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

Produced by Aberdeen HTA Group

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Contribution of authors

Moira Cruickshank and Mari Imamura summarised and critiqued the clinical effectiveness evidence; Neil Scott and Sachin Kumar checked and critiqued the statistical analyses presented in the company submission; Dwayne Boyers and Elisabet Jacobsen reviewed and critiqued the cost-effectiveness evidence; Paul Manson checked and critiqued the company's search strategies; Gavin Preston provided clinical guidance and comments on the draft report. Miriam Brazzelli coordinated and supervised all aspects of this appraisal. All authors contributed to the writing of this report and approved its final version.

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AE	Adverse event
AIC	Akaike information criterion
Auto-SCT	Autologous stem-cell transplant
BC	Base case
BIC	Bayesian information criterion
Auto-SCT	Autologous stem cell transplant
CAR-T	Chimeric antigen receptor-T cell
CDF	Cancer drugs fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRS	Cytokine release syndrome
CS	Company submission
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ED-5D	EuroQol-5 dimensions
EORTC QLD-30	European Organisation for Research and Treatment of Cancer QLQ-30
EQ-5D	EuroQol-5 dimensions
EQ-5D-3L/ EQ-5D-5L	EuroQol-5 dimensions-3 levels/EuroQol-5 dimensions-5 levels
ERG	Evidence review group
FAD	Final appraisal determination
FAS	Full analysis set
GP	General practitioner

HDT	High-dose therapy
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPCW	Inverse probability of censoring weights
IPI	International Prognostic Index
ITT	Intention to treat
IVIg	Intravenous immunoglobulin
KM	Kaplan Meier
LOS	Length of stay
LYG	Life years gained
mEFS	Modified event-free survival
MCM	Mixture cure model
NE	Not evaluable
NR	Not reached
NHL	Non-Hodgkin's lymphoma
NICE	National Institute for Health and Care Excellence
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PF	Physical functioning
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality adjusted life year
QoL	Quality of life
r/r	Relapsed or refractory
RBP	Rituximab, bendamustine and polatuzumab

R-CHOP	Rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone
RCT	Randomised controlled trial
R-DHAP	Rituximab plus dexamethasone, high-dose cytarabine and cisplatin
R-ESHAP	Rituximab plus etoposide, methylprednisolone, cytarabine, cisplatin
R-GDP	Rituximab plus gemcitabine, dexamethasone and cisplatin/carboplatin
R-ICE	Rituximab plus ifosfamide, carboplatin, and etoposide
RPSFT	Rank preserving structural failure time
sAAIPI	Second-line age-adjusted international prognostic index
SAE	Serious adverse event
SAS	Safety analysis set
SCT	Stem-cell transplant
SD	Standard deviation
SD	Stable disease
SF-36	Short form health survey-36
SLR	Systematic literature review
SMR	Standardised mortality ratio
SOC	Standard of care
STA	Single technology appraisal
TE	Treatment emergent
TEAE	Treatment-emergent adverse event
TTNT	Time to next therapy
WPAI: GH	Work productivity and activity impairment questionnaire: general health
VAS	Visual analogue score

1. Executive Summary

1. Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

The focus of the submission received from Kite is axicabtagene ciloleucel (referred to throughout as axi-cel) for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults after one systemic therapy. DLBCL is the most common type of non-Hodgkin's lymphoma and is a high-grade lymphoma with fast growing and enlarged B-cells that spread quickly and requires prompt treatment.

The clinical evidence submitted by the company consists of a single, ongoing, randomised, open-label, international, Phase III trial: ZUMA-7. At the cut-off date of 18th March 2021, 40.0% of participants in the axi-cel group and 45.3% of the standard of care (SOC) group had died. The difference between the groups was not statistically significant (HR 0.73, 95% CI 0.53, 1.01, p=0.054). The proportion of people who had experienced event-free survival outcomes in the axi-cel and SOC groups was [redacted] and [redacted], respectively. The median event-free survival (EFS) was 8.3 months (95% CI 4.5, 15.8 months) for the axi-cel group and 2.0 months (95% CI 1.6, 2.8 months) for the SOC group.

The cost-effectiveness evidence consists of a de novo economic model to determine the cost-effectiveness of axi-cel versus SOC in adults with primary refractory or

relapsed (early relapse within 12 months) DLBCL who have had one systemic therapy and are intended for stem cell transplant. The model presented is a partitioned survival model with three health states: event free, post-event and death. Patients can be on and off treatment whilst in the event-free and post event states. The model input data on the effectiveness of axi-cel and SOC is obtained from mixture cure models of EFS, time to next treatment (TTNT) and overall survival (OS) data for the full analysis set (FAS) population from the ZUMA-7 study. The patient level data from ZUMA-7 suggests that a proportion of patients experience long-term remission and survival, hence the decision to adopt mixture cure modelling. In the company base case, the implied cure fractions for axi-cel and SOC were [redacted] (mean EFS=[redacted] months and median=[redacted] months) and [redacted] (mean EFS=[redacted]months and median=[redacted]months) respectively. A large proportion of the SOC arm also went on to receive CAR T-cell therapies. Due to axi-cel only being available in England through the cancer drug fund (CDF) and NICE's position statement on CDF treatments, OS for the SOC arm was adjusted using a cross-over analysis, specifically a rank preserving structural failure time (RPSFT) model to remove the effectiveness of 3rd line CAR T-cell therapies. Costs and utilities are derived from ZUMA-7, TA567, TA559, UK clinical experts and literature.

Table 1 presents a summary of the key issues identified by the ERG.

Table 1 Summary of key issues

Issues	Summary of issue	Report sections
Issue 1	Axi-cel retreatment costs	Section 4.2.8
Issue 2A	Long-term extrapolation of clinical effectiveness data	Section 4.2.6
Issue 2B	Crossover adjustment for overall survival in the SOC arm of the model	Section 4.2.6

In addition to the key issues of uncertainty around long term extrapolation, the ERG and company preferred base case model configurations differ with regards to: the choice of mixture cure model of OS in the axi-cel arm of the model, whether or not to include axi-cel retreatment costs in the model, the distribution of subsequent (post-event) treatments, the proportion receiving salvage chemotherapy, costing source for autologous stem cell transplant (auto-SCT) costs, cost of treating neurological events (grades 3 and above) and the source of utility values applied post-event.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients that could be 'statistically' cured, thereby increasing event-free survival and ensuring more patients receive higher utility for longer compared with SOC.
- Increasing the proportion of patients who remain alive in the post-event state, thereby accruing further life year gains post-event.
- Utility implications of adverse events were minimal.

Overall, the technology is modelled to affect costs by:

- Increasing the costs of treating relapsed or refractory DLBCL, especially the additional treatment acquisition costs of axi-cel.
- Slightly higher costs of treating axi-cel adverse events.
- A small reduction in 3rd line treatment costs, assuming that axi-cel is not available 3rd line in the SOC arm of the model. If axi-cel was available as 3rd line SOC, the reduction in 3rd line treatment costs would be higher by moving axi-cel forward in the treatment pathway.

The modelling assumptions that have the greatest effect on the ICER are:

- The decision about the most appropriate extrapolation model for EFS and OS, given that data from the ZUMA-7 study are not yet mature and further follow up data are expected to become available in the years ahead.
- Related to point 1, the most appropriate approach to model cross-over to remove the OS benefit of axi-cel as a third line (post-event) treatment in the SOC arm of the model.
- The inclusion or exclusion of axi-cel re-treatment costs from the axi-cel arm of the model.

1.3 The decision problem: summary of the ERG's key issues

In general, the company decision problem is in line with the NICE final scope and the ERG identified no major issues. The company submission (CS) addresses a more specific population than that specified in the NICE final scope, focusing on adults with primary refractory or early relapse (≤ 12 months) DLBCL who are intended for transplant. The ERG in consultation with its clinical expert considers the company's description of the current treatment pathway and treatment options available for people with relapsed or refractory DLBCL accurate and agrees with the company's positioning of axi-cel in the treatment pathway.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The main evidence submitted by the company consists of an RCT, the ZUMA-7 trial. The ERG agrees that ZUMA-7 should form the basis of this submission and has no major concerns about the conduct or reporting of this study. The ERG also notes that,

as follow-up for ZUMA-7 is still ongoing, not all participants provide data for later time points. This has implications for the cost-effectiveness model that requires long-term data on survival and quality of life. The ERG is aware that the company are planning to provide data from a new analysis post FDA review, although this will only include a limited number of additional survival events.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The ERG has identified a few issues and uncertainties with the company submitted cost-effectiveness evidence:

Issue 1 Axi-cel retreatment costs

Report section	Section 4.2.8
Description of issue and why the ERG has identified it as important	The company preferred base case analysis is to exclude axi-cel retreatment costs, even though re-treatment with axi-cel was observed in the ZUMA-7 study. This was to reflect that re-retreatment with axi-cel is unlikely in UK clinical practice. The ERG's concern is that this creates an inconsistency regarding the treatment costs required to deliver the modelled treatment benefits. It may be that the full re-treatment costs (acquisition and administration) may have contributed to the overall survival estimates applied in the model. This is important because it impacts on treatment acquisition and administration costs and hence has a significant impact on the ICER.
What alternative approach has the ERG suggested?	The ERG prefers to apply the axi-cel re-treatment costs to the resource use observed in ZUMA-7 to ensure that the treatment costs incurred are consistent with the resources required to generate the modelled treatment benefits.
What is the expected effect on the cost-effectiveness estimates?	The implication of applying axi-cel retreatment costs is an increase in total axi-cel treatment costs. The impact is therefore an increase to the ICER relative to the company's ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG is satisfied that the company has provided all that is necessary to make an informed decision on this issue regarding the most appropriate application of treatment costs in the model.

Issue 2A Long-term extrapolation of clinical effectiveness data

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	The ZUMA-7 study used to inform the mixture cure models in the economic model has a median follow-up of [redacted]. The trial data are of relatively short duration, with a substantial proportion not reaching the two-year follow-up and with limited data at later time points at the time of the data-cut. This poses a challenge when trying to extrapolate over the longer term, including identification of the most appropriate cure fraction, which is unknown. There is considerable uncertainty regarding the longer-term survival in people with primary refractory or relapsed DLBCL being offered axi-cel or SOC as 2nd line treatments.
What alternative approach has the ERG suggested?	Without longer follow-up from the ZUMA-7 study, there is no alternative approach for the ERG to take.
What is the expected effect on the cost-effectiveness estimates?	It is difficult to determine the expected impact on the ICER without the presence of longer-term follow-up data. The company have used the best available data from the ZUMA-7 study to extrapolate the long-term clinical effectiveness data.
What additional evidence or analyses might help to resolve this key issue?	Considering the current evidence base there is nothing the company can do to address the uncertainty in the longer-term extrapolation of the survival curves, though any further validation of long-term projections that could be achieved would be beneficial. Further follow-up data from the ZUMA-7 study will ultimately provide the additional information required on which to improve extrapolation modelling.

Issue 2B Long-term extrapolation data: crossover adjustment for overall survival in the SOC arm

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	The issue surrounding the use of cross-over models for the SOC arm is twofold: i) uncertainty surrounding the most appropriate cross-over model to use and ii) the impact of the upcoming CDF review of axi-cel as 3rd line plus treatment. CAR-T therapies were allowed in the SOC arm of the ZUMA-7 study as a 3rd line therapy. [redacted] were expected to receive a subsequent cellular therapy. This is an issue because axi-cel is currently only available in England through the CDF. The company's approach to use cross-over analysis is in line with NICE's positioning statement which requires that treatments only available through the CDF are not considered standard of care in England. The company therefore used a cross-over analysis to adjust the OS curve for the SOC arm. Whilst the company's decision to use cross-over modelling is in line with NICE's position statement, the requirement to use a cross-over analysis has important implications for the ICER. The cross-over model used in the company's base case analysis is the rank preserving structural failure time model (RPSFTM) with full re-censoring of all control arm patients. This generates a HR (95% CI) of [redacted]). However, it is important to note that alternative cross-over models produce different HRs that have a substantial impact on the ICER.
What alternative approach has the ERG suggested?	The company's decision to use cross-over analysis is appropriate and consistent with NICE guidelines. The ERG would like to note that if NICE guidelines change upon the next review of axi-cel on the CDF in England, this will have implications for the SOC OS curve and therefore a substantial change to the base case ICER. The ERG agrees with the company's base case cross-over model. However, would like to note that the different cross-over methods presented by the company may also be plausible. The choice of cross-over model has an important impact on the ICER.
What is the expected effect on the cost-effectiveness estimates?	The use of a cross-over analysis instead of ITT analysis and the choice of cross-over method have implications for the OS projection for the SOC arm of the model. Scenario analyses show that different cross-over models can lead to substantial increases in the ICERs. The use of cross-over / ITT analysis + inclusion of subsequent CAR-T costs may also impact the ICER.
What additional evidence or analyses might help to resolve this key issue?	The upcoming review by NICE of the CDF and the use of axi-cel 3rd line plus may have implications for the most appropriate ICER. Any further validation of the clinical plausibility of the cross-over model long-term projections would be welcome.

