R	N/R
Disease type, n (%)						
DLBCL TFL PMBCL Not currently captured	136 (43%) 45 (14%) 18 (6%) 119 (37%)	77 (76%) 16 (16%) 8 (8%) 0 (0%)	N/R	N/R	N/R	N/R
Refractory subgroup, n (%)						
Primary refractory Refractory to second or later therapy	0 (0%) 132 (42%)	2 (2%) 78 (77%) 21 (21%) 0 (0%)	N/R	N/R	N/R	N/R

Patient characteristic	SACT cohort (N=127)	ZUMA-1 mITT population (N=101)	SCHOLAR 1[7] (N=188, limited to ECOG 0-1)	Radford et al.[8] (N=89)	Fuji et al.[9] (N=189)	Nakaya et al.[10] (N=131)
Relapsed Not currently captured	58 (18%) 128 (40%)					
SCT status, n (%)						
Has not had SCT Has had autologous SCT Has had allogeneic SCT Not currently captured	158 (50%) 38 (12%) 3 (1%) 119 (37%)	Has not had autologous SCT: 76 (75%) Has had autologous SCT: 25 (25%)	Sub-grouped into 100% SCT, 10% SCT, 0% SCT	N/R	N/R	N/R
IPI score						
0–1, n (%) 2, n (%) ≥3, n (%) 2-3, n (%) 4-5, n (%) Not Assessed, n (%)	N/R	27 (25) 33 (31) 48 (44) N/A N/A 0	69 (37) 54 (29) 54 (29) N/A N/A 11 (6)	N/R	N/R	Low, 29 (22%) Low-Int, 23 (18%) High-Int, 29 (22%) High, 50 (38%)
Disease stage						
I-II, n (%) III-IV, n (%) IIIS, n (%) IE, n (%) Not Assessed, n (%)	N/R	18 (17) 90 (83) 0 0 0	62 (33) 119 (63) 0 0 7 (4)	N/R 57 (64) N/R N/R N/R	N//R	35 (27) 96 (73) 0 0 0
Total number of lines of chemotherapy						
1, n (%) 2-3, n (%) ≥4, n (%)	N/R	2 (2) 65 (60) 35 (33)	44 (23) 143 (76) 1 (1)	89 (100)* 63 (71)* 41 (46)*	189 (100)* 189 (100)* NR	N/R N/R N/R

Based on appendix Tables 16.1 and 16.2 from CES[2]

* Patients followed up over time, and therefore received multiple treatment lines.

CES = company evidence submission; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; mITT = modified intention-to-treat; N/A = not applicable; N/R = not reported; PMBCL = primary mediastinal large B-cell lymphoma; SACT = systemic anti-cancer therapy; SCT = stem cell transplant; TFL = transformed follicular lymphoma

3.2 Results of the new clinical evidence

EAG comment: As previously explained, the CES fails to integrate evidence from different sources.[2] Instead, results are presented separately, and often without any qualitative comparison.

3.2.1 Overall survival

3.2.1.1 ZUMA-1

Figure 3.1 presents the Kaplan–Meier (KM) curve for OS, with a median OS of [redacted] months (95% confidence interval (CI), [redacted]). At the time of data cut-off providing a maximum actual follow-up of [redacted] months, [redacted] patients ([redacted]%) had died. Estimated OS rates at specific time points are presented in Table 3.3.

Figure 3.1: ZUMA-1 OS in the phase I and II mITT population (N=108, 11 August 2021 data cut)

Based on Figure 1 of the CES[2]
CES = company evidence submission; CI = confidence interval; mITT = modified intention-to-treat; OS = overall survival

Table 3.3: ZUMA-1 survival rate by KM estimation in the Phase I and II mITT population (N=108, 11 August 2021 data cut)

Time point	Survival rate by Kaplan–Meier estimation	
	Phase I (N=7)	Phase II (N=101)
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]
Based on Table 4, CES[2]		

Time point	Survival rate by Kaplan–Meier estimation	
	Phase I (N=7)	Phase II (N=101)
CES = company evidence submission; CI = confidence interval; KM = Kaplan-Meier; mITT = modified intention-to-treat		

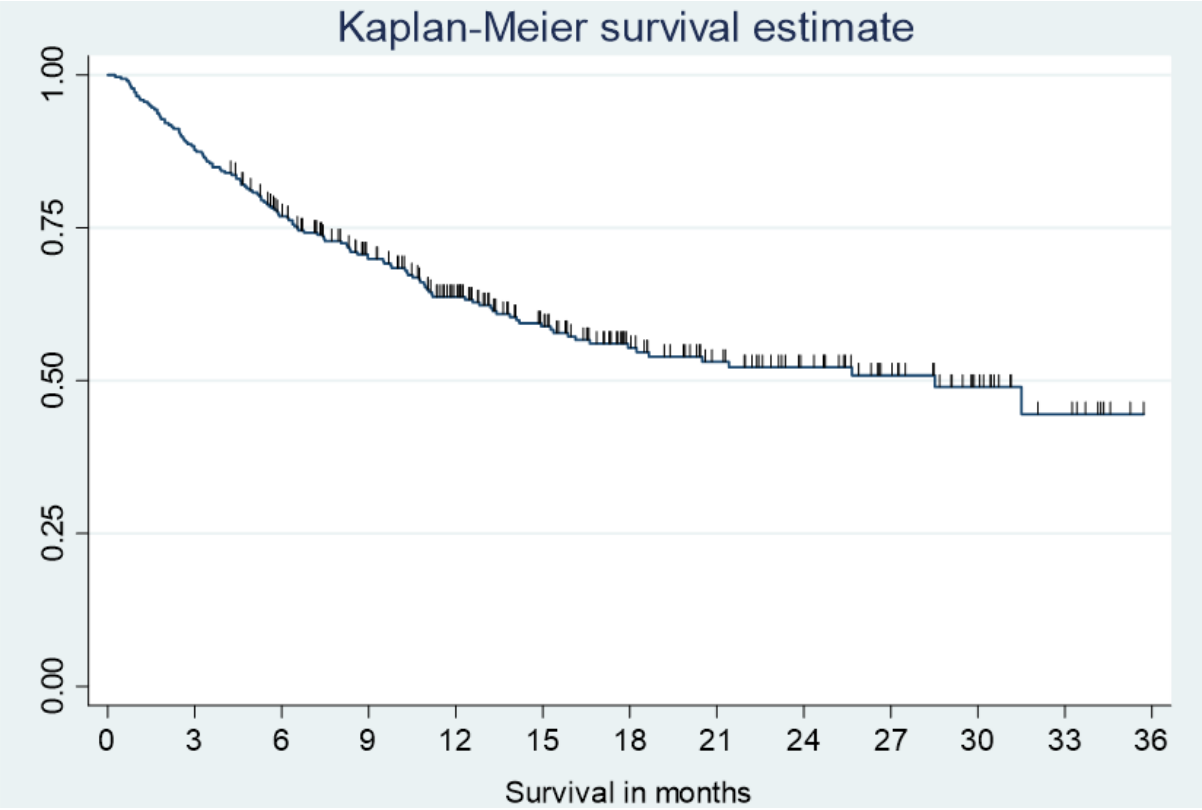
Among patients who achieved a complete response (CR) (N= [redacted]), the estimated 60-month survival rate was [redacted]% in Phase I and [redacted]% in Phase II.

3.2.1.2 SACT data

Of the 318 patients with a treatment record in SACT, the minimum follow-up was four months (121 days) from the last CDF application. Figure 3.2 provides the KM curve for OS, censored at 03 March 2022. The median survival was 28.5 months (N=318).

Survival at 12 months was 64% (95% CI 58% to 69%), survival at 24 months was 52% (95% CI 45% to 58%) and 36-month survival was 45% (95% CI 34% to 55%). A comparison of survival from the SACT cohort with the modelled ZUMA-1 population is provided in Table 3.4.

Figure 3.2: KM survival plot of OS from SACT (N=318)



Based on Figure 4 of the CES[2]
CES = company evidence submission; KM = Kaplan-Meier; OS = Overall survival; SACT = systemic anti-cancer therapy

Table 3.4: Comparison of ZUMA-1 and SACT survival, at specified time intervals

Time point	ZUMA-1 survival rate by KM estimation		SACT dataset overall survival
	Phase I (N=7)	Phase II (N=101)	
6 months	[redacted]	[redacted]	[redacted]

Time point	ZUMA-1 survival rate by KM estimation		SACT dataset overall survival
	Phase I (N=7)	Phase II (N=101)	
12 months	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]

Based on Table 5 of the CES[2] and Table 7 of SACT final report[6]
Comparison made with ZUMA-1 phase I and II mITT population (N=108, 11 August 2021 data cut)[13]
CES = company evidence submission; KM = Kaplan-Meier; mITT = modified intention-to-treat; SACT = systemic anti-cancer therapy

3.2.1.3 SCHOLAR-1 cohort (comparator data)

SCHOLAR-1 was adjusted to ensure comparability with the ZUMA-1 population. The following steps were taken to do this:

- Patients with ECOG performance status 2 to 4 and an unknown ECOG performance status were excluded, consistent with the EAG-preferred approach
- Primary refractory patients were excluded, consistent with the marketing authorisation
- The resulting OS curve was adjusted to reflect outcomes for a population in which 10% of patients underwent subsequent stem cell transplant (SCT).