1.6 Other key issues: summary of the ERG's view

The company argue that axi-cel can be used as an end-of-life treatment. However, the mean and median modelled life expectancy for SOC is [redacted] and [redacted] respectively. Therefore, the mean life expectancy used to calculate the ICER does not strictly meet NICE's end of life criteria with the life expectancy in the comparator arm being greater than 24 months. However, if axi-cel meets the criteria depends on the committee's preferred statistic to assess the criteria, whether that is the mean or the median (see Chapter 7).

1.7 Summary of ERG's preferred assumptions and resulting ICER

Given the uncertainties raised above and other issues raised in the report, mainly around the costs, the key differences between the company's and ERG's preferred base case analyses are:

Cost parameters:

- Apply axi-cel retreatment costs as observed in the ZUMA-7 study, to maintain consistency between the modelled treatment costs and benefits. The cost of axi-cel retreatment was not included in the company base case analysis.
- Apply the cost of salvage therapy for the proportion who received salvage chemotherapy in ZUMA-7 ([redacted]). The company assumed everyone in the SOC arm received salvage therapy.
- Use the most up to date NHS reference costs for the auto-SCT costs rather than use inflated costs from the clinical expert option sought in the development of the NG51 guidance.
- Assume that neurological AEs (grade 3+) would require outpatient investigation as a minimum. The company assume no treatment costs associated with these events.
- Use the distribution of subsequent treatments from the ZUMA-7 study, with CAR-T therapies removed and re-distributed to other therapies received in ZUMA-7, assuming no CAR-T therapies and redistributed to those therapies used in ZUMA-7. To maintain consistency with how the OS benefits are modelled, the ERG prefers to include nivolumab and pembrolizumab despite these not being available in the UK. The company instead sought clinical expert opinion in England that

had experience in the treatment of relapsed or refractory DLBCL and excluded those therapies not routinely used in UK clinical practice.

Clinical parameters:

- Apply the company's scenario analysis using a log-logistic MCM for OS on axi-cel as it provides the best fit to the KM data and is clinically plausible. This model provides a more cautious estimate of OS survival gains than the company's choice of generalised gamma MCM for axi-cel OS, not unreasonable given the highly uncertain OS gains for axi-cel.

Utility parameters:

- Apply the pre-progression EQ-5D utilities sourced from the ZUMA-1 trial (3rd line plus treatment) as more appropriate source for 2nd line post-event in this assessment. The data are from a similar patient population and more in line with NICE reference case. The company preferred approach is to use the JULIET study with SF-36 responses mapped to EQ-5D.

Further scenario analyses around the ERG base case were conducted that explore the impact of using ITT analysis for modelling OS, alternative treatment distribution for subsequent treatments, assumptions regarding the cure time point and the use of different cross-over methods for the SOC arm.

Table 2 Summary of ERG's preferred assumptions and ICER (cumulative)

Scenario	Incremental cost	Incremental QALYs	ICER (cumulative)	ICER (change from company base case)
Company's base case	[redacted]	[redacted]	**£51,996**	**--**
+ Include axi-cel re-treatment costs (as per company clarification response scenario) – Issue 1	[redacted]	[redacted]	£54,902	+£2,906
+ Proportion in SOC arm receiving initial salvage chemotherapy ([redacted])	[redacted]	[redacted]	£55,026	+£3,030
+ Auto-SCT cost source: NHS reference costs (HRG: SA26A)	[redacted]	[redacted]	£56,784	+£4,788
+ Costs of treating Grade 3 and above neurological AEs (Outpatient consultation)	[redacted]	[redacted]	£56,789	+£4,793
+ Subsequent treatment distribution (as per ZUMA-7, with CAR-T treatments in SOC arm re-distributed)	[redacted]	[redacted]	£57,071	+£5,075
+ Axi-cel OS extrapolation: Log logistic MCM	[redacted]	[redacted]	£58,338	+£6,342
+ Post-event utilities, ZUMA-1 pre progression (0.72)	[redacted]	[redacted]	£58,205	+£6,209
ERG's preferred base case	[redacted]	[redacted]	**£58,205**	**+£6,209**

Abbreviations: AE: Adverse events; Auto-SCT: Autologous stem-cell transplant; ICER: Incremental cost-effectiveness ratio; MCM: Mixture cure model; QALY: Quality adjusted life year; SOC: Standard of care

For further details of the exploratory and sensitivity analyses done by the ERG, see Chapter 6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Kite is relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adults after one systemic therapy. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is axicabtagene ciloleucel (axi-cel).

2.2 Background

The Company submission (CS) describes non-Hodgkin's lymphoma (NHL) as a diverse group of cancers that originate in the lymphatic system. The focus of the CS is diffuse large B-cell lymphoma (DLBCL), a high-grade lymphoma with fast growing, abnormal and enlarged B cells that spread quickly and requires prompt treatment. DLBCL is the most common type of NHL comprising around 40% of all cases of NHL.[1] Around 5,000 people in the UK are diagnosed with DLBCL each year.[2] According to Hospital Episode Statistics for admitted patient care in England in the year 2020-2021, there were 35,113 finished consultant episodes for diffuse large B-cell lymphoma (code C83.3), with 31,231 of these being admissions (mean length of stay 9.7 days).[3] There were 20,443 males and 14,664 females with a mean age of 66 years.

The most common symptom of DLBCL is painless swellings which can grow quickly. Other general symptoms (known as B symptoms) include night sweats, high temperatures, and unexplained weight loss and/or itching. More specific symptoms may occur, depending on the location of DLBCL; for example, people with lymphoma in the abdomen may experience pain, diarrhoea or bleeding.[1] DLBCL impacts both physical and emotional quality of life (QoL)[4] and health-related QoL in patients with relapsed or refractory disease is affected due to the lack of effective treatment and treatment-related adverse events.[5] DLBCL is also associated with a high burden on carers who have to manage their own day-to-day life and their own feelings as well as those of the person they are caring for. Over time, this can become physically and mentally exhausted and carers may experience stress and anxiety.[6]

People diagnosed with DLBCL will generally be assessed for risk factors using the validated International Prognostic Index (IPI), with one risk factor assigned to each of the following: age >60 years, lactate dehydrogenase levels above upper limit of normal, Ann Arbor disease staging III or IV, performance status >1, and more than one extranodal sites of disease. Prognostic risk ranges from low (0 or 1 risk factor) to high (4 or 5 risk factors).[7] A further age-adjusted version of the IPI developed to assess people having second-line treatment for DLBCL (sAAIPI) includes three prognostic factors: performance status, lactate dehydrogenase levels and disease stage). The sAAIPI ranges from low risk (no risk factors) to high (2 or 3 factors).[8] Other prognostic factors include tumour size >7.5 cm and genetic aberrations (known as double- or triple-hit lymphomas).[9, 10]

First-line treatment for patients with DLBCL is chemotherapy consisting of rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (known as R-CHOP) and around two-thirds of patients are thus cured. However, around 10-15% have primary refractory disease and another 20-25% of patients relapse and outcomes for these patients are poor.[5, 9, 11-15] The recommended treatment for those patients who are fit enough for intensive treatment is re-induction therapy (consisting of multi-agent immunochemotherapy) followed by high-dose therapy (HDT) plus autologous stem-cell transplant (auto-SCT) in responders.[9] It has been estimated that around half of patients with relapsed or refractory DLBCL (r/r DLBCL) will be eligible for this intensive treatment, of which half again will proceed to auto-SCT and less than half of these will be cured.[16] In addition, patients who do proceed to auto-SCT may experience late side effects and negative effects on their quality of life.[17-19]

The proposed place of axi-cel in the treatment pathway is presented in Document B, Figure 4 of the CS and is reproduced below as Figure 1. The ERG notes that the NICE Pathways service has been withdrawn since the company accessed the treatment pathway in January 2022. The ERG agrees that the company's proposed pathway is representative of current clinical practice and the anticipated positioning of axi-cel is within its licensed indication.

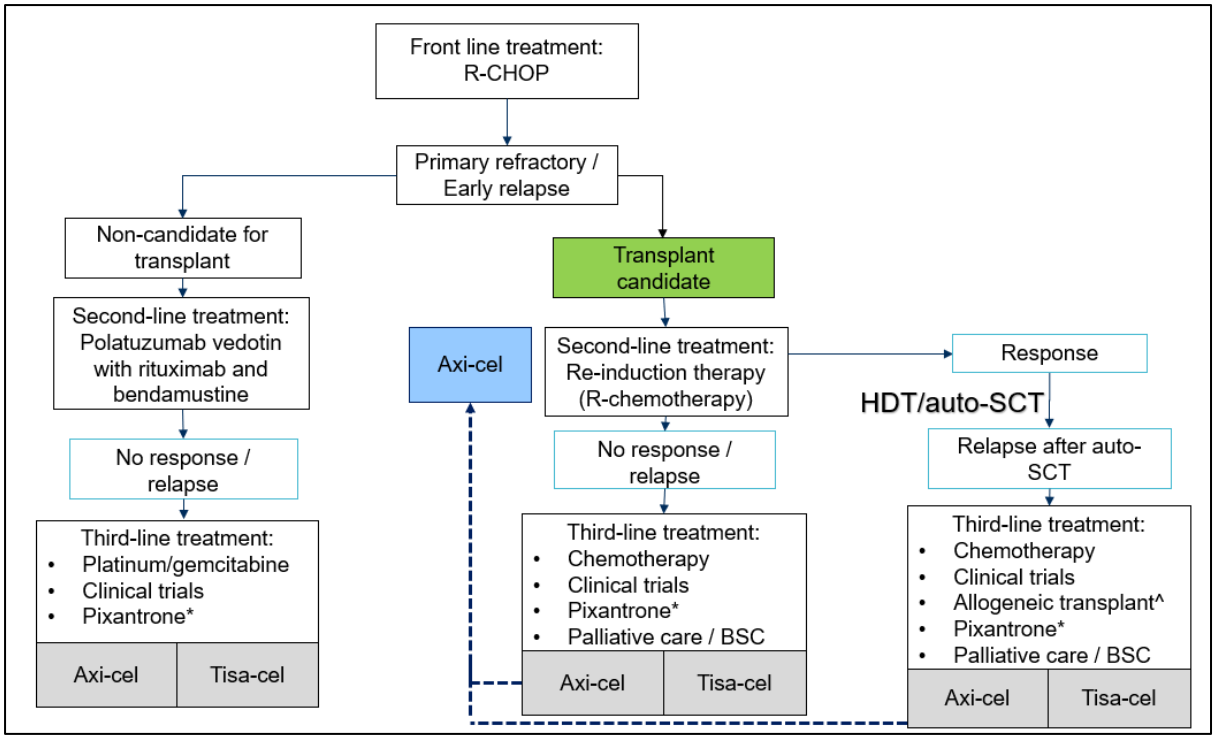

Figure 1 Clinical pathway of care for DLBCL and proposed axi-cel positioning [reproduced from Document B, Figure 4 of the CS]

Key: auto-SCT, autologous stem cell transplant; BSC, best supportive care; DLBCL, diffuse large B-cell lymphoma; HDT, high dose therapy; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone.
Notes: * Pixantrone is rarely used in clinical practice but is included here for completeness.
^ An allogeneic transplant can also be considered instead of auto-SCT where stem cell harvesting is not possible.
Green refers to the target population for axi-cel.
Blue refers to the proposed positioning of axi-cel at second-line.
Grey refers to treatments currently recommended within the Cancer Drugs Fund.
Source: Adapted from the NICE pathway for treating DLBCL[20] and the British Society for Haematology guidelines for the management of DLBCL.[9]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Population	Adults with relapsed or refractory DLBCL after one systemic therapy.	Adults with primary refractory or early relapse (≤ 12 months) DLBCL who are intended for transplant.	Population aligned to the ZUMA-7 trial population.	The ERG agrees that the population addressed in the CS is appropriate for this appraisal
Intervention	Axicabtagene ciloleucel	Axicabtagene ciloleucel	Not applicable	The intervention described in the CS matches that described in the NICE final scope. Axicabtagene ciloleucel has a marketing authorisation for treating relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma, after 2 or more lines of systemic therapy. The application for EMA filing was submitted in [redacted] for a marketing authorisation extension. The anticipated indication of Yescarta of relevance to this submission is for '[redacted]'. The target date for GB filing is [redacted] and the anticipated

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
				date of marketing authorisation for this licence extension is [redacted].
Comparator(s)	Established clinical management without axicabtagene ciloleucel, including but not limited to: • Salvage chemotherapy with or without rituximab and with or without stem cell transplantation, such as: – DHAP (dexamethasone, cytarabine, cisplatin) – ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) – GDP (gemcitabine, dexamethasone, cisplatin) – GEMOX (gemcitabine and oxaliplatin) – ICE (ifosfamide, carboplatin, etoposide) – IVE (ifosfamide, etoposide, epirubicin)	Re-induction therapy with HDT-auto-SCT consolidation in responders.	As detailed in the NICE pathway for treating DLBCL, patients who are fit enough to tolerate intensive therapy should be offered multi-agent immunochemotherapy at first relapse, primarily to obtain sufficient response to allow consolidation with auto-SCT. Of the salvage chemotherapy options listed, GEMOX is generally reserved for less fit patients who are not able to tolerate intensive HDT plus auto-SCT, and who would therefore not be included in the target population of patients intended for transplant. The term 'salvage chemotherapy' has potential negative connotations and is arguably inaccurate in a market where novel treatments are available at later lines. We have therefore replaced this terminology with 're-induction therapy' from this point in the document, which is more aligned with the medical community. Polatuzumab vedotin with rituximab and bendamustine is only	The ERG agrees that the company's choice of comparators is appropriate for this appraisal

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
	• Polatuzumab vedotin with rituximab and bendamustine (only when stem cell transplantation is not suitable) • Tafasitamab with lenalidomide (only when stem cell transplantation is unsuitable and subject to ongoing NICE appraisal)		a treatment option for patients who have been determined as non-candidates for transplant, as per its marketing authorisation and NICE recommendation.[21] Tafasitamab with lenalidomide is also being assessed for use in patients who have been determined as non-candidates for transplant. It is not yet reimbursed for use in England. As we are submitting for reimbursement in patients intended for transplant, these are not relevant comparators to the decision problem that we will address.	
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rates • Adverse effects of treatment • HRQL	The outcome measures to be considered include: • EFS • OS • PFS • Response rates • Adverse effects of treatment • HRQL	EFS as a primary endpoint is defined as the time from randomisation to the earliest date of disease progression, commencement of new anti-lymphoma therapy, death from any cause or a best 'response' of stable disease. This is the most clinically relevant endpoint for relapsed/ refractory DLBCL given the curative intent of treatment. Additionally, patients who do not respond to re-induction therapy in	The ERG agrees that the outcomes included in the CS are appropriate for addressing the topic of this appraisal. The ERG's clinical advisor is happy with the choice of EFS as the main survival outcome.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
			the second-line setting (i.e. patients who have either progressive disease or stable disease) will not benefit from HDT plus auto-SCT, and so an immediate change in therapeutic intervention is often needed. Reflecting its relevance to this setting, EFS is an established endpoint in DLBCL trials and is the primary endpoint in the ZUMA-7 trial. EFS will therefore be used alongside OS and HRQL data to capture the most important health-related benefits of axicabtagene ciloleucel in the cost-effectiveness modelling.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or	As per the NICE reference case.	Not applicable	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
	outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.			
Subgroups to be considered	None.	The ZUMA-7 primary outcome findings were consistent across pre-planned subgroups, including those defined by baseline demographics, clinical characteristics and treatment history, therefore no subgroup analyses were conducted.	Not applicable.	
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Time horizon is 50 years, which is considered long enough to reflect all important differences in costs and outcomes.	Not applicable.	
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers, and use of EQ-5D-3L.	ZUMA-7 EQ-5D-5L cross-walked to EQ-5D-3L values for pre-event states. Utilities from a previous NICE appraisal (TA567)[22] were used for post-event states.	Since EQ-5D-5L data were not routinely collected post-event in the ZUMA-7 trial, data was not considered appropriate to use in model due to the sparsity of results. Therefore, data from the JULIET study was used for this health state, which was obtained from NICE technology appraisal guidance TA567, Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
			2 or more systemic therapies.[22] This was considered representative of the UK population.	
Key: auto-SCT, autologous stem cell transplant; DHAP, dexamethasone, cytarabine and cisplatin; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; GDP, gemcitabine, dexamethasone and cisplatin; GEMOX, gemcitabine and oxaliplatin; HDT, high dose therapy; HRQL, health-related quality of life; ICE, ifosfamide, carboplatin and etoposide; IVE, ifosfamide, etoposide and epirubicin; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival.				

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG's appraisal of the company's systematic review methods is summarised in Table 4.

Table 4 ERG's appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details are provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research. Relevant conference proceedings and trial registers were also searched. Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	Searches were not restricted by eligibility criteria so all results were discovered and only those relevant to the scope were selected.
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D, Section D.1.1.2 (original SLR) and Appendix D, Section 1.2.2 (SLR update): "*Abstracts and full text publications were independently assessed by two reviewers*"
Was data extraction conducted by two or more reviewers independently?	No	Original SLR report, Section 3.5: "*Data extraction was performed by one researcher and validated by another independent researcher*" SLR update report, Section 3.4: "*All extracted data were verified*

		against the original source by a second researcher" The ERG considers the company's strategy to be satisfactory
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	RCTs were assessed using the Cochrane risk of bias tool for interventions. Non-randomised studies were assessed using the Downs and Black checklist. The CS reports quality assessment of ZUMA-7 using both the Cochrane risk of bias tool and the NICE checklist. The ERG considers the company's assessments to be appropriate
Was the risk of bias assessment conducted by two or more reviewers independently?	No	The risk of bias assessments in both the original SLR and update were performed by one reviewer and independently verified by a second reviewer
hWas identified evidence synthesised using appropriate methods?	Yes	The main evidence came from one study (ZUMA-7). The ERG agrees that meta-analysis would not be appropriate.

The company conducted a systematic literature review (SLR) which aimed to identify, select and synthesise clinical evidence on treatments for people with r/r DLBCL after one prior therapy (Document B, Appendix D of CS). The SLR was conducted in 2020 and updated between December 2021 and February 2022. Searches were conducted in parallel with searches for quality of life and cost-effectiveness evidence.

A total of 28 studies in the original SLR and 19 further studies in the update were included in the review. However, the CS included evidence from only one of these studies (ZUMA-7). Although certain details of these studies are tabulated in Appendix D of the CS (Table 2, Document B, Section D.1.1.4; Table 6, Document B, Section D.1.2.4), the possibility of including these studies within a meta-analysis is not explicitly discussed and there has been no attempt to document the reasons why each study was not suitable for inclusion in either a possible meta-analysis or an indirect comparison along with ZUMA-7.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria.[23] The results are presented in Table 6.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Details of key clinical effectiveness evidence are reported in Document B, Section B.2 of the CS. The company presents clinical effectiveness evidence from one ongoing, randomised, open-label, international, Phase III trial: ZUMA-7. A summary of the trial is reported in Document B, Table 4 of the CS and reproduced as Table 6 below.

3.2.1 Included studies

Table 6 Summary of clinical effectiveness evidence [reproduced from Table 4, Document B of the CS]

Study	ZUMA-7				
Study design	ZUMA-7 is an ongoing Phase III, randomised, open-label study evaluating the efficacy of axi-cel compared with SOC treatment.				
Population	Adults with primary refractory (no CR to frontline therapy) or early relapse (CR followed by relapse within 12 months of frontline therapy) DLBCL after one systemic therapy who are intended for transplant.				
Intervention(s)	Axi-cel				
Comparator(s)	Re-induction therapy with HDT plus auto-SCT consolidation in responders				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	ZUMA-7 presents the pivotal, regulatory, clinical evidence in support of axi-cel in r/r DLBCL				
Reported outcomes specified in the decision problem	• **EFS** • **OS** • PFS • Response rate • **Adverse effects of treatment** • **HRQL**				
All other reported outcomes	• Duration of response • **Time to next treatment** • Clinically significant changes in safety laboratory test values, including antibodies to axi-cel				

Key: auto-SCT, autologous stem cell transplant; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HDT, high dose therapy; HRQL, health-related quality of life; OS, overall survival; PFS, progression-free survival; r/r, relapsed or refractory; SOC, standard of care.
Notes: Bolded outcomes are those used in the economic modelling.

The methods of ZUMA-7 are reported in Document B, Section 2.3 of the CS and the participant flow is reported in Appendix D, Section D.2, Figure 4 of the CS. The objective of ZUMA-7 was to investigate whether axi-cel was superior to standard of care (SOC), as measured by event-free survival (EFS), according to blinded central assessment, as second-line treatment in people with r/r DLBCL. ZUMA-7 was conducted at 77 sites in 14 countries, including the UK. The key eligibility criteria for ZUMA-7 are reported in Document B, Section B.2.3, Table 5 of the CS. In brief, participants were required to have histologically proven DLBCL, relapsed or refractory disease after frontline therapy (at a minimum, an anti-

CD20 monoclonal antibody or an anthracycline-containing chemotherapy regimen) and intent to proceed to HDT and auto-SCT if response to second-line chemotherapy. The study schema for ZUMA-7 is presented in Document B, Section B.2.3, Figure 5 of the CS and reproduced as Figure 2 below.

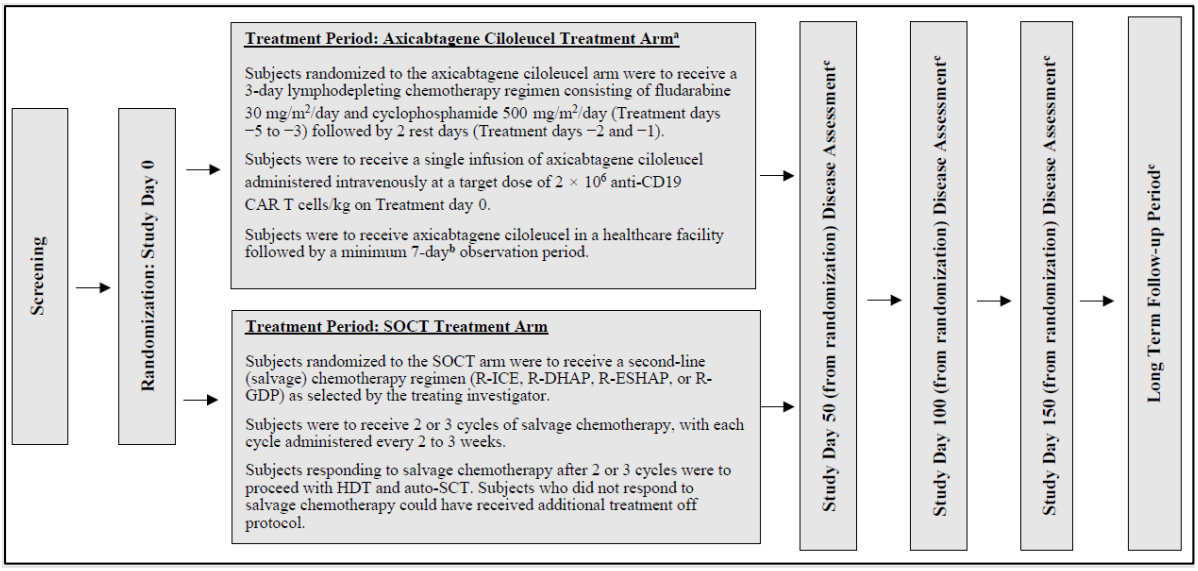

Figure 2 Study scheme for ZUMA-7 [reproduced from Figure 5, Document B of the CS]

Key: auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; HDT, high-dose therapy; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SCT, stem cell transplant; SOCT, standard of care therapy.
Notes: [a] At the discretion of the investigator, corticosteroid bridging therapy could have been considered for patients with high disease burden at screening. [b] Minimum observation period of 7 days unless otherwise required by country regulatory agencies (e.g. 10 days for patients treated in Germany, Switzerland, and France). [c] Disease assessments were to be calculated from the date of randomisation and not the date of dosing with axi-cel or SOCT. Independent of the treatment arm, study procedures and disease assessments were to occur at the same protocol-defined timepoints.
Source: ZUMA-7 CSR.[24]

The CS reports quality assessment of ZUMA-7 using both the NICE checklist (Appendix D, Section D.3, Table 10) and the Cochrane risk of bias tool for RCTs (Appendix D, Section D.1.2.5, Table 7). The ERG notes an inconsistency in the response to ostensibly equivalent items across the two instruments. In the NICE checklist, the item "Was the allocation adequately concealed?" was assigned a response of "Yes", whereas the item "Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment" was

assessed as "High risk of bias". The ERG is of the opinion that the method of allocation in ZUMA-7 (using an interactive voice/web response system) was adequate and of a Low risk of bias. In general, the ERG agrees with the company's assessment of ZUMA-7 and that the overall risk of bias is low, albeit with the bias inherent in open-label studies. In addition, ZUMA-7 was funded by Kite, but it is unclear to the ERG whether the company also had any role in study-related aspects.