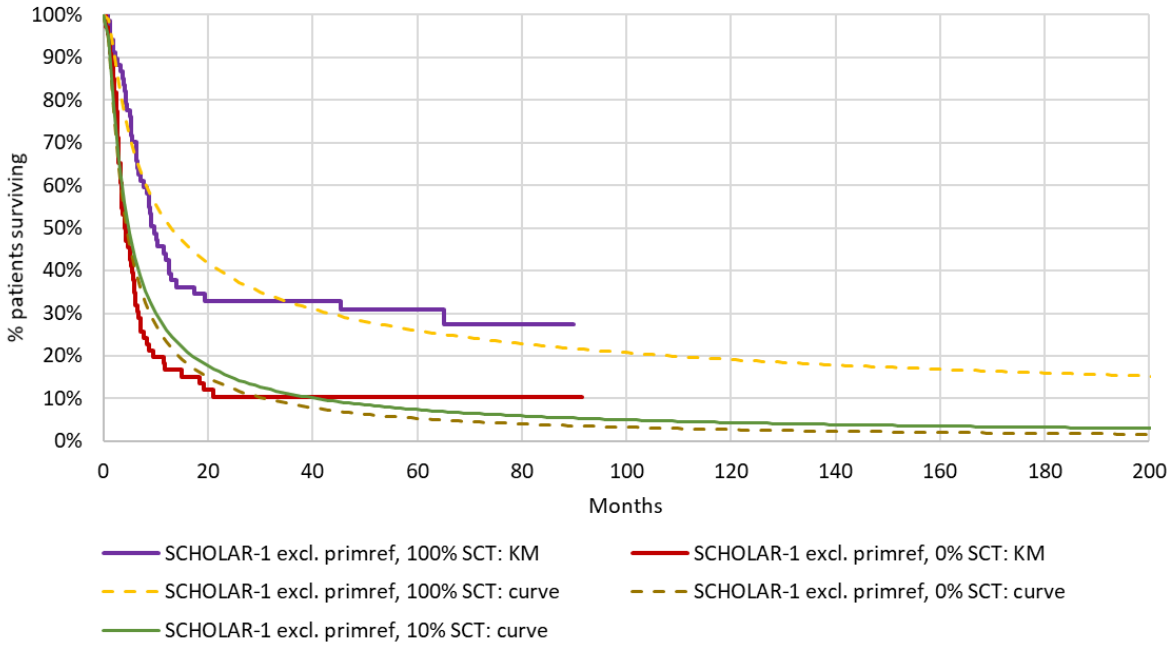
Regarding the adjustment for SCT, the 10% estimate was based on clinical opinion (CDF discussions and tisagenlecleucel appraisal meeting) that approximately 10% of patients would receive SCT in clinical practice after undergoing two or more lines of systemic treatment.[14]

To adjust the OS for SCT, separate survival curves were used to generate a weighted survival estimate based on whether or not patients had received an SCT. This approach was consistent with the EAG's approach outlined in the National Institute for Health and Care Excellence (NICE) Appraisal Consultation Document (ACD) slides for tisagenlecleucel DLBCL technology appraisal (TA567).[14]

Figure 3.3 presents the KM and selected parametric curves (generalised gamma) for the non-SCT and SCT populations (SCHOLAR-1 with ECOG performance status 2 to 4 and unknowns and primary refractory patients excluded) and the derived curve fit for the base-case 10% SCT population.

The generalised gamma model was selected based on the committee's commentary in the final appraisal determination (FAD): *"The Committee concluded that a single parametric survival model applying a generalised gamma distribution curve to OS data was the most clinically plausible extrapolation and was appropriate to model salvage chemotherapy"*.[15]

Figure 3.3: OS of salvage chemotherapy: SCHOLAR-1 (ECOG performance status 0 to 1 only and excluding primary refractory) with 10% SCT



Based on Figure 5 of the CES[2]
CES = company evidence submission; ECOG = Eastern Cooperative Oncology Group; KM = Kaplan-Meier; OS = overall survival; SCT = stem cell transplant

3.2.1.4 Additional comparator data from three additional sources

The only data reported were a median OS of 195 days (6.4 months), taken from the UK study.{Radford, 2019 #87} Data from the other two studies were not used as they were not UK studies. However, this is not a strong rationale as the ZUMA-1 trial did not include participants from the UK.

EAG comment: The SACT data were of limited use for validation of ZUMA-1 data as no 60-month data were available.

3.2.1.5 Indirect treatment comparison

Figure 3.4 compares OS between axi-cel and salvage chemotherapy.

ERG comment: The comparison between axi-cel and salvage chemotherapy is made without any measures of uncertainty, making interpretation of findings difficult. The data for salvage chemotherapy were composed only of data from SCHOLAR-1 and did not include the single data-point from Radford et al. 2019.{Radford, 2019 #87}

Figure 3.4: Base case lifetime overall survival and progression-free survival projections for axi-cel and salvage chemotherapy

Based on Figure 13 of the CES[2]
CES = company evidence submission; OS = overall survival; PFS = progression-free survival

3.2.2 Overall survival by best objective response

3.2.2.1 ZUMA-1

The primary outcome measure in ZUMA-1 was overall response rate, defined as CR or partial response (PR; based on International Working Group (IWG) response criteria for malignant lymphoma).[11]

Figure 3.5 presents OS by best objective response and shows a substantial extension to life for patients experiencing a CR to axi-cel treatment (compared with patients experiencing a PR).

Figure 3.5: ZUMA-1 overall survival by best overall response group in the phase I and II mITT population (N=108, 11 August 2021 data cut)

Based on Figure 1 of the CES[2]
CES = company evidence submission; CI = confidence interval; CR = complete response; mITT = modified intention-to-treat; NE = not estimable; NR = non-response; PR = partial response

3.2.2.2 SACT data

No data provided in the CES.

3.2.2.3 SCHOLAR-1 cohort

No data provided in the CES.

3.2.2.4 Additional comparator data from three additional sources

No data provided in the CES.

EAG comment: The lack of any comparator data relevant to this precise population means that it is very difficult to interpret the ZUMA-1 data on this outcome. It is impossible to know how much of any apparent treatment benefit is due to axi-cel and how much is a function of the natural course of the condition in the specified population.

3.2.3 Progression-free survival

3.2.3.1 ZUMA-1

Per the ZUMA-1 study protocol, there was no protocol-defined mandate to collect progression data beyond 24 months. Instead, this assessment was done per institutional standard of care. Therefore, any PFS data collected beyond 24 months may not be consistent with the criteria applied in ZUMA-1. For this reason, PFS data collected up to month 24 are presented here and used in the economic model.

Figure 3.6 shows that the median PFS for the mITT population was [redacted] months after a median potential follow-up of [redacted] months in phase I and [redacted] months in phase II, using investigator assessment as defined by IWG criteria. Median actual follow-up was [redacted] months in phase I and [redacted] months in phase II.

Figure 3.6: ZUMA-1 PFS in the phase I and II mITT (N=108, 11 August 2018 data cut)

Based on Figure 3 of the CES[2] and ZUMA-1[16]
CES = company evidence submission; CI = confidence interval; mITT = modified intention-to-treat; PFS = progression-free survival

3.2.3.2 SACT data

No data provided in the CES.

3.2.3.3 SCHOLAR-1 cohort

No individual data relating to PFS provided in the CES, or in the primary source{Crump, 2017 #94}.

3.2.3.4 Additional comparator data from three additional sources

No data provided in the CES.

EAG comment: The lack of any comparator data relevant to this precise population means that it is very difficult to interpret the ZUMA-1 data on this outcome. It is impossible to know how much of any apparent treatment benefit is due to axi-cel and how much is a function of the natural course of the condition in the specified population.

3.2.1.4 Indirect treatment comparison

Figure 3.4 (above) compares PFS between axi-cel and salvage chemotherapy.

ERG comment: The comparison between axi-cel and salvage chemotherapy is made without any measures of uncertainty, making interpretation of findings difficult. The source of the data for PFS is unclear, because PFS data are not presented in the primary source of the SCHOLAR-1{Crump, 2017 #94}, nor are they presented as individual results from SCHOLAR-1 in the CES. Further clarification is required on the origin of the presented PFS data.

3.2.4 Intravenous immunoglobulins use

3.2.4.1 ZUMA-1 data

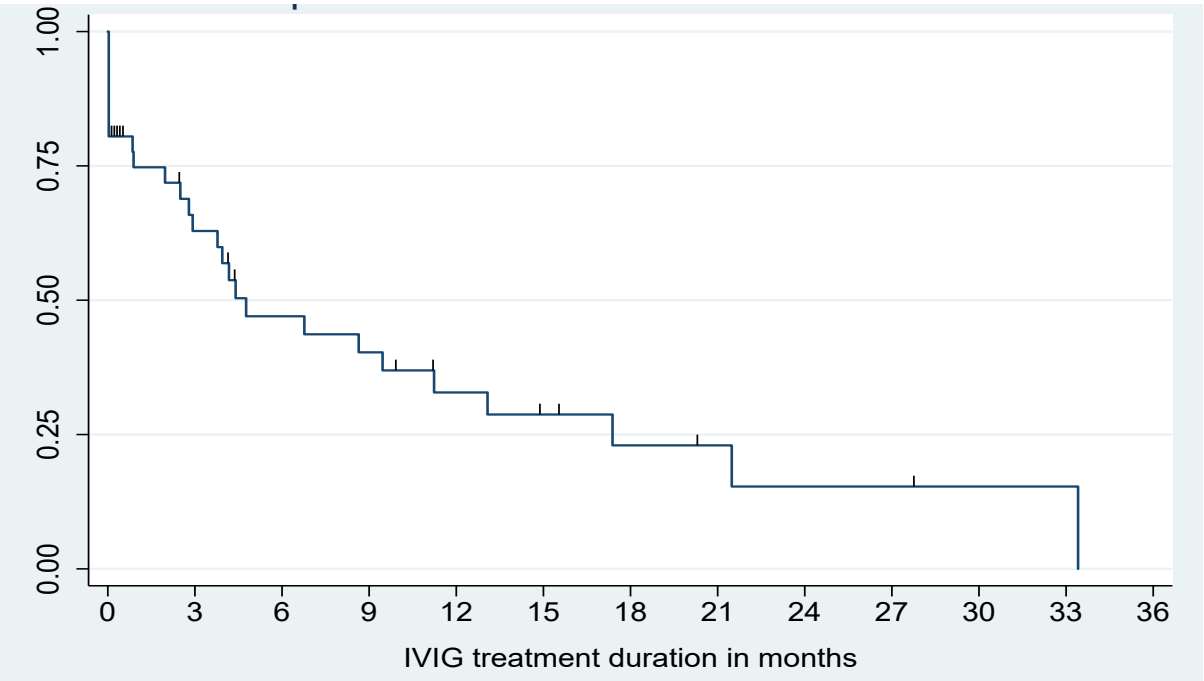
The proportion of patients receiving IVIG that was used in the original submitted economic model for TA559 was [redacted].[17] This is reported by the CES to be consistent with the expected low rates in today's clinical practice, as confirmed by expert clinical opinion.[2]

3.2.4.2 SACT data

No data were provided in the CES, but data were provided in the axi-cel final SACT report [6] This showed that 41/262 patients (16%) received IVIG. Of these 41 patients, nine (22%) died, 18 (44%) ceased treatment and in 14 (34%) treatment was ongoing.

The KM curve shown in Figure 3.8 shows the median treatment duration for all patients was 4.8 months (95% CI 2.8 to 11.2, 146 days).

Figure 3.7: KM treatment duration (N=41)



Based on Figure 4 of the final SACT report[6]
CES = company evidence submission; KM = Kaplan-Meier; IVIG = intravenous immunoglobulin; SACT = systemic anti-cancer therapy

3.2.4.3 SCHOLAR-1 cohort

No individual SCHOLAR-1 data provided in the CES, and no data for this outcome available in original source{Crump, 2017 #94}.

3.2.4.4 Additional comparator data from three additional sources

No data provided in the CES.