Details of the baseline characteristics of the full analysis set (FAS; i.e. all randomised participants) are presented in Document B, Table 6 of the CS and reproduced as Table 7.

Table 7 Baseline characteristics of participants in ZUMA-7 [reproduced from Table 6, Document B of the CS]

Characteristic, n (%)	Axi-cel (N = 180)	SOC (N = 179)	Overall (N = 359)
Age			
Median, years (range)	58 (21–80)	60 (26–81)	59 (21–81)
Mean, years (SD)	[redacted]	[redacted]	[redacted]
≥ 65, n (%)	51 (28)	58 (32)	109 (30)
Male, n (%)	110 (61)	127 (71)	237 (66)
Ethnicity[a], n (%)			
American Indian or Alaska Native	0 (0)	1 (1)	1 (< 1)
Asian	12 (7)	10 (6)	22 (6)
Black	11 (6)	7 (4)	18 (5)
Native Hawaiian or other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Hispanic or Latino ethnic group[a], n (%)			
Yes	10 (6)	8 (4)	18 (5)
No	167 (93)	169 (94)	336 (94)
Not reported	3 (2)	2 (1)	5 (1)
ECOG performance status[b], n (%)			
1	85 (47)	79 (44)	164 (46)
Disease stage, n (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	146 (82)	285 (79)
sAAIPI[c], n (%)			
2 or 3	82 (46)	79 (44)	161 (45)
Molecular subgroup according to central laboratory[d], n (%)			

Characteristic, n (%)	Axi-cel (N = 180)	SOC (N = 179)	Overall (N = 359)
Germinal centre B-cell-like	109 (61)	99 (55)	208 (58)
Activated B-cell-like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing data	28 (16)	41 (23)	69 (19)
Response to frontline therapy at randomisation, n (%)			
Primary refractory disease	133 (74)	131 (73)	264 (74)
Relapse ≤ 12 months after the initiation or completion of frontline therapy	47 (26)	48 (27)	95 (26)
Disease type according to central laboratory, n (%)			
DLBCL[e]	126 (70)	120 (67)	246 (69)
High-grade B-cell lymphoma, not otherwise specified	0 (0)	1(1)	1 (< 1)
High-grade B-cell lymphoma, including rearrangement of MYC with BCL2 or BCL6 or both	31 (17)	25 (14)	56 (16)
Not confirmed or missing data	18 (10)	28 (16)	46 (13)
Other	5 (3)	5 (3)	10 (3)
Disease type according to the investigator, n (%)			
Large B-cell lymphoma, not otherwise specified	110 (61)	116 (65)	226 (63)
T-cell- or histiocyte-rich large B-cell lymphoma	5 (3)	6 (3)	11 (3)
Epstein-Barr virus-positive DLBCL	2 (1)	0 (0)	2 (1)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)
High-grade B-cell lymphoma, including rearrangement of MYC with BCL2 or BCL6 or both	43 (24)	27 (15)	70 (19)
Primary cutaneous diffuse large B-cell lymphoma, leg type	1 (1)	0 (0)	1 (< 1)
Other	0 (0)	3 (2)	3 (1)
Extranodal disease, n (%)			
Yes	[redacted]	[redacted]	[redacted]
Prognostic marker according to central laboratory, n (%)			
High-grade B-cell lymphoma, double- or triple-hit	31 (17)	25 (14)	56 (16)
Double-expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)

Characteristic, n (%)	Axi-cel (N = 180)	SOC (N = 179)	Overall (N = 359)
Not applicable	74 (41)	70 (39)	144 (40)
Missing data	3 (2)	15 (8)	18 (5)
CD19+ status on immunohistochemical testing[f], n (%)	144 (80)	134 (75)	278 (77)
Bone marrow involvement[g], n (%)	17 (9)	15 (8)	32 (9)
Elevated lactate dehydrogenase level[h], n (%)	101 (56)	94 (53)	195 (54)
Median tumour burden, mm^2 (range)	2,123 (181–22,538)	2,069 (252–20,117)	2,118 (181–22,538)

Key: DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; sAAIPI, second-line age-adjusted International Prognosis Index; SD, standard deviation; SOC, standard of care.
Notes: [a] Ethnicity group were determined by the investigator. [b] ECOG performance status scores were assessed on a 5-point scale, with a score of 0 indicating no symptoms and higher scores indicating greater disability. A score of 1 indicates that the patient is ambulatory but restricted from strenuous activity. [c] Values are the sAAIPI at randomisation, which were similar to the sAAIPI according to the investigator as entered into the clinical database. The sAAIPI is used to assess prognostic risk based on various factors after adjustment for patient age and extranodal status at the time of diagnosis of refractory disease. Risk categories are assessed as low (0 factors), intermediate (1 factor), or high (2 or 3 factors). [d] The molecular subgroup as assessed by the investigator was as follows: germinal centre B-cell-like in 96 patients (53%) in the axi-cel group, 84 (47%) in the SOC group, and 180 (50%) overall; non-germinal centre B-cell-like in 47 (26%), 54 (30%), and 101 (28%), respectively. The molecular subgroup was not assessed in 37 patients (21%) in the axi-cel group, 41 (23%) in the SOC group, and 78 (22%) overall. [e] The definition of diffuse large B-cell lymphoma according to the central laboratory included cases of incomplete evaluation that were caused by inadequate sample amount or sample type, for which further classification of the subtype was not possible. Diffuse large B-cell lymphoma, not otherwise specified, according to the World Health Organization 2016 definition, is also included. [f] CD19 staining was not required for participation in the trial. Testing was conducted by the central laboratory. [g] The data shown were as collected on the diagnosis history case-report form. [h] An elevated lactate dehydrogenase level was defined as a level that was above the upper limit of the normal range according to the local laboratory. [I] Tumour burden was determined based on the sum of product diameters of the target lesions, according to the Cheson criteria, and was assessed by the central laboratory.
Source: Locke et al. 2021; ZUMA-7 CSR[24, 25]

The mean age of participants was [redacted] years, with around one-third being 65 years of age or older. There was a larger proportion of males in the standard of care (SOC) group (127/179, 70.9%) than the axi-cel group (110/180, 61.1%). The ERG's clinical expert notes that males generally do better in lymphoma outcomes, probably due to the way that women metabolise rituximab. Around half of participants had respective ECOG scores of 0 or 1 and sAAIPI scores of 0/1 or 2/3, respectively. At least three-quarters of participants had stage III or IV disease and around three-quarters had primary refractory disease as compared to relapse within 12 months. Considering the disease type categories reported by the company, 23.9% of the axi-cel group and 15.1% of the standard care group were classified as having 'high-grade B-cell lymphoma, including rearrangement of MYC with BCL2 or BCL6 or both'. The ERG notes that people with this category of disease will tend to have a worse prognosis and, thus, the smaller proportion of participants in the standard care group is in favour of the

outcomes of that group. Extranodal disease is reported as [redacted]% in the axi-cel group and [redacted]% in the standard care group. At clarification, the company provided further details of extranodal involvement at baseline, which are reproduced as Table 8 below.

Table 8 Extranodal involvement at baseline (FAS) [reproduced from Table 1 of the company's clarification response]

	Axi-cel (N = 180)	SOC (N = 179)	Overall (N = 359)
Type of extranodal involvement, n (%)			
Abdominal cavity	[redacted]	[redacted]	[redacted]
Bone marrow	[redacted]	[redacted]	[redacted]
Chest	[redacted]	[redacted]	[redacted]
CNS/spinal	[redacted]	[redacted]	[redacted]
Cutaneous	[redacted]	[redacted]	[redacted]
Gastrointestinal tract	[redacted]	[redacted]	[redacted]
Kidney	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]
Number of extranodal lesions, n (%)			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]

Key: CNS, central nervous system; FAS, full analysis set; SOC, standard of care.
Notes: Patients with multiple types of extranodal involvement are counted in each category corresponding to their sites of extranodal disease. Screening target/non-target lesions with 'body site' other than lymph node or spleen are included; Lesions contains wording 'NODE', 'LYMPHADENOPATHY', 'ADENOPATHY', 'LYMPH' in free-text section 'If Other Body Site, specify' or 'Body Site Description' are excluded. Lesions for patients with no extranodal disease and not stage IV are excluded. Patients with screening bone marrow assessment with lymphoma present were considered to have one bone marrow site. [a] Two patients in the axi-cel group with three lesions (one patient with two lesions of Chest Wall and one patient with lesion of Neck Left Parotid) considered as extranodal lesions per query response, were counted under 'Other' type of extranodal involvement.

The ERG's clinical expert notes that two or more extranodal sites (at any location) predict a worse outcome. Some specific sites of disease are high risk for progression and central nervous system (CNS) disease: CNS, liver and kidney. In ZUMA-7, there are slight differences between the axi-cel and SOC groups but they are reasonably matched for two or more extranodal sites. In addition, numbers are very small in the site-specific subgroups so any effect on outcomes is likely to be very small.

In general, the ERG's clinical expert is of the opinion that the baseline characteristics of participants in ZUMA-7 are representative of patients with r/r DLBCL seen in clinical practice in the UK.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: overall survival (OS), progression-free survival (PFS), response rates, adverse effects and health-related quality of life (HRQoL). Primary and secondary outcomes are presented in the CS in terms of the full analysis set (FAS), consisting of all randomised participants, analysed by the protocol therapy to which they were randomised.

Primary endpoint: ZUMA-7

The primary endpoint of ZUMA-7 was event-free survival (EFS; with progression events and censoring) defined as time from randomisation to the earliest date of disease progression per the Lugano classification,[26] commencement of new lymphoma therapy, death from any cause, or a best response of stable disease (SD) up to, and including, the response on the day 150 assessment after randomisation, as determined by blinded central assessment. The CS presents data from the primary analysis of EFS at the cut-off date of 18th March 2021. The median potential follow-up time was 24.9 months, with a median actual follow-up of [redacted] months. Table 9 summarises the EFS outcomes.

Table 9 Summary of EFS outcomes

EFS Outcome	Axi-cel (n=180)	SOC (n=179)
EFS events, n (%)	[redacted]	[redacted]
Stratified HR (95%CI)	0.40, 95% CI 0.31, 0.51, stratified log rank p<0.0001	
Median EFS, months (95%CI)	8.3 (4.5, 15.8)	2.0 (1.6, 2.8)
Estimated EFS at 24 months, % (95%CI)	41 (33, 48)	16 (11, 22)
Median follow-up using reverse KM method, months (95%CI)	[redacted]	[redacted]
EFS event, n (%)		
Disease progression	[redacted]	[redacted]
Best response of SD	[redacted]	[redacted]
New lymphoma therapy	[redacted]	[redacted]
Axi-cel retreatment	[redacted]	[redacted]
Death from any cause	[redacted]	[redacted]

Note. EFS, event-free survival, CI, confidence interval; KM, Kaplan-Meier; SD, stable disease

At the cut-off date, 252 events had occurred by blinded central assessment in [redacted]/180 ([redacted]%) of the axi-cel group and [redacted]/179 ([redacted]%) of the SOC group. Axi-cel was superior to SOC (stratified HR 0.40, 95% CI 0.31, 0.51, stratified log rank p<0.0001). The median EFS was 8.3 months (95%CI 4.5, 15.8 months) for the axi-cel group and 2.0 months (95% CI 1.6, 2.8 months) for the SOC group.

[redacted].

The Kaplan-Meier plot for EFS is presented in Document B, Figure 6 of the CS and reproduced as Figure 3 below.

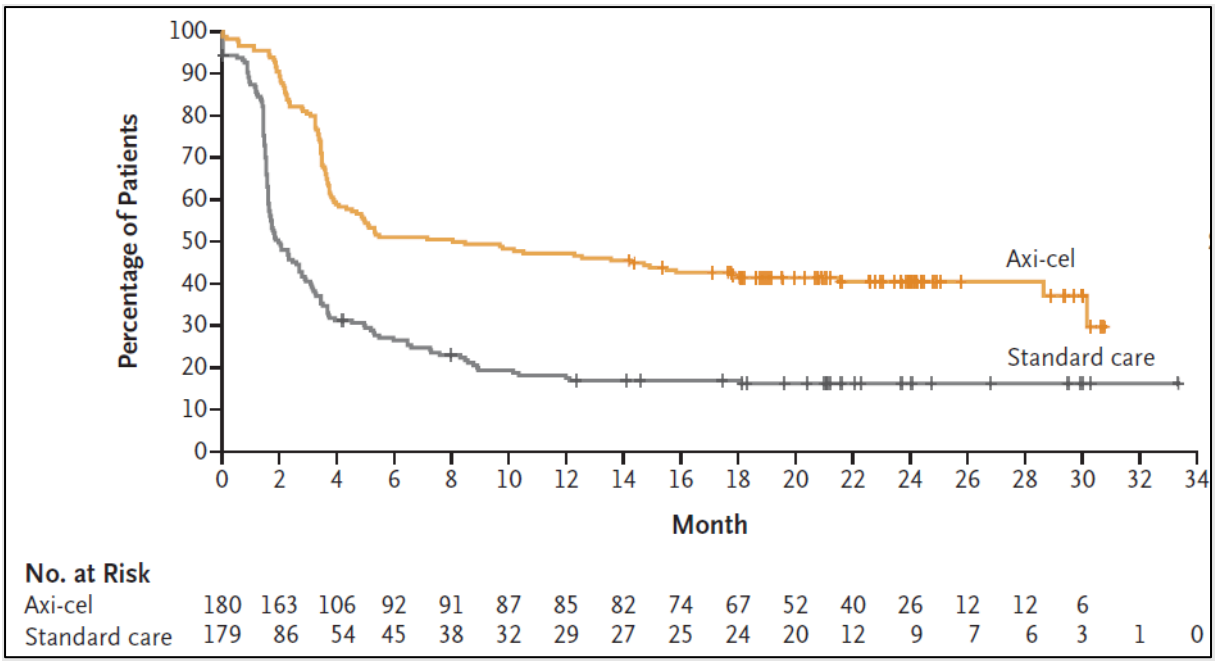

Figure 3 Kaplan-Meier plot for EFS as per central assessment, FAS [reproduced from Figure 6, Document B of the CS]

Key: EFS, event-free survival; FAS, full analysis set.
Source: Locke et al. 2021.[25]

Secondary endpoints: ZUMA-7

The key secondary endpoints of ZUMA-7 are the following:

- **Objective response rate (ORR)** per blinded assessment (defined as the incidence of either a PR or CR by the Lugano classification): ORR was 150/180 (83.3%; 95% CI [redacted]) for the axi-cel group and 90/179 (50.3%; 95% CI [redacted]) for the SOC group. The difference (95% CI) in ORR between groups was 33.1% ([redacted]; p<0.001). The odds ratio (95% CI) comparing the axi-cel group with the SOC group was 5.31 (3.08, 8.90), p[redacted]. The CS presents a summary of ORR and best overall response per central assessment in Document B, Table 8, reproduced as Table 10 below.

Table 10 Summary of ORR and best overall response per central assessment, FAS [reproduced from Table 8, Document B of the CS]

	Axi-cel (N = 180)	SOC (N = 179)
Number of objective responders (CR + PR), n (%) [95% CI]	150 (83) [redacted]	90 (50) [redacted]
Difference in ORR (95% CI)	[redacted]	-
Stratified CMH test p-value	[redacted]	-
Best objective response		
Complete response, n (%) [95% CI]	117 (65) [redacted]	58 (32) [redacted]
Partial response, n (%) [95% CI]	33 (18) [redacted]	32 (18) [redacted]
Stable disease, n (%) [95% CI]	5 (3) [redacted]	33 (18) [redacted]
Progressive disease, n (%) [95% CI]	21 (12) [redacted]	38 (21) [redacted]
Undefined/no disease, n (%) [95% CI]	0 (0) [redacted]	4 (2) [redacted]
Not evaluable, n (%) [95% CI]	[redacted]	[redacted]
Not performed, n (%) [95% CI]	4 (2) [redacted]	14 (8) [redacted]

Key: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; FAS, full analysis set; ORR, objective response rate; PR, partial response; sAAIPI; second-line age-adjusted International Prognostic Index
Notes: Response assessments per Lugano Classification.[26] A one-sided p-value from the CMH test is presented. Undefined/no disease included patients who were found to have no disease at baseline or follow-up by central assessment but had disease by investigator assessment. Not evaluable disease assessments were performed but no conclusion could be made.
Source: Table 14. ZUMA-7 CSR; Locke et al. 2021[24, 25]

- **OS** (defined as the time from randomisation to death from any cause): 72/180 (40.0%) participants in the axi-cel group and 81/179 (45.3%) in the SOC group had died at the time of analysis. The Kaplan-Meier median was not reached in the axi-cel group (NR, 95% CI 28.3 months, NE) and was 35.1 months (95% CI 18.5, NE) in the SOC group. The difference between the groups was not statistically significant (HR 0.73, 95%CI

0.53, 1.01, p=0.054). The estimated OS (95% CI) at 2 years was 60.7% ([redacted]) in the axi-cel group and 52.1% ([redacted]) in the SOC group (interim analysis). Median follow-up time for OS (reverse Kaplan-Meier method) was [redacted] months (95% CI [redacted]) for the axi-cel group and [redacted] months (95%CI [redacted]) in the SOC group. Document B, Figure 7 of the CS presents the Kaplan-Meier plot for OS, reproduced as Figure 4 below.

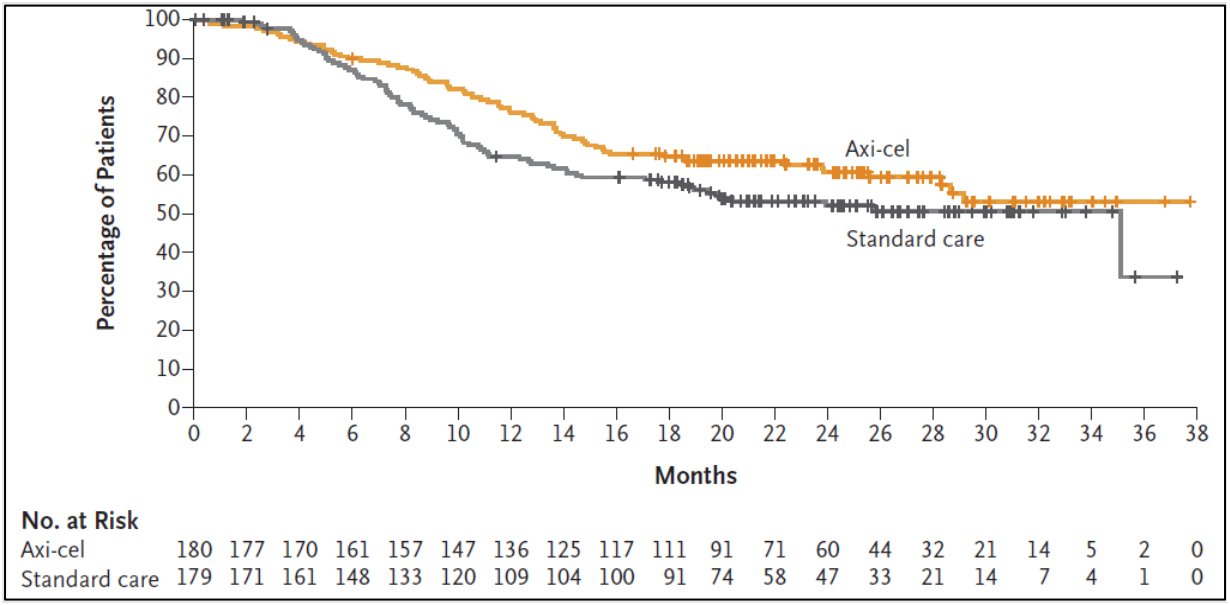

Figure 4 Kaplan–Meier plot for OS, FAS [reproduced from Figure 7, Document B of the CS]

Key: FAS, full analysis set; OS, overall survival.
Source: Locke et al. 2021[25]

In the SOC group, 56% of participants received subsequent cellular immunotherapy. The confounding effects of such treatment switching in the SOC group were addressed by the company with a pre-specified sensitivity analysis using the rank-preserving structural failure time (RPSFT) method, the result being a difference in OS favouring axi-cel (stratified HR 0.58, 95% CI 0.42, 0.81). The inverse probability of censoring weights (IPCW) model also favoured axi-cel (stratified HR 0.70, 95% CI 0.46, 1.05). Document B, Figure 8 of the CS presents the Kaplan-Meier plot of OS using the RPSFT model and is reproduced as Figure 5 below.

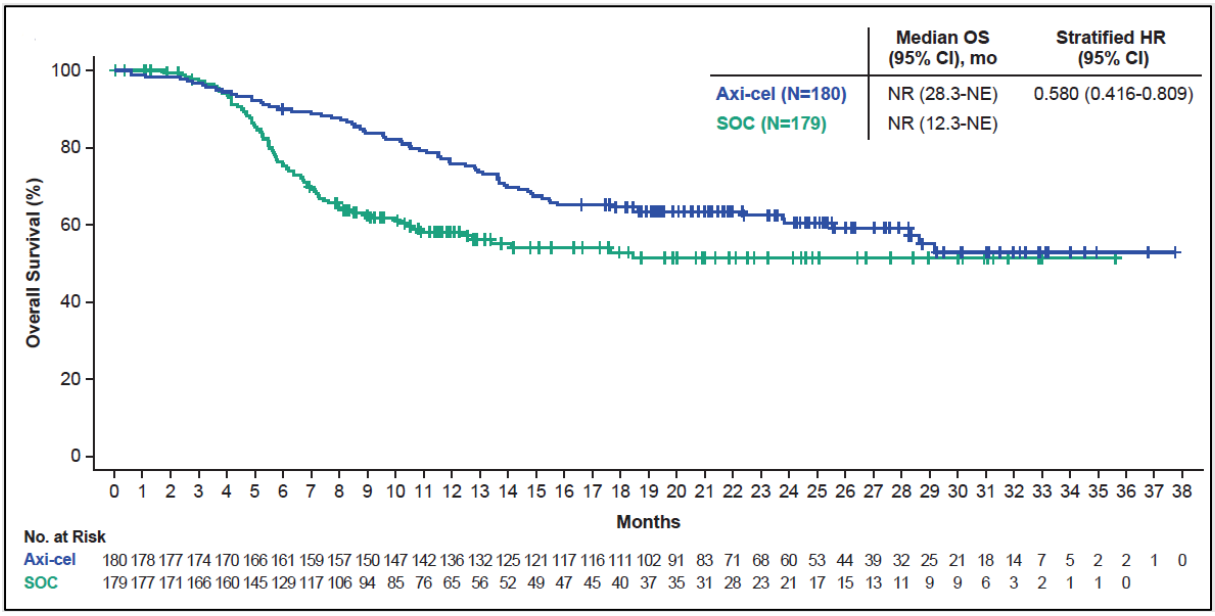

Figure 5 Kaplan–Meier plot of OS – sensitivity analysis using RPSFT model, FAS [reproduced from Figure 8, Document B of the CS]

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NE, not estimable; NR, not reached; OS, overall survival; RPSFT, rank-preserving structural failure time; SOC, standard of care.
Source: Locke et al. 2021[25]

Additional secondary endpoints are reported in Document B, Section B.2.6.3 of the CS and are summarised in Table 11 below. The exploratory endpoint, time to next therapy (TTNT), which was used in the economic model, is also reported. TTNT events were experienced by [redacted]/180 of participants ([redacted]%) in the axi-cel group and [redacted]/179 of participants ([redacted]%) in the SOC group. The KM median TTNT was [redacted] months (95%CI [redacted]) for the axi-cel group and [redacted] months (95%CI [redacted]) for the SOC group (stratified HR was [redacted] (95%CI [redacted], p[redacted]). At the cut-off date, [redacted]/180 participants ([redacted]%) in the axi-cel group and [redacted]/179 participants ([redacted]%) in the SOC group had not received subsequent therapy and were still alive.