EAG comment: The lack of any comparator data relevant to this precise population means that it is very difficult to form relativistic interpretations of the ZUMA-1 data for this outcome. However, the current data show that axi-cel carries an absolute risk of harm, which needs to be considered.

3.3 Summary of new clinical effectiveness evidence according to the ToE for the CDF review

The new ZUMA-1 evidence suggests that OS for patients on axi-cel is approximately [redacted]% at 60 months. Similar OS results to ZUMA-1 were observed from the SACT data at 36 months (46.5% and 45%, respectively), but SACT data were not available for 60 months, i.e. SACT data cannot be used to support the 60-month ZUMA-1 results.

Importantly, it is unclear how much of the [redacted]% survival observed at 60 months in the ZUMA-1 study is due to the action of axi-cel, and how much of it might also be observed with the best available comparator. This is partly because there is no adequately rigorous analysis linking the ZUMA-1 and SCHOLAR-1 data, such as a formal ITC. This means that the ability to estimate the treatment effect is compromised.

Data from the three additional studies were not utilised in the analysis, and the methods used to source additional studies were likely to be insensitive and may therefore have missed potentially useful studies.[8-10] Therefore, it is likely that the comparator data were incomplete in addition to being unclear, further reducing confidence in findings. Given this, it is difficult to ascertain the extent to which the observed duration of OS was the result of axi-cel, and the extent to which it reflected the expected behaviour of the condition in the specified population.

This is compounded by the fact that for the scope outcomes other than OS, no comparator outcomes from any source were used in the analyses. Therefore, it is impossible to know the extent to which other outcomes like PFS were the result of axi-cel, and the extent to which they reflected the normal behaviour of the condition in the specified population. It should be noted that a graph plotting PFS for axi-cel versus salvage chemotherapy was presented in the CES, but because the source of the PFS salvage chemotherapy were not adequately explained in the CES it is not possible to make an informed interpretation of these data.

The IVIG data suggest a potential risk of harm from axi-cel, which also needs to be considered (see Section 3.2.4.2).

The ToE were particularly focussed on the need to frame efficacy in terms of new and updated comparator data, and so the EAG concludes that the ToE have not been fully met in this respect.

4. COST EFFECTIVENESS

4.1 Population

ToE: *"Adults with relapsed or refractory DLBCL, PMBCL or transformed follicular lymphoma who have had two or more systemic therapies are the relevant population for the CDF review"*.[1]

As noted in Section 2.2.1, the population used in the model is in line with the population considered by the committee for entry into the CDF and it was anticipated that the population would not change for the CDF review.

4.2 Comparator

ToE: *"The company should present clinical and cost-effective evidence for axi-cel compared to salvage chemotherapy, excluding pixantrone"*.[1]

As discussed in Section 3.1.1, during the original submission, SCHOLAR-1 was identified as the most relevant source of comparator data for decision-making.

EAG comment: The EAG does not agree that this was completely adhered to in the CES. As discussed in Section 3.1.1, the ToE requested that any new sources of evidence akin to SCHOLAR-1 should also be included as comparator evidence.[1] The company conducted a targeted PubMed search and identified three additional sources of comparative data published since September 2018.[8-10] However, the data from these studies were not used in the indirect treatment comparison analyses, see Section 2.2.3.

The EAG also questioned whether using salvage chemotherapy as a comparator arm for axi-cel is still representative of current clinical practice in the UK. In response to clarification question B4, the company stated that CAR T-cell therapies are now widely used in the UK clinical practice via the CDF, indicating that SCHOLAR-1 outcomes do not match current UK practice.[3] However, in absence of those CAR T-cell therapies, the company expects that outcomes in UK practice would match the adjusted SCHOLAR-1 data outcomes.

4.3 Indirect treatment comparison

ToE: *"The company should fully explore the most appropriate approach for establishing the relative effectiveness of axicabtagene ciloleucel, utilizing any data that has become available during the period of managed access"*.[1]

EAG comment: The EAG considers that this assumption was not adequately adhered to in the CES.[2] Firstly, as explained in Sections 2.2 and 3.1.1, data from comparators are inadequately analysed and presented. Secondly, the company did not make sufficiently thorough attempts to seek new data during the period of managed access - as explained in Section 3.1.2. The CES describes a 'targeted PubMed search' which was conducted to obtain newly available comparator data. However, such a search strategy may have missed important sources because 'PubMed' is only one of several databases that would be appropriate. This represents a clear failure to achieve the agreed terms of agreement, which was to update the comparator evidence.

4.4 Sources of comparator data

ToE: *"The company should use SCHOLAR-1 and any additional data that has become available during the period of managed access to inform the comparator arm"*.[1]

As discussed in Section 4.2 above, during the original submission, SCHOLAR-1 was identified as the most relevant source of comparator data for decision-making.

EAG comment: The EAG considers that this assumption was not adequately adhered to in the CES.[2] SCHOLAR-1 and the three additional data sources found have not been utilised effectively in this submission.[8-10] Please refer to Sections 3.1.1 and 3.1.2 for further details.

4.5 Subsequent treatments

ToE: *"The company should use more mature data from ZUMA-1, any data that has become available during the period of managed access, and data collected through Blueteq to inform the proportion of people who subsequently have IVIG, and the length of time this is required"*.[1]

The CES assumed the same proportion of patients receiving IVIG as was used in the original submitted economic model for TA559 ([redacted] of patients received IVIG) because data from Blueteq were not available on time for the CES.[17] The IVIG treatment duration in the CES was also set at 12 months, as per the original submission.

The CES indicated that *"this is consistent with the expected low rates in today's clinical practice, as confirmed by expert clinical opinion and backed up by real-world data from Kings College Hospital"*.[2] In the request for clarification, the EAG asked justification for this based on real-world data and clinical opinion.[4] The company responded that data from the Kings College Hospital on patients being treated with axi-cel or tisagenlecleucel for relapsed/refractory high-grade B non-Hodgkin lymphoma showed that about 6% of patients (3/53) received IVIG post- CAR T-cell therapy.[3] Furthermore, the EAG found that the company's additional evidence in the CES focused only IVIG usage and not on the duration of treatment, and asked for further evidence on IVIG treatment duration from longer follow-up data of the ZUMA-1 study.[4] The company responded that appropriate duration data were not available from ZUMA-1, but did not provide any further justification.[3]

Data collected through Blueteq to inform the proportion of patients who have IVIG following axi-cel, and the length of time this is required were not available in time for the CES but became available at a later stage (30 May 2022).[6] Of the 318 patients in the SACT data who received axi-cel, 262 (82%) patients were included in the analysis on IVIG usage due to the data being available at the time point the SACT report was produced. All patients who received axi-cel were followed up in the immunoglobulin database (MDSAS) on 24 May 2022. Of the 262 patients, 41 (16%) patients received IVIG, with 39 patients receiving IVIG following a single infusion of axi-cel. The average duration of IVIG therapy was 6.5 months (197 days), with duration ranging from less than one month and up to 33 months. Of the 41 patients who received IVIG, 27 (66%) of them were identified as having completed treatment by 24 May 2022. Completion of IVIG treatment was assumed for patients in case of death, or if they have not received treatment with IVIG in at least three months.

EAG comment: The EAG considers that this assumption was not adequately met in the CES, see Section 2.2.5.[2] The company failed to acquire or adequately utilise more mature data from ZUMA-1 to reduce uncertainty around the treatment duration of IVIG usage following axi-cel, relying primarily on the data collected through Blueteq. Considering IVIG usage, the company also acknowledged in the CES that *"ZUMA-1 is a controlled clinical trial environment where investigations/interventions are strictly adhered to according to defined protocol based on clinical management that is determined at the time of the study; this is therefore not necessarily entirely reflective of real-world clinical practice"*.[2]

The EAG noted that the SACT data on the IVIG usage indicate a higher proportion of patients using IVIG therapy compared to ZUMA-1 trial and the data from the Kings College Hospital.[1] The EAG also noted the data from the Kings College Hospital consisted of a smaller patient population compared to the SACT cohort. Therefore, the EAG's preferred base-case employed the proportion of patients using

IVIG treatment as well as treatment duration post axi-cel from the SACT cohort. Additional scenario analysis in Section 5.4, considered a longer IVIG treatment duration up to 33 months, aligned with the longest treatment duration observed in the SACT cohort.

4.6 Extrapolation of OS and PFS

ToE: *"The company should use the latest data cut from ZUMA-1 to inform the survival outcomes and SACT dataset to validate the trial outputs"*.[1]

The EAG considers that this assumption was partly met in the CES.[2] The model structure was identical to that previously submitted to NICE. This entailed modelling of OS and PFS. For OS, the 60-month data cut from the ZUMA-1 study were used, whilst for PFS, the 24-month data cut from the ZUMA-1 study were used. As shown in Table 3.4 above, the SACT dataset was used to validate the ZUMA-1 trial outputs for OS, considering that PFS data were not available for the SACT cohort, and therefore, PFS could not be validated. Specific details about OS and PFS extrapolations methods employed by the company are provided below.

4.6.1 Overall survival

To model long-term OS of patients receiving axi-cel, the company fitted, mixture cure models (MCMs) and flexible splines models to patient level data following the recommendations in the Technical Support Document 21 (TSD 21) for flexible methods in survival analysis.[18] The company followed this approach because as stated in the CES, in the original submission the committee noted that standard parametric models generally did not fit the ZUMA-1 data well, producing clinically implausible results.[2, 15] To provide further support, the company referred to the study of Vadgama et al. 2022, which looked at different survival extrapolation methods to empirically test which methods predicted better long-term survival data when fitted with early data cuts.[19] They concluded that the cure-based models provided the best and most plausible fit to the observed data. The CES also refers to a recent poster, showing that mixture cure models produce similar ICERs at earlier ZUMA-1 data cuts when compared with mixture cure models fitted to the 60-month ZUMA-1 data cut.[20]

The parametric distributions informing the company's new base-case analysis were selected on grounds of statistical goodness-of-fit, visual inspection and clinical plausibility. The estimated long-term cure fractions for the mixture cure models are reported in Table 4.1Table 4.1: . The long-term cure fractions varied from [redacted]% for the log-normal model to [redacted]% for the exponential model. The EAG noted that range of the cure fractions based on the more mature ZUMA-1 OS trial data was narrower compared to the respective range in the original submission which varied between [redacted]% and [redacted]%.[2]

Table 4.1: Axi-cel overall survival: mixture cure model implied cure fractions

Model	Implied cure fraction
Exponential	[redacted]
Weibull	[redacted]
Gompertz	[redacted]
Log-logistic	[redacted]
Log-normal	[redacted]
Generalised gamma	[redacted]