Table 11 Summary of additional secondary outcomes reported in the CS

Outcome	Axi-cel (n=180)	SOC (n=179)
EFS per investigator assessment		
Number (%) of events	[redacted]	[redacted]
Stratified HR (95%CI)	[redacted]	
Overall concordance with central EFS assessment	[redacted]	
PFS[a] per investigator assessment		
Median PFS, months (95%CI)	14.7 (5.4, NE)	3.7 (2.9, 5.3)
Estimated PFS, % (95%CI) at 24 months	46 (38, 53)	27 (20, 35)
Median follow-up time, months (95%CI)	[redacted]	[redacted]
PFS[a] per central assessment		
Median (95%CI) PFS, months	[redacted]	[redacted]
Estimated PFS (95%CI), % at 24 months	[redacted]	[redacted]
Median (95%CI) follow-up time, months	[redacted]	[redacted]
DOR[b] per central assessment		
Median time to first objective CR or PR response, months (range)	[redacted]	[redacted]
Median (95%) DOR for all responders, months	[redacted]	[redacted]
Stratified HR (95%CI)	[redacted]	
Median follow-up time (95%CI), months	[redacted]	[redacted]
Ongoing response at 24 months (95%CI), %	[redacted]	[redacted]
DOR[b] per investigator assessment		
Median time to first objective CR or PR response, months (range)	[redacted]	[redacted]
Median (95%) DOR for all responders, months	[redacted]	[redacted]
Stratified HR (95%CI)	[redacted]	
Median follow-up time (95%CI), months	[redacted]	[redacted]
Ongoing response at 24 months (95%CI), %	[redacted]	[redacted]
mEFS[c] per central assessment		
Number (%) of participants with events	[redacted]	[redacted]
Stratified HR (95%CI)	[redacted]	
Median (95%CI) mEFS, months	[redacted]	[redacted]
Median follow-up time, months	[redacted]	[redacted]
mEFS[c] per investigator assessment		
Number (%) of participants with events	[redacted]	[redacted]
Stratified HR (95%CI)	[redacted]	
Median (95%CI) mEFS, months	[redacted]	[redacted]
Median follow-up time, months	[redacted]	[redacted]
TTNT		
Number (%) of participants with events	[redacted]	[redacted]
Stratified HR (95%CI)	[redacted]	
Median (95%CI) TTNT, months	[redacted]	[redacted]
Estimated proportion of participants (95%CI) event-free at 24 months, %	[redacted]	[redacted]

Note. [a]defined as the time from randomisation to disease progression per the Lugano classification or death from any cause; [b]defined as the time from first response to disease progression per the Lugano classification or death from any cause; [c]defined as time from randomisation to the earliest date of disease progression per the Lugano classification, commencement of new lymphoma therapy or death from any cause up to, and including, the response on the day 150 assessment after randomisation, as determined by blinded central assessment. EFS: event-free survival; HR: hazard ratio; PFS: progression-free survival; CI: confidence interval; DOR: duration of response; CR: complete response; PR: partial response; mEFS: modified event-free survival; TTNT: time to next therapy

Health-related quality of life (HRQoL) was assessed in ZUMA-7 using three patient-reported instruments: the European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-30), the EQ-5D-5L and the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI: GH).

The full report of the patient-reported outcomes is available as an embedded document within Appendix T (Document B, p.217) of the CS. Data were collected on screening and at various other time points up to two years after randomisation. The three prespecified primary hypotheses relate to the Physical Functioning (PF) and Global Health Status / Quality of Life (QL) domains of the EORTC QLQ-C30 and the EQ-5D Visual Analogue Score (VAS); these were all based on the change from screening to day 100 after randomisation. Results for other time points and for the other 13 domains of the EORTC QLQ-C30, the utility score of the EQ-5D and the four domains of the WPAI: GH are also presented within Appendices L and T of the CS.

Analyses used mixed models for repeated measures adjusting for covariates. The models suggested that those randomised to axi-cel had improved quality of life compared with SoC for the three primary outcomes (change from screening to Day 100): [redacted]. Many other HRQoL domains show a similar pattern favouring the axi-cel group at Day 100 and sometimes also at Day 150. The ERG also notes that there is no evidence of HRQoL benefits for axi-cel at time points beyond 9 months and that later point estimates often favour the SoC group. On clarification, the company pointed to the fact that later time points could be affected by selection bias because only presenting patients were asked to complete questionnaires and because collection of HRQoL data usually stopped after a patient had an EFS event.

3.2.3 Adverse events

The company presents details of adverse reactions in Document B, Section B.2.10 of the CS. The safety analysis set (SAS; i.e. all randomised patients who received at least one dose of axi-cel or SOC immunochemotherapy as protocol therapy; axi-cel group, n=170; SOC group, n=168) was used to describe treatment-emergent AEs (TEAEs; i.e. any AE with onset on or after the axicabtagene ciloleucel infusion for the axi-cel arm, and any AE with onset on or after the first dose of salvage chemotherapy for the SOC arm). All participants in ZUMA-7 experienced at least one TEAE and [redacted]% of participants in the axi-cel arm and [redacted]% of the SOC groups experienced TEAEs of ≥Grade 3. In addition, [redacted]% and [redacted]% of participants in the axi-cel and SOC groups, respectively, experienced any treatment-related TEAE and these were at least Grade 3 in [redacted]% and [redacted]% participants, respectively. The company presents details of TEAEs and treatment-related TEAEs in Table 9, Table 10 and Table 11, Document B of the CS, respectively and a summary is presented in Table 12 below, including TEAEs and treatment-related TEAEs occurring in at least 30% of participants in either arm of ZUMA-7.

Table 12 Summary of AEs occurring in at least 30% of participants in either arm of ZUMA-7 (SAS)

Type of AE, n (%)	Axi-cel (n=170)		SOC (n=168)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Fatal AEs	**7 (4.1%); n=1 related to axi-cel**		**2 (1.2%); both related to high-dose chemotherapy**	
Any serious TEAE	**85 (50.0)**	**72 (42.4)**	**77 (45.8)**	**67 (39.9)**
Any serious treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Any TEAE	**170 (100.0)**	**155 (91.2)**	**168 (100)**	**140 (83.3)**
Pyrexia	158 (92.9)	15 (8.8)	43 (25.6)	1 (<1.0)
Nausea	69 (40.6)	3 (1.8)	116 (69.0)	9 (5.4)
Anaemia	71 (41.8)	51 (30.0)	91 (54.2)	65 (38.7)
Fatigue	71 (41.8)	11(6.5)	87 (51.8)	4 (2.4)
Diarrhoea	71 (41.8)	4 (2.4)	66 (39.3)	7 (4.2)
Headache	70 (41.2)	5 (2.9)	43 (25.6)	2 (1.2)
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	75 (44.1)	19 (11.2)	25 (14.9)	5 (3.0)
Decreased neutrophil count	[redacted]	[redacted]	[redacted]	[redacted]
Decreased platelet count	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	44 (25.9)	10 (5.9)	49 (29.2)	11 (6.5)

Type of AE, n (%)	Axi-cel (n=170)		SOC (n=168)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Constipation	34 (20.0)	0 (0.0)	58 (34.5)	0 (0.0)
Vomiting	33 (19.4)	0 (0.0)	55 (32.7)	1 (<1.0)
Any treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Decreased platelet count	[redacted]	[redacted]	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	[redacted]	[redacted]

Note. AE: adverse event; TEAE: treatment-emergent adverse event

Seven participants (4.1%) in the axi-cel arm and 2 (1.2%) in the SOC arm died as a result of TEAEs. One death in the axi-cel arm was considered to be related to axi-cel treatment (reactivation of hepatitis B virus) and both deaths in the SOC arm were considered to be due to high-dose chemotherapy. Serious TEAEs occurred in 50.0% of participants in the axi-cel arm and 45.8% of the SOC arm, of which 42.4% and 39.9%, respectively, were of Grade 3 or higher. Serious treatment-related TEAEs were experienced by [redacted] and [redacted] respectively, of the axi-cel and SOC arms, with [redacted] and [redacted] respectively, being at least grade 3.

All participants experienced at least one TEAE with [redacted]% in the axi-cel arm and [redacted]% in the SOC arm of ≥Grade 3. The most frequent TEAEs of Grade 3 or above were neutropenia ([redacted] in the axi-cel group and [redacted] in the SOC group) and decreased neutrophil count ([redacted] and [redacted] respectively). Treatment-related TEAEs were experienced by nearly all participants ([redacted] in the axi-cel arm and [redacted]% in the SOC group), with [redacted] and [redacted] respectively, classified as Grade 3 or above. The most commonly-reported treatment-related TEAEs in the axi-cel arm were pyrexia ([redacted]), hypotension ([redacted] headache ([redacted] sinus tachycardia ([redacted] and fatigue [redacted] In the SOC group, the most common treatment-related TEAEs were nausea ([redacted] anaemia ([redacted] and fatigue [redacted].

Adverse events of special interest

Section B.2.10.4, Document B of the CS presents adverse events of special interest, consisting of neurological events, cytokine release syndrome (CRS), cytopenia events, infections and hypogammaglobulinaemia. An overall summary is presented in Table 13 below.

Table 13 Summary of adverse events of special interest (SAS)

Type of AE, n (%)	Axi-cel (n=170)		SOC (n=168)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TE neurological event	[redacted]	[redacted]	[redacted]	[redacted]
Any serious TE neurological event	[redacted]	[redacted]	[redacted]	[redacted]
Any TE CRS	157 (92.4)	11 (6.5)	NA	NA
Any serious TE CRS	[redacted]	[redacted]	[redacted]	[redacted]
Any TE cytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Any TE infection	70 (41.2)	24 (14.1)	51 (30.4)	19 (11.3)
Any TE hypogammaglobulinaemia	19 (11.2)	[redacted]	1 (<1.0)	[redacted]

Note. AE: adverse event, TE: treatment emergent, CRS: cytokine release syndrome, NA: not applicable

- **Neurological events:** The CS presents a summary of treatment-emergent neurological events occurring in ≥5% of participant in either group in Table 12, Document B. 60.0% of the axi-cel arm and 19.6% of the SOC group had a treatment-emergent neurological event, with Grade 3 or higher events in 21.2% and <1%, respectively. The most commonly reported neurological events were tremor (25.9% and <1%, respectively), confusional state (23.5% and 2.4%, respectively), aphasia (21.2% and 0.0%, respectively) and encephalopathy (17.1% and 1.2%, respectively). Common serious treatment-emergent neurological events in the axi-cel group included encephalopathy ([redacted] and aphasia ([redacted]. Median time to onset of neurological events was 7 days (range [redacted]) in the axi-cel arm and 23 days (range [redacted]) in the SOC group; median duration was 9 days (range [redacted]) and 23 days (range [redacted]), respectively. No participants died due to neurological events.
- **Cytokine release syndrome (CRS):** The CS presents a summary of CRS events and CRS symptoms in Table 13, Document B. 157/170 (92.4%) of the axi-cel arm experienced CRS of any grade, with 11 (6.5%) being Grade 3 or higher. Symptoms of CRS of ≥Grade 3 reported in at least 5% of participants were hypotension (18/170;

10.6%), pyrexia (14/170; 8.2%) and hypoxia (13/170; 7.6%). Median time to onset of CRS was 3 days (range 1-10) following axi-cel infusion and median duration was 7 days (2-43). All the CRS events resolved and there were no CRS-related deaths.

- **Cytopenia events:** The CS presents a summary of treatment-emergent cytopenia events in both treatment groups in Table 14, Document B. The number of participants experiencing cytopenia events [redacted] in the axi-cel and SOC groups for events of any grade ([redacted]/170 [[redacted]%] and [redacted]/168 [[redacted]%], respectively) and those of ≥Grade 3 ([redacted]/170 [[redacted]%] and [redacted]/168 [[redacted]%], respectively). Cytopenia of any grade reported in the axi-cel and SOC arms, respectively, were thrombocytopenia ([redacted] and [redacted]), neutropenia ([redacted] and [redacted] and anaemia ([redacted] and [redacted]. Cytopenia of ≥Grade 3 were thrombocytopenia ([redacted] and [redacted] neutropenia ([redacted] and [redacted]) and anaemia ([redacted] and [redacted]. Prolonged cytopenia (i.e. present on, or after Therapy Day 30) occurred in 70/170 (41.2%) participants of the axi-cel group and [redacted]/168 ([redacted]%) of the SOC group. Prolonged cytopenia ≥Grade 3 was experienced by 49/170 (28.8%) and [redacted] ([redacted] respectively. In addition, 22/62 participants (35.5%) of the SOC group who proceeded to SCT experienced prolonged cytopenia, which was ≥Grade 3 in 12 participants (19.4%).
- **Infections:** 70/170 (41.2%) of the axi-cel group and 51/168 (30.4%) of the SOC group experienced ≥1 treatment-emergent infection, with 24/170 (14.1%) and 19/168 (11.3%) being ≥Grade 3. In the axi-cel group, the most common infections were unspecified ([redacted] viral infections ([redacted] bacterial infections ([redacted] upper respiratory tract infections [redacted] and opportunistic infections [redacted]. The most common infections of ≥Grade 3 were pneumonia [redacted] and upper respiratory tract infection [redacted]. In the SOC arm, the most common infections were unspecified [redacted] bacterial infections [redacted] and viral infections [redacted]. The most common infections of at least Grade 3 were pneumonia [redacted] and sepsis [redacted]. COVID-19 infections were experienced by [redacted]/170 participants ([redacted]%; [redacted]) in the axi-cel group and [redacted]/168 ([redacted]%) in the SOC group ([redacted]).
- **Hypogammaglobulinaemia:** A summary of treatment-emergent hypogammaglobulinaemia is reported in Table 12, Appendix F of the CS. 19/170 (11.2%)

participants of the axi-cel arm and 1/168 (<1%) of the SOC group experienced any treatment-emergent hypogammaglobulinaemia event, all Grade 1 or 2.