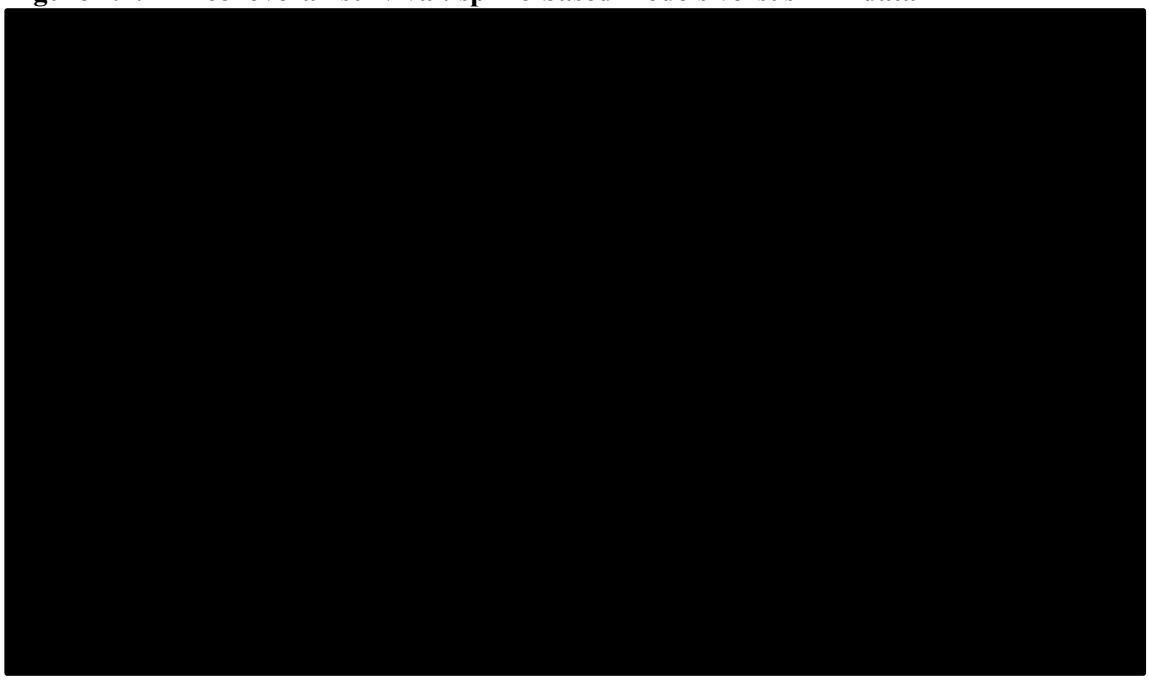
Based on Table 6 of the CES.[2]
Axi-cel = axicabtagene ciloleucel; CES = company evidence submission

Figures 4.1 and 4.2 show the estimated OS for each mixture cure model and for each of the spline models, respectively, compared with the ZUMA-1 OS KM data. The MCMs provide consistent long-term survival projections and seem to be able to capture the plateau in the OS KM plot (Figure 4.1). Therefore, the base-case MCM was selected by the company for the base-case based on the best statistical goodness-of-fit criteria (Table 4.2). The spline models on the other side, also provide a good fit to the observed data producing similar long-term survival projections (Figure 4.2). Nonetheless, when compared to the MCMs, according to the CES the splines models do not present a long-term plateau.[2]

Figure 4.1: Axi-cel overall survival: mixture cure models versus KM data

Based on Figure 6 of the CES[2]
Axi-cel = axicabtagene ciloleucel; CES = company evidence submission; KM = Kaplan-Meier; MCM = mixture cure models; OS = overall survival

Figure 4.2: Axi-cel overall survival: spline-based models versus KM data



Based on Figure 7 of the CES[2]
Axi-cel = axicabtagene ciloleucel; CES = company evidence submission; KM = Kaplan-Meier; onekhaz = one knot hazards; oneknor = one knot normal; onekodd = one knot odds; thrkhaz = three knots hazards; thrknor = three knots normal; thrkodd = three knots odds; twokhaz = two knots hazards; twoknor = two knots normal; twokodd = two knots odds

Goodness-of-fit statistics for MCMs and splines models are presented in Tables 4.2 and 4.3, respectively. For axi-cel, the log-logistic MCM was selected in the base-case analysis because as indicated in the CES, the 60-month data from the ZUMA-1 study seems to be confirming the assumption that a proportion of patients have more favourable outcomes, rendering mixture cure modelling suitable for use in the model base-case, with the log-logistic model also providing the best statistical goodness-of-fit (as shown in Table 4.3).[2]

Table 4.2: Axi-cel overall survival: mixture cure model AIC and BIC statistics

Model	N	AIC	BIC
Exponential	108	[redacted]	[redacted]
Weibull	108	[redacted]	[redacted]
Gompertz	108	[redacted]	[redacted]
Log-logistic	108	[redacted]	[redacted]
Log-normal	108	[redacted]	[redacted]
Generalised gamma	108	[redacted]	[redacted]

Based on Table 7 of the CES[2]
Bold values (log-logistic) represent best statistical fit.
AIC = Akaike information criterion; Axi-cel = axicabtagene ciloleucel; BIC = Bayesian information criterion; CES = company evidence submission; N = number of observations

Table 4.3: Axi-cel overall survival: spline-based model AIC and BIC statistics

Model	N	AIC	BIC
1 knot(s) hazard spline	108	[redacted]	[redacted]

Model	N	AIC	BIC
1 knot(s) odds spline	108	[redacted]	[redacted]
1 knot(s) normal spline	108	[redacted]	[redacted]
2 knot(s) hazard spline	108	[redacted]	[redacted]
2 knot(s) odds spline	108	[redacted]	[redacted]
2 knot(s) normal spline	108	[redacted]	[redacted]
3 knot(s) hazard spline	108	[redacted]	[redacted]
3 knot(s) odds spline	108	[redacted]	[redacted]
3 knot(s) normal spline	108	[redacted]	[redacted]

Based on Table 8 of the CES[2]
Bold values (2 knot(s) normal spline) represent best statistical fit.
AIC = Akaike information criterion; Axi-cel = axicabtagene ciloleucel; BIC = Bayesian information criterion; CES = company evidence submission; N = number of observations

To model OS of salvage chemotherapy, as per the original submission (also described in Section 3.1) the generalised gamma model was selected based on the committee's commentary in the FAD: *"The Committee concluded that a single parametric survival model applying a generalised gamma distribution curve to OS data was the most clinically plausible extrapolation and was appropriate to model salvage chemotherapy"*.[15]

EAG comment: The EAG agrees that OS survival extrapolations for axi-cel was mostly adhered to in the CES. Cure fractions based on the more mature ZUMA-1 trial data for OS varied between (approximately) [redacted]% and [redacted]%, which represents a clear reduction in uncertainty compared to the respective range of OS cure fractions estimated in the original submission, which was from [redacted]% to [redacted]%.[2] The longer term 60-month OS data from ZUMA-1 were reported by the company to support the hypothesis that around [redacted]% of patients receiving axi-cel will experience long-term remission. Nonetheless, this was not effectively validated considering that follow-up in the SACT database only continued to 36 months (Table 3.4).

Regarding the company's base-case analysis for OS, the EAG agrees with the choices made by the company in both treatment arms. It was noticed though that, especially for MCMs, the OS KM curve beyond 50 months was lower than all MCM extrapolations considered by the company (Figure 4.1), suggesting a potential overestimation of long-term survival for axi-cel. The same holds for the splines models as can be seen in Figure 4.2, but in this case, the extrapolations seem to be closer to the KM curve, implying a potentially minor overestimation of OS, compared to mixture cure models. However, long-term predictions seem to be more conservative (there is no plateau and lower OS is predicted) compared with MCMs. Therefore, in Section 5.4 the EAG conducted additional scenario analyses for OS of axi-cel using the spline models with the most conservative long-term OS predictions, i.e. one knot odds and one knot normal.

In the original submission, the committee noted that using single parametric survival curves to model OS for axi-cel produced clinically implausible results, because many of the extrapolated axi-cel curves crossed the OS curve for salvage chemotherapy which was not reflective of ZUMA-1.[15] Using this limitation of the single parametric survival curves in the original submission as an explanation, the CES did not explore the model fit of single parametric models for OS based on the more mature 60-month ZUMA-1 trial data. The EAG noted that the model included the option to fit single parametric models to the 60-month ZUMA-1 data for OS, with details on AIC/BIC statistics and smoothed hazard plots provided in Appendix A.16.3 of the CES.[2] Nonetheless, the EAG also noted that Figure 17 in the

Appendix A.16.3 of the CES does not match with the OS extrapolations included in the model for axi-cel from single parametric models. Therefore, the EAG reproduced Figure 17 of Appendix A.16.3 in the CES based on the model inputs with results shown below in Figure 4.3. Figure 4.3 below shows the estimated OS for each of the parametric models compared with the ZUMA-1 OS KM data. From the model it could also be seen that none of the adjusted extrapolations based on the single parametric curves crosses the OS curve of salvage chemotherapy. Based on the visual assessment of the extrapolations of the single parametric models and the AIC/BIC statistics shown in Table 16 of appendix A.16.3 in the CES, the EAG considered that the Gompertz and generalised gamma distributions provided a good fit to the data and explored their impact in the scenario analyses presented in Section 5.4.

Figure 4.3: Axi-cel overall survival: standard parametric curves

Based on electronic model submitted with clarification letter response[3]
Axi-cel = axicabtagene ciloleucel; K-M = Kaplan-Meier; OS = overall survival

Regarding OS extrapolation for salvage chemotherapy, as discussed in Section 3.1, the EAG considers that the company did not sufficiently explore alternative options to appropriately model long-term OS for salvage chemotherapy using more up-to-date evidence. Thus, despite the committee's preference of modelling OS in the salvage chemotherapy arm using a generalised gamma distribution (based on clinical plausibility), the EAG explored the impact of alternative OS extrapolations for salvage chemotherapy in the scenario analyses presented in Section 5.4.[15]

4.6.2 Progression-free survival

Page 21 of the CES mentioned that in order *"to inform the long-term PFS estimates in the model, the 24-month data cut from ZUMA-1 data was used. Per the ZUMA-1 study protocol, there was no protocol-defined mandate to collect progression data beyond 24 months. Instead, this assessment was done per institutional standard of care"*.[2]

Following the EAG's clarification request, the company provided further explanation indicating that based on the ZUMA-1 study protocol, progression data were collected by positron emission tomography–computed tomography (PET-CT) every 3 months and confirmed by blinded central review

committee until 24 months. Beyond 24 months, there was no protocol-defined mandated PET-CT to collect progression data and therefore PFS assessment was done per institutional standard of care.[3] In the CES the company continues as follows: *"Therefore, any PFS data collected beyond 24 months may not be consistent with the criteria applied in ZUMA-1. For this reason, PFS data collected up to month 24 is presented here and used in the economic model"*.[2] Considering the relative short PFS data compared to OS data, the EAG requested PFS data collected beyond 24 months (e.g. 60-month data) to be provided and used in the model for a scenario analysis, but the company refused to provide this analysis arguing that *"since the model is informed by mature survival data and survival estimates are stable (as demonstrated by the small variation in cure fractions in the cure models), further follow-up data on PFS will likely not change cost-effectiveness in a meaningful way"*.[3]

The CES also states that the *"PFS curve plateaus and continues to support the hypothesis that a proportion of patients receiving axi-cel will experience long-term remission"*.[2] The EAG noted that there is substantial censoring around month 24 in the PFS of the ZUMA-1 trial as can be seen in Figure 3.5, deeming the plateau assumption for PFS uncertain. To resolve this uncertainty the EAG suggested the company to use PFS data beyond 24 months to validate the assumption in the CES that patients remain progression-free for 2 years are likely to remain progression-free in the long-term.[4] The company responded that long-term ZUMA-1 data demonstrate few progression events between 2 and 4+ years but did not provide any evidence on this as also explained in the previous paragraph.[3]

To model long-term PFS of patients receiving axi-cel, the company fitted, MCMs, standard parametric survival curves and flexible splines models to patient-level data. In the base-case analysis, the company selected the best standard parametric model based on statistical goodness-of-fit, visual inspection and clinical plausibility. Figure 4.4 presents the PFS estimated for each of the parametric models compared with the ZUMA-1 PFS KM data.

Figure 4.4: Axi-cel progression-free survival: standard parametric curves

Based on Figure 10 of the CES[2]
Axi-cel = axicabtagene ciloleucel; CES = company evidence submission; PFS = progression-free survival

To model the long-term PFS for axi-cel, the Gompertz distribution was rendered in the CES as the only standard parametric model able to capture the observed and anticipated plateau in the PFS KM plot.[2]

Goodness-of-fit statistics for the parametric models of PFS for axi-cel are presented in Table 4.4. Based on statistical AIC and BIC criteria, the Gompertz distribution was also the best-fitting model and was, therefore, selected for the base-case analysis.

Table 4.4: Axi-cel progression-free survival: standard parametric curve AIC and BIC statistics

Model	N	AIC	BIC
Exponential	108	[redacted]	[redacted]
Weibull	108	[redacted]	[redacted]
Gompertz	108	[redacted]	[redacted]
Log-logistic	108	[redacted]	[redacted]
Log-normal	108	[redacted]	[redacted]
Generalised gamma	108	[redacted]	[redacted]

Based on Table 9 of the CES[2]
Bold values (Gompertz) represent best statistical fit.
AIC = Akaike information criterion; Axi-cel = axicabtagene ciloleucel; BIC = Bayesian information criterion; CES = company evidence submission; N = number of observations

Progression status was not collected in SCHOLAR-1. Therefore, PFS of salvage chemotherapy was estimated by assuming that the same ratio of OS/PFS at each time point in the axi-cel arm can be applied to estimate the ratio of OS/PFS in the salvage chemotherapy arm as per the original submission.[17]

EAG comment: The company selected a Gompertz distribution to extrapolate PFS in the axi-cel arm. The EAG noted that by considering standard parametric curves, the only distribution showing the anticipated plateau in the PFS is the Gompertz. Therefore, all other standard parametric curves used to model PFS in the axi-cel arm, could be deemed as implausible.

Moreover, the EAG considers that the anticipated PFS plateau is still uncertain, considering that the company used data from the 24-month data cut of the ZUMA-1 trial and the large amount of censoring observed after 24 months. The EAG requested the company to use longer follow-up data for PFS to explore the plausibility of the plateau assumption.[4] However, the company in the clarification letter responded that long-term ZUMA-1 data demonstrate few progression events between 2 and 4+ years but did not provide any further data nor details on this aspect.[3]

The EAG also noticed that PFS MCMs for axi-cel were not considered by the company despite being argued (by the company) that the PFS curve for axi-cel shows a similar plateau as the OS curve.[2] In Section A.16.4 of the CES, the company states that *"these* [PFS] *projections capture the observed and anticipated plateau in the PFS Kaplan–Meier plot"*.[2] This statement would suggest the same modelling approach might be used for PFS as for OS in case there is sufficient evidence to support the long-term survival plateau for patients remaining in long-term progression-free disease. The EAG noted that the estimated cure fractions based on the 24-month ZUMA-1 trial data for PFS were stable, varying between [redacted]% and [redacted]%. This was in the same range of variation observed in the original submission (between [redacted]% and [redacted]%).[2] Therefore, the EAG considers that MCMs could have also been appropriate to extrapolate axi-cel PFS (as stipulated in the ToE) allowing for consistent modelling between OS and PFS.[1]

Spline models for PFS are discussed in Appendix A.16.4 of the CES, but no scenarios were presented by the company despite this option being included in the model and the company concluding that all spline-based models appear to provide a good fit to the observed data, produce similar long-term

projections that capture the anticipated plateau in PFS (although to a lesser extent, compared with the mixture cure models).[2]

In conclusion, the EAG considers that the anticipated plateau in the PFS for axi-cel remains uncertain. Given this unresolved uncertainty around PFS, the EAG considered the impact of using the second-best single parametric fit of PFS (the generalised gamma), the best MCM fit (lognormal) and the best spline model fit (two-knots normal) in the scenario analyses of Section 5.4.

4.6.3 Validation with SACT data

A comparison of OS for axi-cel from the SACT cohort with the modelled ZUMA-1 population using the 60-month data cut is provided in Table 3.4, indicating slightly better OS outcomes for the SACT cohort. However, as discussed in Section 3.2, the SACT data were of limited use for validation of long-term ZUMA-1 data as follow up in the SACT database only continued up to 36 months. Therefore, the SACT data could not be used to validate the hypothesis by the company based on ZUMA-1 data that around [redacted]% of patients receiving axi-cel will experience long-term remission (Section 4.6.1). Furthermore, PFS data from ZUMA-1 were available up to 35 months follow-up, and it is anticipated to demonstrate a prolonged plateau. However, this was not validated by SACT data and, as mentioned in Section 3.2, there were no SCHOLAR-1 data to provide comparator data for PFS.

EAG comment: The EAG is concerned that insufficient data and expert feedback were used to externally validate the modelled PFS. The EAG is not completely satisfied with the company's PFS approach considering an anticipated plateau for the PFS curve of axi-cel considering the shorter 24-month ZUMA-1 data for PFS compared to the 60-month OS data as also explained in Section 4.6.2.

4.7 Assumption of cure

ToE: *"The company should fully explore assumptions of cure using the more mature ZUMA-1 data and other updated data that has become available during the period of managed access"*.[1]

The EAG considers that this assumption was partly adhered to in the CES.[2] The company's original model assumed that people who were alive after 2 years in the pre-progression state were functionally cured and they reverted to age-matched general population mortality. The committee concluded that the company's cure assumption at 2 years was optimistic and the assumption of no excess mortality risk for functionally cured patients compared with the general population was not appropriate. In response to committee's request, the company's base-case analysis used a SMR of 1.09 applied to patients in both treatment arms who were alive after 60 months.

The company's original model used a MCM for OS, with around [redacted]% long-term survivors at 2 years, whereas MCM for PFS produced cure fractions of [redacted]% to [redacted]%. The EAG's preferred approach in the original submission 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 and that with longer follow-up, the cure fraction for OS for axi-cel would converge towards the cure fraction for PFS.[2] The cure fraction for OS in the CES using the 60-month data cut from the ZUMA-1 study is lower than in the original model varying from [redacted]% for the log-lognormal model to [redacted]% for the exponential model, with the base-case model using the log-lognormal prediction at [redacted]%, as shown in Table 4.1. The cure fraction estimates for PFS using the 24-month data cut from the ZUMA-1 trial vary from [redacted]% for the log-logistic to [redacted]% for the Weibull, while the log-normal provides the best model fit with a cure fraction of [redacted]%.[2]

EAG comment: The EAG agrees with the company that in this setting, MCMs seem more appropriate than standard parametric survival distributions to model long-term OS. The updated OS and PFS cure fractions are stable across all parametric model and seem to converge as per the expectation of the EAG in the original submission. It should also be noted that it is estimated that a small proportion of patients (up to a maximum of [redacted]%) who experience long-term survival after disease progression. The cure assumption for PFS should be validated with available long-term data.

4.8 Most plausible ICER

ToE: *"The committee agreed that axicabtagene ciloleucel demonstrated plausible potential to be cost-effective".*[1]

The company's base-case ICER following the FAD of the original submission was £45,917 per QALY gained compared with salvage chemotherapy.[1] The EAG's ICER per terms of engagement was £[redacted] per QALY gained.[1] However, in the CES, the company referred to an upper-bound EAG base-case of [redacted] per QALY gained.[2] In response to clarification question B12, the company explained that in the EAG's commentary on the response submitted by the company to the ACD, a range of ICERs was presented, with £[redacted] per QALY gained being the highest, and that this ICER was obtained assuming a Gompertz distribution for OS in the salvage chemotherapy arm.[3] The company also indicated that the EAG concluded that the generalised gamma distribution may provide a more appropriate choice than the Gompertz distribution for salvage chemotherapy OS, and under this assumption, the resulting ICER was £[redacted] per QALY gained. Given that the FAD mentions that *"using the EAG's alternative analysis and the combined costing approach (taking into account the use of higher proportion of post-treatment autologous stem cell transplants, a cure assumption at 5 rather than 2 years, IVIG use for 3 years and the use of the intention-to-treat population) with a gamma distribution for overall survival for salvage chemotherapy, the ICER was above £50,000 per QALY gained"*, the company interpreted £[redacted] per QALY gained to reflect the EAG's base-case ICER.[15] The ICERs in all company's scenario analyses were lower than £50,000 per QALY gained, whereas of the EAG's scenario and exploratory analyses, all but one scenario led to an ICER above £50,000 per QALY gained.[1] Therefore, the committee agreed that the most plausible ICER is between the company's and the EAG's revised base-case estimates.[1]

In the CES, the updated company's base-case ICER was £49,159 per QALY gained.[2] The updated ICER used the log-logistic mixture cure model for OS of axi-cel based on the 60-month ZUMA-1 data cut, a generalised gamma distribution for OS for salvage chemotherapy, applied a SMR of 1.09 to patients in both treatment arms who were alive after 60 months, PFS for axi-cel modelled based on ZUMA-1 24-month data cut, updated population life tables using 2021 ONS data, and assumed a [redacted] that was used in the original submission. These changes also included a correction of an error found in the application of the SMR, which is now applied to the mortality rate rather than to the probability of death, as in the previous version of the model.