The ERG's clinical expert is satisfied that the adverse events reported in both the axi-cel and SOC arms of ZUMA-7 are as expected in these patients.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

In general, the ERG has no major concerns about the conduct or reporting of ZUMA-7. The ERG also notes that this trial is still ongoing and that the number of available participants, particularly at later follow-up times, is relatively small.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

No meta-analyses or network meta-analyses were conducted. The company state that this was because ZUMA-7 provided head-to-head data, but they do not justify their decision by confirming whether any other studies could have been included in a meta-analysis. Moreover, they do not clearly document why each study in the SLR is not suitable for inclusion in a meta-analysis.

The ERG's clinical adviser has examined the RCTs identified in the company's literature reviews and has confirmed that no other trials would be suitable for inclusion within a head-to-head meta-analysis with ZUMA-7 as none include axi-cel as a comparator. He has also confirmed that it would not be straightforward to include any of the studies within an indirect comparison, as none share a comparator group or a population that is sufficiently similar to that of ZUMA-7. Although a network meta-analysis might still be possible with very inclusive population and treatment definitions, such an analysis would not provide additional evidence for the comparison between axi-cel and standard care because of the lack of closed loops within the network diagram.

Therefore, the ERG agrees with the company that ZUMA-7 should be the main source of evidence for this submission.

3.5 Additional work on clinical effectiveness undertaken by the ERG

None.

3.6 Conclusions of the clinical effectiveness section

The ERG agrees that ZUMA-7 should form the basis of this submission and that other randomised studies identified were too heterogeneous in terms of participants, interventions and outcomes to be included. The ERG believes the conduct and analysis of ZUMA-7 to be appropriate and has no major concerns.

The ERG notes that, as ZUMA-7 is still ongoing, the number of participants with data at later time points is somewhat limited. This has implications for the cost-effectiveness model, leading to substantial uncertainty regarding the true long-term extrapolations of EFS and OS. The ERG notes that the company are planning to provide data from a new data cut but that the number of additional EFS events that will be available is still relatively small. The ERG believes that further long-term follow up data of the ZUMA-7 study would help to substantially reduce the uncertainty in the long-term survival modelling used for the cost-effectiveness analyses, further discussed in Section 4.2.6.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review of economic evaluations and HRQoL studies in adults with relapsed or refractory DLBCL. Searches were restricted to studies investigating post first line therapy only, and studies published in English / German. Only studies published since 2010 were included. Searches were initially conducted in May 2020 and updated between December 2021 and February 2022. Supplementary searches of relevant congress abstracts (2018-2020) were also conducted. Full details of the company's search strategy and results are provided in Appendix G of the company submission.

Five economic evaluation studies were included, but only one was deemed relevant to the current decision problem, as it was the only identified study conducted in the UK.[27] Wang 2017 conducted a cost-effectiveness analysis reporting incremental cost per life year gained of various treatments in patients eligible and ineligible for transplant as first or second line treatment.

The company also identified four NICE single technology appraisals (STAs) of treatments for treatments for adults with B cell lymphoma (TA649: Polatuzumab vedotin with rituximab and bendamustine; TA306 (Pixantrone monotherapy); TA559 (Axicabtagene ciloleucel) and TA567 (Tisagenlecleucel).[21, 22, 28, 29] The latter two were CAR-T therapies, for later lines of therapy were used to inform the current assessment and are summarised in Table 18 of the company submission.[22, 29]

The ERG is satisfied that the company have undertaken a thorough review of the published economic evidence and existing NICE assessments of relevance to this appraisal. The ERG notes that of the four identified studies, only three (TA649, TA559 and TA567) are for r/r DLBCL.[21, 22, 29] The ERG notes the company have identified Wang, 2017 as a potentially relevant study, but agrees that the company's decision to focus on the two appraisals of CAR-T therapies (TA559 and TA567) as the basis of informing the modeling approach for the current appraisal is appropriate.[22, 29]

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with the reference case
Perspective on costs	NHS and PSS	Aligns with the reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with the reference case
Synthesis of evidence on health effects	Based on systematic review	Aligns with the reference case. A systematic review was conducted, but all relevant evidence on health effects comes from the single, company conducted Zuma 7 study.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Partially aligns with the reference case. EQ-5D-5L data obtained from the Zuma 7 study, mapped to 3L utilities for the event free state. Post-event EQ-5D data were not routinely collected in the ZUMA-7 study and available data may be subject to selection bias and could lead to poor face validity. The company instead use SF-36 data, mapped to EQ-5D from the JULIET study for post-event utilities for the duration of the model time horizon.[22] The ERG considers pre-progression EQ-5D utilities from the ZUMA-1 study (3rd line plus treatment)[29] to be a more appropriate source for post-event

		utilities that maintains consistency with the NICE reference case. Patients who are long term event free past 5 years were assumed to incur age and sex specific general population utilities.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with the reference case, up until five years pre-event, after which general population utility is assumed. The ERG considers the assumption potentially optimistic and longer-term survivors of r/r DLBCL may incur QoL decrements beyond the assumed cure time point.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with the reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	There were some instances where NHS reference costs are available but were not used in the submission without appropriate justification (e.g., Auto-SCT costs).
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with the reference case.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

Section 3.3.2 of the company submission describes the de novo economic model constructed in MS Excel for this appraisal. A simple partitioned survival model with three health states (event-free, post-event and death) was developed. Event-free and post-event states were split into the proportion of ‘on treatment’ and ‘off treatment’, according to data from the ZUMA-7 study. Health state occupancy in the ‘dead’ and

'event-free' states is determined by mixture-cure models fitted to overall survival (1-OS) and event-free survival (EFS) data from the ZUMA-7 study respectively. The proportion in the post-event state is calculated as OS – EFS. Time to next treatment (TTNT) mixture cure model survival curves are then used to further partition the post-event state into those receiving / not receiving subsequent post-event treatments.

The model assumes that a proportion of those who remain alive and event free for five years in both the axi-cel and SOC arms of the model are long term survivors and can be considered effectively cured. The proportion of the cohort in the 'event-free' state beyond the 5-year cure time point are no longer assumed to be at risk of disease progression or events and are thus assumed to receive age and sex specific general population utility norms, with minimal follow-up costs (6-monthly GP appointments). These long-term survivors are however assumed to incur an excess mortality risk relative to the age and sex adjusted UK general population mortality risks (standardised mortality ratio (SMR = 1.09) for the remainder of the model time horizon, reflecting the SMR used in NICE appraisals of 3rd line plus CAR-T therapies, derived from Maurer 2014.[22, 29, 30]

A limitation of the company's 'Part-SA' modelling approach is that it creates challenges in accurately modelling and estimating valid expected costs and QALYs associated with subsequent lines of treatment post-event. This is despite an expectation that increasing lines of therapy are associated with poorer response rates, reduced EFS and OS, lower QoL and higher costs. Furthermore, the model predicts additional OS post-event for axi-cel compared to SOC patients, without any associated additional costs of more than one subsequent line of treatment. Whilst these issues create some uncertainty, the ERG acknowledges that robust long-term data to populate a more complex Markov model with multiple treatment lines are not available and would be difficult to model accurately. On balance, the ERG is satisfied that the Part-SA model remains an appropriate modelling approach for decision making, but the committee should be aware of the limit capacity of the model to consider more than one post-event round of treatment.

The company has chosen to partition the cohort using 'event free survival' rather than 'progression free' survival. The ERG is satisfied that the company's approach is

reasonable and is clearly justified in the company submission (page 81 of the CS). Using EFS further ensures that the modelling is consistent with the primary outcome from the ZUMA-7 trial. The ERG's clinical expert confirms that EFS is more appropriate than PFS for modelling costs and outcomes, because, in UK clinical practice, an outcome of stable disease (SD) would not be considered a satisfactory pre-progression outcome for patients, hence further lines of treatment ('events') would be offered to patients who have not achieved an overall or partial clinical response.

The use of mixture cure modelling to partition the cohort is plausible but it is important to note that there is substantial residual uncertainty regarding the most plausible long-term cure fraction for both EFS and OS in both the axi-cel and SOC arms. The ZUMA-7 study is still ongoing and the number of participants with data at later time points is somewhat limited. Despite the noted uncertainty, the ERG considers the prospect of 'cure' to be an achievable treatment goal for people with r/r/DLBCL. In clinical practice, patients could be considered 'cured' after a 'sustained' period without experiencing events. The event free duration before which a patient might be considered cured is less clear, and subject to debate. The company's base case analysis assumes 5-years, in line with the ERG preferences from a previous appraisal of CAR-T therapy (TA559)[29] and the ERG's clinical expert considers this to be a conservative estimate. Some clinicians may consider a time of two years event free to be a good indicator for identifying patients who will go on to be long-term survivors and will not suffer further disease progression. Because of the noted uncertainties, the company's decision to conservatively model a 5-year, rather than 2-year cure time point for the base case analysis is appropriate. Further long-term follow up of the ZUMA-7 study will help reduce the magnitude of uncertainty and will enable more accurate estimation of the cure-fraction and long-term extrapolations for both EFS and OS.

The true excess mortality risk among long term r/r DLBCL survivors is uncertain. However, in the absence of long-term studies, the ERG considers the company's modelled excess mortality risk (SMR = 1.09) to be plausible and aligned with the excess mortality risks applied in previous appraisals of CAR-T therapies. Given the plausibility of an excess mortality risk, the company's decision to assume age and

sex-adjusted general population utility for long-term survivors may be somewhat optimistic. Further discussion around the model utilities is provided in Section 4.2.7.

4.2.3 Population

The modelled cohort are adults with primary refractory or relapsed (early relapse within 12 months) DLBCL who have had one systemic therapy and are intended for stem cell transplant. The average baseline age is 57.2, with 34% female.

The ERG is satisfied that the modelled population is aligned with the ZUMA-7 trial data from which the treatment effectiveness (EFS and OS) data are modelled.

4.2.4 Interventions and comparators

Intervention – axi-cel

The intervention is axi-cel, an anti-CD19 CAR T-cell treatment. The following treatments compose the intervention:

- Axi-cel, administered as a single intravenous infusion of dose of $2x10^6$ CAR-positive viable T-cells per kg of body weight. Infusion bags are pre-prepared, tailored to the individual's body weight.
- Lymphodepleting chemotherapy (cyclophosphamide 500mg/m^2) and IV fludarabine (30mg/m^2) on 3 days prior to infusion (5^{th}, 4^{th} and 3^{rd}).
- Some patients also receive bridging chemotherapy.

Further details of the process of manufacturing and administration of axi-cel are provided in Section B.1.2 of the company submission.

The ERG's clinical expert confirms that the manufacturing and administration approach as described by the company is consistent with his understanding of the usage of axi-cel on the CDF in England and routine practice in Scotland for 3^{rd} line plus treatment. The company state that the approach is consistent with the expected marketing authorisation (expected [redacted]). However, in the absence of a final approved marketing authorisation, the validity of this statement would need to be re-assessed when the marketing authorisation becomes available.

Comparator – standard of care (SOC)

The comparator consists of platinum-containing salvage chemotherapy to achieve a sufficient response to enable consolidation with HDT (BEAM) and auto-SCT. A basket of chemo regimens was included in the ZUMA-7 study, consisting of R-ICE, R-ESHAP, R-GDP or R-DHAP, but was adapted to assume that only R-ICE (50%) and R-GDP (50%) would be used in UK clinical practice.

The ERG's clinical expert notes that the distribution of the basket of chemotherapies used in clinical practice is likely to be both centre and patient specific, and substantial heterogeneity would exist across the UK. For example, some centres may use R-DHAP, but the ERG agree with the company's clinical experts that the use of R-ESHAP is uncommon in the UK. To the ERG's knowledge, there is no evidence to suggest that different chemotherapy regimens would lead to meaningful differences in treatment effectiveness (EFS or OS). Therefore, the ERG is satisfied that a basket distribution departing from the ZUMA-7 trial distribution is only likely to impact on the ICER through treatment acquisition and administration costs, discussed in Section 4.2.8.

4.2.5 Perspective, time horizon and discounting

The model takes an NHS and PSS perspective and direct health effects from a patient perspective (QALYs).

The ERG is satisfied that the analysis perspective is in line with the NICE reference case.