In the clarification letter response, the company indicated that the use of the updated ZUMA-1 data cut for OS (60-month) and PFS (24-month) increased the costs and reduced the life years (LYs)/QALYs for the axi-cel arm; using a generalised gamma single parametric model to model OS for salvage chemotherapy, instead of Gompertz reduced the LYs/QALYs and costs for the salvage chemotherapy arm; updating the life tables and SMR increased costs and LYs/QALYs for both salvage chemotherapy and axi-cel arms.[3]

EAG comment: The EAG noted that the CES used cost prices from the year 2015/2016 as per the original submission. Therefore, the EAG requested in the clarification letter the model to be updated using the most recent NHS Reference costs (i.e. version 2019/2020),[21] and align the other cost inputs (e.g. sourced from the Personal Social Services Research Unit (PSSRU),[22] electronic Market Information Tool (eMIT),[23] British National Formulary (BNF)[24]) to the same cost year. Following the cost updating, the base-case ICER of the company increased to £50,251 per QALY gained.

5. COST EFFECTIVENESS RESULTS

The company confirmed that the economic model submitted by the company in response to the ACD consultation named *"[ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC]"* was used for the CDF review.[3] The ERG successfully verified all functionalities as stated in the ToE.[1] The updated model of the company included a new base-case based on the changes described in Section 4 before the clarification phase, i.e. results shown in Sections 5.1 and 5.2 are based on 2015/2016 costs.

5.1 Company's deterministic cost effectiveness results

Table 5.1 shows the deterministic cost effectiveness results of the originally submitted company's base-case (at CDF entry) and the new base-case analysis. Compared to salvage chemotherapy, axi-cel accrued [redacted] incremental QALYs at £[redacted] additional costs. Therefore, the ICER was £49,159 per QALY gained. The new base-case results are broadly in line with those at CDF entry, showing an increase in the ICER of £3,243.

The cumulative impact of each individual change on the ICER is shown in Table 5.2. The individual (non-cumulative) impact of each change is not shown in this report but can be found in Table 20 of the CES.[2] The changes with the largest impact on the results were the use of the updated 60-month and 24-month data from ZUMA-1 data for OS and PFS respectively, the use of a generalised gamma distribution for OS for salvage chemotherapy, and the assumed [redacted].

Table 5.1: Company's deterministic cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Change in ICER (£)
Company's new base-case								
BSC	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,159	+3,243
Company's base-case at CDF entry								
BSC	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,917	NA

Based on Table 11 of the CES.[2]

Axi-cel = axicabtagene ciloleucel; BSC = best supportive care (salvage chemotherapy); CDF = Cancer Drug Funds; CES = company evidence submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; LYG = life years gained; NA = not applicable; QALY = quality-adjusted life year

Table 5.2: Cumulative impact of each model change (from base-case at CDF entry to new base-case)

Preferred assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	Change in ICER (%)	Change in ICER (£)
Base-case at CDF entry	[redacted]	[redacted]	45,917	0%	0
1. ZUMA-1 data cut OS 60 months	[redacted]	[redacted]	50,547	+10.1%	+4,630
2. 1 + ZUMA-1 data cut PFS 24 months	[redacted]	[redacted]	52,466	+14.3%	+6,549
3. 1-2 + BSC, OS generalised Gamma	[redacted]	[redacted]	44,885	-2.2%	-1,032
4. 1-3 + axi-cel, OS log-logistic	[redacted]	[redacted]	44,812	-2.4%	-1,105
5. 1-4 + updated life tables	[redacted]	[redacted]	45,005	-2.0%	-912
6. 1-5 + correct SMR method**	[redacted]	[redacted]	47,656	3.8%	1,739
7. 1-6 + SMR 60 months cut-off; SMR applied: 1.09	[redacted]	[redacted]	47,606	+3.7%	+1,690
8. 1-7 + axi-cel discount percentage: [redacted] (new base-case)	[redacted]	[redacted]	49,159	+7.1%	+3,243

Based on Table 21 of the CES.[2]

Preferred assumption	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)	Change in ICER (%)	Change in ICER (£)
Axi-cel = axicabtagene ciloleucel; BSC = best supportive care (salvage chemotherapy); CDF = Cancer Drug Funds; CES = company evidence submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SMR = standardised mortality ratio					

5.2 Company's sensitivity and scenario analyses

5.2.1 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) in which all relevant input parameters were sampled simultaneously from their corresponding probability distributions over 1,000 iterations. The input parameters and the probability distributions used in the PSA have not been changed with respect to the previous model version and, therefore, are not shown in this report.

The average PSA results were in line with the deterministic ones shown in Table 5.1, and compared to salvage chemotherapy, axi-cel accrued [redacted] incremental QALYs at £[redacted] additional costs. Therefore, the probabilistic ICER was £49,700 per QALY gained.

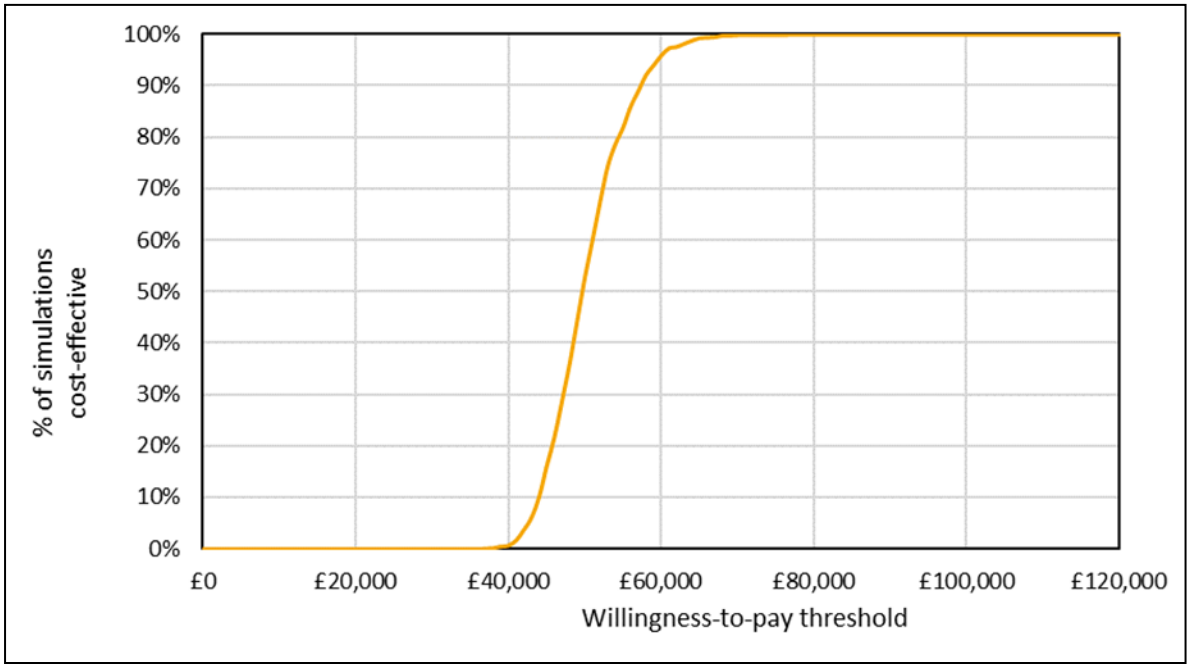
The company also plotted the PSA outcomes on a CE-plane, as can be seen in Figure 5.1. [redacted]. From the PSA results, a cost effectiveness acceptability curve (CEAC) was also calculated and plot in Figure 5.2. At the threshold of £50,000 per QALY gained, the estimated probability that axi-cel is a cost-effective alternative to salvage chemotherapy was [redacted].

Figure 5.1: Probabilistic sensitivity analysis cost effectiveness plane

[redacted]

Based on Figure 14 of the CES[2]
CES= company evidence submission; QALY = quality-adjusted life year

Figure 5.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve

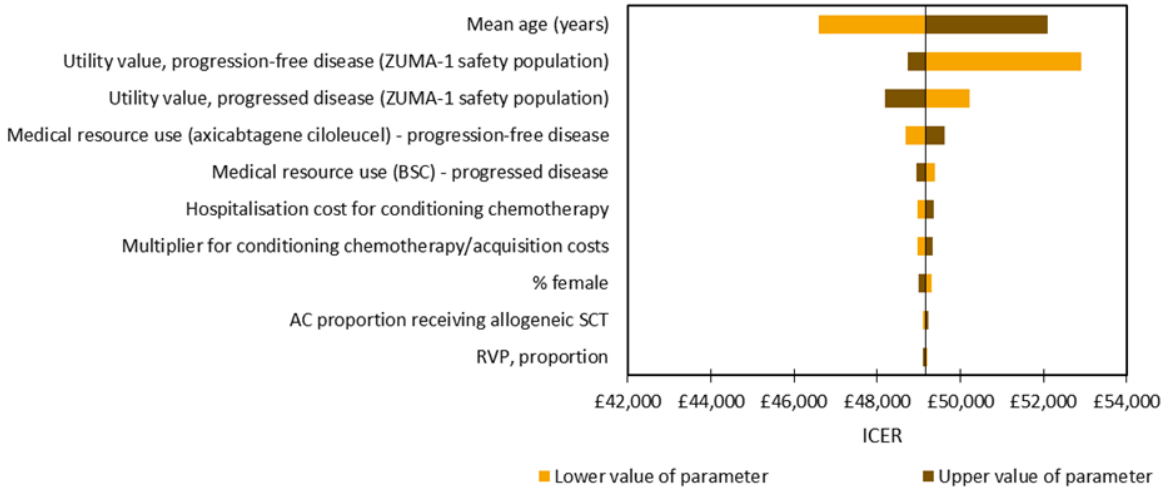


Based Figure 2 of the response to the request for clarification[3]

5.2.2 Deterministic sensitivity analysis

The company also conducted deterministic one-way sensitivity analyses (OWSAs) to quantify how much the deterministic base-case results would change when a parameter was varied individually. Each parameter was set to its lower and upper bounds, as in the previous version of the model, and the results were recorded. The OWSA results were presented by the company in the form of a tornado diagram showing the top 10 most influential parameters on the ICER, which can be seen in Figure 5.3. In general, the most influential parameters, except survival-related parameters, which were not included in the analysis, seemed to be those relating to patients' age and utilities. None of the ICERs were below £46,000 or above £54,000 per QALY gained.

Figure 5.3: OWSA tornado diagram (top 10 most influential parameters on the ICER, excluding survival parameters)



Based on Figure 16 of the CES.[2]

AC = axicabtagene ciloleucel; BSC = best supportive care; CES = company evidence submission; ICER = incremental cost effectiveness ratio; OWSA = one-way sensitivity analysis; RVP = rituximab, vincristine and prednisolone; SCT = stem cell transplant

5.2.3 Scenario analysis

The company presented only three additional scenario analyses to assess the robustness of the model results to changes in modelling assumptions. A summary of the results of these scenarios is provided in Table 5.3. These included exploring alternative OS and PFS extrapolations and modelling mortality without applying an SMR. The ICERs in these scenarios were similar to the base-case ICER and all of them were below £50,000 per QALY gained.

Table 5.3: Summary of company scenario analyses

Scenario	Description	Rationale	ICER (£/QALY)	ICER difference vs. base-case (£)
Base-case	See Chapter 4 of this report		49,159	N/A
Axi-cel OS – alternative extrapolation	Best fitting spline model used for axi-cel OS (two knots, Normal)	Splines model explored based on NICE guidance in TSD 21[18]	49,415	+255
Axi-cel PFS – alternative extrapolation	MCM (log-logistic) used for axi-cel PFS	PFS MCM used to match the preferred model used for OS	49,802	+642
No SMR	SMR (1.09 after 60 months) not applied	Consistent with originally submitted model	46,493	-2,667

Based on Table 13 the CES[2]
Axi-cel = axicabtagene ciloleucel; CES = company evidence submission; ICER = incremental cost-effectiveness ratio; MCM = mixture cure model; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SMR = standardised mortality ratio; TSD = Technical Support Document

5.3 Model validation and face validity check

Unlike the original company submission (CS), there was no validation-specific section in the CES.

In response to clarification question B8, the company indicated that the updated model was basically the same as in the original appraisal and, therefore, has already gone through the validation processes within the NICE appraisal process.[3] Consistent with the CDF resubmission process, minimal changes were made to the model, including the updated OS, PFS and IVIG data, per the ToE. As mentioned above, real-world IVIG usage and duration data were not available at the time of submission.

Regarding validation of model outcomes, the long-term OS data from ZUMA-1 were used to validate the extrapolations included in the original model. The extrapolation methods used to model the OS with the more recent ZUMA-1 data were followed the recommendations in Vadgama et al. 2021, and Bullement et al. 2022, which found that cure-based models provided the best fit to the observed data.[19, 20] Additionally, the SACT OS data were used to validate that the outcomes observed in ZUMA-1 were replicable in UK clinical practice.

Regarding assessment tools, the company indicated that, following the updates, the model underwent internal reviews and quality control checks, in line with Drummond, Phillips, and TechVER.[25-27]

Finally, in clarification question B9, the EAG asked the company to provide a summary about how the new evidence and clinical expert opinion were used to validate assumptions in this CES.[4] The company explained that a targeted search was undertaken to identify any relevant source of evidence on the comparator arm that was published since the beginning of this appraisal.[3] This search confirmed that there were no further data to supplant the SCHOLAR-1 study, which was previously identified by the committee as suitable for decision making. The company referred to the study by Nastoupil et al. 2020 to provide supportive evidence of the outcomes of patients treated with axi-cel in the United States of America (USA).[28]

5.4 Exploratory and sensitivity analyses undertaken by the EAG

In clarification question B7, the EAG asked the company to update the model using 2019/2020 NHS Reference costs and to align all the other cost inputs to the same cost year.[4] Additionally, the EAG considered the proportion of patients using IVIG treatment to be 16% and a treatment duration at 6.5 months, as observed in the SACT cohort (and explained in Section 4.5). The overview of the changes and the bookmarks for the justification of the EAG changes are presented in Table 5.4.

Table 5.4: Company and EAG base-case preferred assumptions

Base-case preferred assumptions	Company	EAG	Justification for change
Survival model OS	Log-logistic mixture cure model for axi-cel Generalised gamma for BSC	Same as company	None
Survival model PFS	Gompertz single parametric model for axi-cel Ratio of OS/PFS of axi-cel used for PFS of BSC	Same as company	None
Reference year for costs	2015/2016	2019/2020	Costs need to be updated to reflect 2019/2020 NHS Reference costs
IVIG usage	[redacted] of patients used IVIG treatment after axi-cel for 12 months	16% of patients used IVIG treatment after axi-cel for 6.5 months	SACT cohort deemed more appropriate source for IVIG usage following axi-cel (Section 4.5)

Axi-cel = axicabtagene ciloleucel; BSC = best supportive care (salvage chemotherapy); EAG = Evidence Assessment Group; IVIG = intravenous immunoglobulin; NHS = National Health Service; OS = overall survival; PFS = progression-free survival; SACT = systemic anti-cancer therapy

After the proposed changes were implemented in the company's model, additional scenario analyses were explored by the EAG in order to assess the impact of alternative assumptions on the cost effectiveness results. These uncertainties were related to the survival modelling of OS for both the axi-cel and salvage chemotherapy arms, the survival modelling of axi-cel PFS, and the duration of IVIG treatment. A summary of the scenarios conducted by the EAG is presented in Table 5.5.

Table 5.5: EAG additional scenarios

Scenarios	EAG preferred Assumption	Change	EAG comment
Survival model OS for axi-cel	Mixture cure: log-logistic	Spline: one knot odds	All mixture cure models provided similar fit to observed data. OS KM curve beyond 50 months was lower than mixture cure model extrapolations (Figure 4.1), suggesting potential overestimation of long-term survival for axi-cel (Section 4.6.1). Spline models were closer to the OS KM curve. OS single parametric curves produced clinically implausible results in the original model. This has been resolved with the most recent data. Best and second-best fit spline and single parametric models explored in scenarios.
		Spline: one knot normal	
		Single parametric: Gompertz	
		Single parametric: generalised gamma	
Survival model OS for BSC	Single parametric: Generalised gamma	Single parametric: Gompertz	Unresolved uncertainty around long-term OS for BSC (Section 4.6.1). Gompertz, log-logistic and log-normal based on goodness of fit (page 48 and Table 31 of committee papers).[29]
		Single parametric: Log-logistic	
		Single parametric: Lognormal	
Survival model PFS for axi-cel	Single parametric: Gompertz	Single parametric: Generalised gamma	Plateau in the PFS KM plot for axi-cel remains uncertain (Section 4.6.2). Scenarios with second best standard model fit, best mixture cure model fit and best spline model fit.
		Mixture cure: Lognormal	
		Spline: two-knots normal	
IVIG treatment duration	6.5 months	33 months	The longest treatment duration observed in the SACT cohort for IVIG usage (Section 4.5) to be considered as an upper limit scenario.

Axi-cel = axicabtagene ciloleucel; BSC = best supportive care (salvage chemotherapy); EAG = Evidence Assessment Group; IVIG = intravenous immunoglobulin; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; SACT = systemic anti-cancer therapy

Table 5.6: EAG preferred base-case deterministic cost effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	Change in ICER (£)*
EAG change 1 – updated costs**								
BSC	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,251	+1,092
EAG changes 1 + 2 – updated costs + IVIG use per SACT data								
BSC	[redacted]	[redacted]	[redacted]					
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,480	+1,321

Based on economic model submitted with the response to the request for clarification[3]

* Change in ICER with respect to the base-case ICER in the CES; ** Company's base-case results after clarification

Axi-cel = axicabtagene ciloleucel; BSC = best supportive care (salvage chemotherapy); CES = company evidence submission; EAG = Evidence Assessment Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; IVIG = intravenous immunoglobulin; LYG = life years gained; QALY = quality-adjusted life year; SACT = systemic anti-cancer therapy

5.5 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 5.6 shows the step-by-step changes made by the EAG to the company's deterministic base-case, resulting in the EAG preferred ICER. With these changes, the EAG preferred ICER increased from £49,159 per QALY gained to £50,480 per QALY gained.

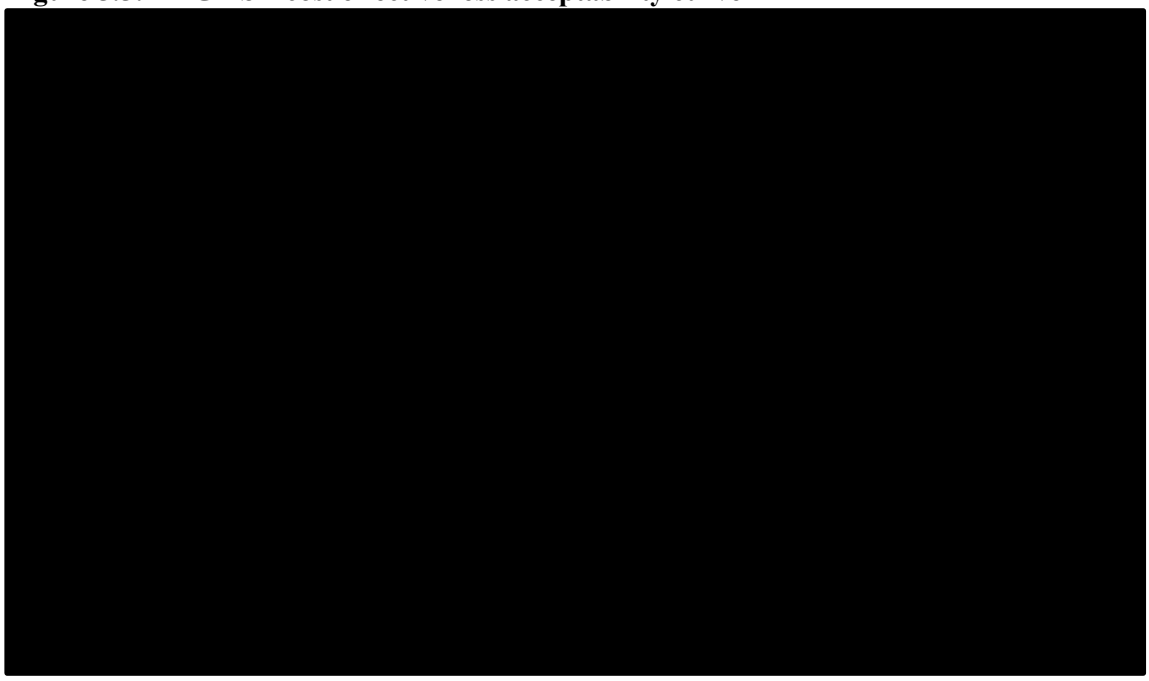
The average PSA results of the EAG preferred base-case were broadly in line with the deterministic ones shown in Table 5.6. Compared to salvage chemotherapy, axi-cel accrued [redacted] incremental QALYs at £[redacted] additional costs. Therefore, the probabilistic ICER was £49,921. The PSA outcomes on the cost effectiveness-plane were plotted in Figure 5.4. [redacted]. From the PSA results, the CEAC shown in Figure 5.5 was also calculated. This indicated at the threshold of £50,000 per QALY gained, the estimated probability that axi-cel is a cost-effective alternative to salvage chemotherapy was [redacted].

Figure 5.4: EAG PSA cost effectiveness plane

[redacted]

Based on economic model submitted with the response to the request for clarification[3]
EAG = Evidence Assessment Group; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year

Figure 5.5: EAG PSA cost effectiveness acceptability curve



Based on economic model submitted with the response to the request for clarification[3]
EAG = Evidence Assessment Group; PSA = probabilistic sensitivity analysis

The results of the additional scenario analyses conducted by the EAG are provided in Table 5.7. These indicated that the ICER was stable to changes in axi-cel OS extrapolations. Additionally, all MCMs resulted in ICERs similar to the base-case ICER, with a difference less than £200 in absolute value (results not shown). Based on these results, it can be concluded that collecting 60-month follow up data from ZUMA-1 greatly reduced the uncertainty around axi-cel OS extrapolations.

Despite the limitations of IVIG data discussed in Section 4.5, the results of the scenario analysis assuming a treatment duration of 33 months (the longest treatment duration observed in the SACT cohort) suggest that the impact of IVIG treatment assumptions on cost effectiveness is minor.

The model results are still sensitive to changes in OS for the salvage chemotherapy arm and to changes in PFS for the axi-cel arm. Assuming a Gompertz, a log-logistic and a lognormal OS extrapolation for salvage chemotherapy resulted in an ICER of £55,787, £46,048 and £46,977 per QALY gained, respectively. As discussed in Section 4.6.1, the EAG considers that the company did not sufficiently explore alternative options to appropriately model long-term OS for salvage chemotherapy using more up-to-date evidence. More recent data should be used to confirm what scenario is more clinically plausible for modelling OS in the salvage chemotherapy arm.

Likewise, assuming a generalised gamma (the second-best single parametric fit) PFS extrapolation for axi-cel resulted in an ICER of £67,765 per QALY gained. When a lognormal MCM (best fit) was assumed for axi-cel PFS, the ICER was £51,096 per QALY gained. Given the plateau-like shape of the standard Gompertz distribution (used in the base-case), assuming PFS MCMs for axi-cel resulted, as expected, in ICERs similar to the base-case ICER, with a difference with respect to the base-case ICER less than £1,000 in absolute value (results not shown). Assuming a two-knots normal spline model (best fit) resulted in an ICER of £55,257 per QALY gained. All ICERs based on the other possible spline models were above £55,000 per QALY gained (results not shown). As discussed in Section 4.6.2, the EAG considers that the company could have used longer follow-up data for PFS to explore the

plausibility of the plateau assumption for PFS and, since this was not explored, the anticipated plateau in the PFS for axi-cel remains uncertain.

Table 5.7: EAG scenario analyses results

Scenarios	BSC		Axi-cel		Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
	Total costs (£)	Total QALY	Total costs (£)	Total QALY			
EAG base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,480
Survival model OS for axi-cel							
Spline model: one knot odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,341
Spline model: one knot normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,265
Single parametric: Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,542
Single parametric: generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,834
Survival model OS for BSC							
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,787
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,048
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,977
Survival model PFS for axi-cel							
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67,765
Lognormal mixture cure model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,096
Spline model: two knots normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,257
IVIG treatment duration 33 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,857

Based on economic model submitted with the response to the request for clarification[3]

Axi-cel = axicabtagene ciloleucel; BSC = best supportive care (salvage chemotherapy); EAG = Evidence Assessment Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; IVIG = intravenous immunoglobulin; OS =overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SACT = systemic anti-cancer therapy

5.6 Conclusions of the cost effectiveness section

The cost effectiveness results presented in this report seem to suggest that the new evidence (60-month follow up data) from ZUMA-1 have greatly reduced the uncertainty around axi-cel long-term OS extrapolations.

Despite the limitations of IVIG data discussed in Section 4.5, the results of the scenario analysis assuming a treatment duration of 33 months (the longest treatment duration observed in the SACT cohort), combined with 16% of patients using IVIG treatment (as observed in the SACT cohort), suggest that the impact of IVIG treatment assumptions on cost effectiveness is minor.

The EAG considers that the company did not sufficiently explore alternative options to appropriately model long-term OS for salvage chemotherapy using more up-to-date evidence. Thus, despite the committee's preference of modelling OS in the salvage chemotherapy arm using a generalised gamma distribution (based on clinical plausibility), the alternative scenarios explored by the EAG indicated that the model results are still sensitive to changes in OS extrapolations for salvage chemotherapy. Thus, assuming a Gompertz, a log-logistic and a lognormal OS extrapolation for salvage chemotherapy resulted in an ICER of £55,787, £46,048 and £46,977 per QALY gained, respectively. More recent data should be used to confirm what scenario is more clinically plausible for modelling OS in the salvage chemotherapy arm.

The EAG also considers that the company could have used longer follow-up data for PFS to explore the plausibility of the plateau assumption for PFS and, since this was not explored, the anticipated plateau in the PFS for axi-cel remains uncertain. The alternative scenarios explored by the EAG indicated that the model results are still sensitive to changes in PFS extrapolations for axi-cel. Thus, assuming a generalised gamma (the second-best single parametric fit) PFS extrapolation for axi-cel resulted in an ICER of £67,765 per QALY gained. Assuming a two-knots normal spline model (best fit) resulted in an ICER of £55,257 per QALY gained.

Overall, the EAG concludes that the (cost effectiveness) ToE have not been completely met.

6. REFERENCES

[1] National Institute for Health and Care Excellence. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [TA558]: Terms of engagement for CDF review*. London: NICE, 2022. 8p.

[2] Kite/Gilead. *Cancer Drugs Fund Review of TA559. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID3980]: Submission to National Institute of Health and Care Excellence: Company evidence submission for committee*: Kite/Gilead, 2022. 63p.

[3] Kite/Gilead. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980] – Response to request for clarification from the ERG*. Kite/Gilead, 2022. 31p.

[4] National Institute for Health and Care Excellence. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]: Clarification questions*. London: NICE, 2022. 12p.

[5] Faria R, Hernandez Alava M, Manca A, Wailoo AJ. *NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: Methods for comparative individual patient data*. Sheffield: Decision Support Unit, ScHARR, 2015. 86p. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD17-DSU-Observational-data-FINAL.pdf

[6] National Disease Registration Service. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma - data review. Commissioned by NHS England and NHS Improvement [Data on file]*. Leeds: NHS Digital, 2022. 30p.

[7] Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017;130(16):1800-1808.

[8] Radford J, White E, Castro FA, Chaturvedi A, Spielewoy N, Gibb A, et al. Treatment patterns and outcomes in patients with relapsed or refractory diffuse large B-cell lymphoma: experience from a single UK centre. *Blood* 2019;134:2917.

[9] Fuji S, Kida S, Nakata K, Morishima T, Miyashiro I, Ishikawa J. Analysis of real-world data in patients with relapsed/refractory diffuse large B cell lymphoma who received salvage chemotherapy in the rituximab era. *Ann Hematol* 2021;100(9):2253-2260.

[10] Nakaya A, Fujita S, Satake A, Nakanishi T, Azuma Y, Tsubokura Y, et al. Trend of salvage treatment in diffuse large B cell lymphoma in the outpatient chemotherapy era. *Mol Clin Oncol* 2019;11(6):557-562.

[11] Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;25(5):579-86.

[12] Kite/Gilead. *Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma [ID1115]: Submission to National Institute of Health and Care Excellence: Document B - Company evidence submission*: Kite/Gilead, 2018. 164p.

[13] Kite/Gilead. KTE-C19-101. ZUMA-1 60 month data - Additional figures and tables [Data on file]. 2022.

[14] National Institute for Health and Care Excellence. *Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies [TA567]*. London: NICE, 2018. 24p. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10269/documents

[15] National Institute for Health and Care Excellence. *Final appraisal document: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies*. London: NICE, 2018. 33p.

[16] Kite/Gilead. KTE-C19-101. 24-month follow-up analysis of ZUMA-1 cohorts 1 and 2 [Data on file]. 2018.

[17] National Institute for Health and Care Excellence. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]: Committee Papers*. London: NICE, 2018. 673p. Available from: https://www.nice.org.uk/guidance/ta559/documents/committee-papers-3

[18] Rutherford MJ, Lambert PC, Sweeting MJ, Pennington R, Crowther MJ, Abrams KR, et al. *NICE DSU Technical Support Document 21: Flexible methods for survival analysis*. Sheffield: Decision Support Unit, ScHARR, 2020. 97p. Available from: http://nicedsu.org.uk/wp-content/uploads/2020/11/NICE-DSU-Flex-Surv-TSD-21_Final_alt_text.pdf

[19] Vadgama S, Mann J, Bashir Z, Spooner C, Collins GP, Bullement A. Predicting survival for chimeric antigen receptor T-cell therapy: a validation of survival models using follow-up data from ZUMA-1. *Value Health* 2022;25(6):1010-17.

[20] Bullement A, Critchlow S, Castaigne G, Vagdama S. How long is long-enough? An investigation into the relationship between trial maturity and uncertainty in cost-effectiveness, the case of the first commercially available CAR T-cell therapy: axicabtagene ciloleucel [PDF provided by company]. *EBMT*. Virtual, 2022.

[21] Department of Health. *2019/20 National Cost Collection Data Publication [Internet]*. London: Department of Health, 2021 [accessed 16.6.22] Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/

[22] Personal Social Services Research Unit. *Unit Costs of Health and Social Care 2021*. Canterbury: University of Kent, 2021 [accessed 6.6.22]. 185p. Available from: https://kar.kent.ac.uk/92342/

[23] Drugs pharmaceutical electronic market information tool. *eMIT national database [Internet]*, 2020 [accessed 16.6.22] Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

[24] British National Formulary (BNF) [Internet]. London: BNF Publications, 2022 [accessed: 6.6.22]. Available from: https://bnf.nice.org.uk/

[25] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford: Oxford University Press, 2005.

[26] Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;8(36).

[27] Büyükkaramikli NC, Rutten-van Mölken MP, Severens JL, Al M. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. *Pharmacoeconomics* 2019;37(11):1391-408.

[28] Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol* 2020;38(27):3119.

[29] National Institute for Health and Care Excellence. *Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]: Committee Papers*. London: NICE, 2018. 74p. Available from: https://www.nice.org.uk/guidance/ta559/documents/committee-papers-2