The model time horizon used in the base case analysis is a lifetime horizon, running from a starting age of 57.2 (as per the ZUMA-7 study) for a maximum of 50 years, in monthly cycles (30.44 days) with a half cycle-correction applied.

The ERG considers a monthly cycle length over a modelled 50-year time horizon to be appropriate and necessary to capture all meaningful differences in costs and outcomes between axi-cel and SOC. Given the starting age of 57, running the model for 50 years represents a full lifetime horizon.

Costs and QALYs were discounted at 3.5% per annum and a reduced discount rate of 1.5% per annum is explored in scenario analyses.

The ERG considers the company's approach to discounting to be appropriate and consistent with NICE guidance.[31]

4.2.6 Treatment effectiveness and extrapolation

Clinical parameters used in the economic model.

Treatment effectiveness data (EFS, TTNT and OS) were obtained from the most recent available data cut for the FAS population from the ZUMA-7 study. Data are available for N=180 and N=179 participants randomised to axi-cel and SOC respectively. The median follow-up time was [redacted] months, and an updated analysis post-FDA review is expected during the technical engagement phase. Long tails from the EFS, OS and TTNT curves are all suggestive of long-term remission and survival among a fraction of treatment patients in both the axi-cel and SOC arms, hence the company chose to model EFS, TTNT and OS using mixture cure models estimated from patient-level data from ZUMA-7 for the base case analysis. For EFS, TTNT and OS modelling, the process for selecting the most appropriate underlying survival curve fitted to KM data followed NICE DSU recommendations and involved inspection of log cumulative hazard plots and assessing different survival curves in terms of visual fit to the KM data, goodness of fit statistics (AIC and BIC). Validation of long-term extrapolations was achieved through comparison of model output with other literature where available, and with UK clinical oncologists experienced in treating patients with r/r DLBCL.

The ERG considers the use of mixture cure models to be an appropriate approach that allows for the estimation of more complex hazard functions, allowing for a proportion of patients (the cure fraction) to be statistically cured. The ERG's clinical expert supports the validity of the assumption of cure, and the ERG is satisfied that the validity of mixture cure modelling in r/r/ DLBCL is supported using 5-year follow up data from the ZUMA-1 study (for 3rd line plus treatment). The approach is also consistent with previous NICE technology appraisals in r/r DLBCL. However, data at later time points is somewhat limited, meaning that there is substantial residual

uncertainty surrounding the estimate of the cure fractions. That uncertainty can be mitigated through longer follow up of the ZUMA-7 study.
Whilst the ERG considers the general approach for assessing and selecting parametric survival curves to fit the KM data to be appropriate and in line with NICE DSU guidance, the ERG was concerned that some additional uncertainties with regards to the plausibility of the base case extrapolations of EFS, TTNT and OS for the uncured fraction within the mixture cure modelling required further exploration. These uncertainties are addressed and discussed in the respective sections that follow.

Event-free survival

Kaplan Meier data for EFS (per central assessment) are available in Figure 19 of the CS. Appendix O of the company submission provides a full description of all considered models, including standard parametric models and landmark models as well as an assessment of each curves appropriateness for modelling EFS, including visual inspection against KM data, AIC / BIC, cox regression results and reporting of log cumulative hazards plots. The proportional hazards assumption was deemed valid, but the parallelism of the curves for axi-cel and SOC was lost towards the end of the log-log plots, hence independent survival curves were fitted to the axi-cel and SOC arms.

Across six standard parametric curves explored, the implied cure fractions are similar regardless of the chosen model specification, ranging from [redacted] to [redacted] for axi-cel and from [redacted] to [redacted] for SOC. The parametric curve with the lowest AIC and BIC for axi-cel was a log-logistic curve with an implied cure fraction of [redacted] and a mean EFS of [redacted] months (median = [redacted] months). For SOC, the best fitting curve (lowest AIC and BIC) was an exponential curve, with an implied cure fraction of [redacted]% and a mean EFS of [redacted] months (median = [redacted] months). The modelled base case EFS curves are reproduced in Figure 6 below.

Figure 6 Modelled base case EFS curves [reproduced from Figure 25, Document B of the CS]

The ERG considers modelling EFS per central assessment, rather than per investigator assessment to be appropriate as this minimises the potential for bias. The ERG is satisfied that the company's general approach to selecting standard parametric curves for EFS (assessment of curves visual fit to KM data, AIC / BIC criteria and clinical validation) is reasonable and follows NICE DSU recommendations for standard parametric curve selection in survival analysis.

The ERG raised a query at the clarification stage that the survival extrapolations for the uncured fraction were unclear and may have been optimistic if the chosen parametric curves used to estimate the survival probabilities for the 'uncured' fraction were obtained from parametric curves fitted to the KM data for the full cohort. In response to the clarification query, the company provided further details regarding the mixture cure modelling process, the assumptions made, and clinical validation (See company clarification response B1). The ERG acknowledges the company's description of the mixture cure modelling assumptions and is satisfied that the company's description is accurate. However, the response did not fully address the ERG's central concern that it was unclear whether the parametric curves for EFS quickly tended to zero in the uncured fraction as would be anticipated in clinical practice. If this was not the case, the selected survival curves might have been

considered optimistic. The ERG view is that the survival curves for the un-cured fraction should have been independently verified with clinical experts. The ERG has therefore re-produced EFS curves illustrating the survival projections for the cured and uncured fractions alongside the overall mixture cure model projections. This information is provided for SOC and axi-cel in figures 7 and 8 respectively.

Figure 7 Company base case EFS extrapolations, SOC [reproduced from the company's economic model]

Figure 8 Company base case EFS extrapolations, axi-cel [reproduced from the company's economic model]

Based on the information provided by the company in their original submission, and in response to clarification queries, together with further inspection of the curves in Figures 7 and 8, the ERG makes the following observations:

1) *The most appropriate EFS cure fraction remains uncertain because the ZUMA-7 study is ongoing with a substantial proportion of the cohort not reaching their 2 years follow up time point at the time of the data-cut. Further longer-term follow-up data from the ZUMA-7 study would be required to validate the projections of the mixture cure modelling.*

2) *The choice of EFS parametric survival curve for the mixture cure model does not have a major impact on the ICER because all six parametric survival curves explored in each model arm generate similar cure fractions longer-term extrapolations.*

3) *After further assessment of the EFS projections for the cured and un-cured fractions separately, the ERG is satisfied that the projections for the uncured fraction tend quickly to zero in both arms and so could be considered to have a good degree of face validity. The modelling therefore aligns with the ERG clinical expert's view that patients who are not cured often experience rapid deterioration in their condition and quickly progress through an event, either through progression or transition onto further lines of treatment.*

In summary, whilst there is substantial remaining uncertainty surrounding the most appropriate cure fractions and extrapolations, due to immature data from the ZUMA-7 study, the ERG is satisfied that the company's approach to modelling EFS is reasonable.

Overall survival

There are two key aspects to the modelling approach for OS in this appraisal. The first is the use of mixture-cure modelling to estimate longer-term OS extrapolations in both the axi-cel and SOC arms of the model, reflecting that a clinical cure is plausible in both the pre- and post-event states. The second is the use of a cross-over adjusted analysis, specifically a rank preserving structural failure time (RPSFT) model in the

company's base case analysis to remove the benefit of CAR-T therapies as third line treatments from the SOC arm of the model.

Mixture cure modelling

The company explored a full range of standard parametric models and spline models fitted to KM data from the ZUMA-7 study, results of which are provided in Appendix O for information. However, mixture cure models were deemed more appropriate for modelling OS, because, as described for EFS, the KM curves show potential for long-tails and that the prospect of clinical cure for r/r DLBCL is feasible and desirable. The process of selecting an appropriate parametric survival curve for the mixture cure model followed the same approach as described for EFS above. The company found that the proportional hazards assumption was not held for OS and hence independent survival models were fitted for SOC and axi-cel respectively. The cured fraction are assumed to be at slightly higher mortality risk than the general population with a SMR of 1.09 applied to age and sex adjusted all-cause mortality.

As described for EFS, the ERG agrees that mixture cure modelling is clinically appropriate and that the prospect of cure is supported by 5-year follow up from the ZUMA-1 study, where axi-cel as a 3rd line plus treatment showed [redacted]% of patients to be alive after 5 years. As described for OS, the ERG's clinical expert confirms that the prospect of cure is an achievable treatment goal for r/r DLBCL. Whilst the prospect of cure is feasible, concerns about the accuracy of long-term extrapolations remain because data from the ZUMA-7 study are not yet mature and further follow up data will provide additional information on which to improve extrapolation modelling in the future. The ERG considers the SMR of 1.09 applied to the cured fraction to be reasonable.

Axi-cel OS

Different survival functions for the mixture cure model fitted to the ZUMA-7 data generate substantial variation in the implied cure fraction, varying from [redacted] (Log-Normal) to [redacted] (Gompertz) for the axi-cel arm and from [redacted] (Exponential) to [redacted] (Weibull) for the SOC arm. However, because NICE methods guidance precludes the consideration of CAR-T therapies as a third line plus treatment for the base case analysis (only available through the CDF in England), the cure-fractions fitted to

ZUMA-7 data for the control arm are not used in the base case economic modelling. Instead, a generalised gamma mixture cure model ([redacted] implied cure fraction) was selected for the axi-cel arm of the model, because the company stated it had the best statistical fit and was validated by clinical expert opinion. Figure 9 illustrates the OS extrapolations from different mixture cure models for the axi-cel arm of the model.

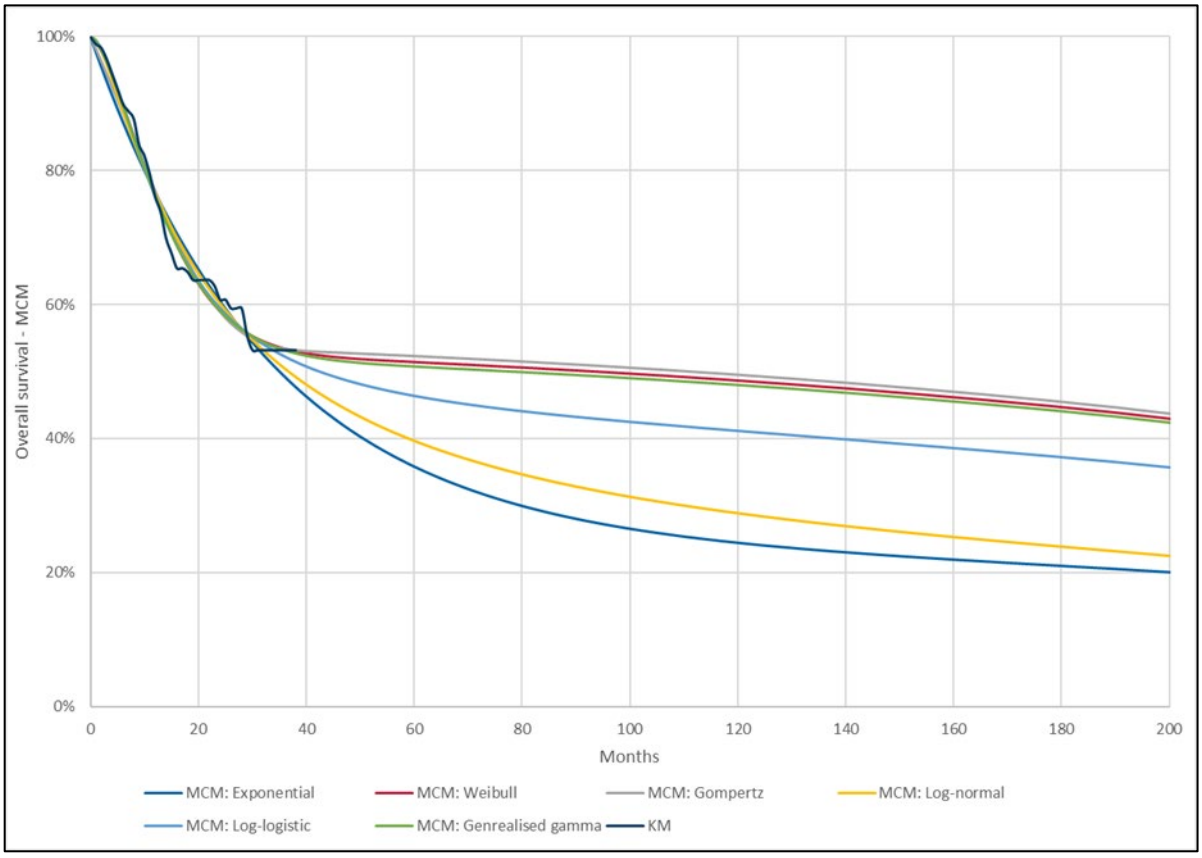

Figure 9 Axi-cel, alternative mixture cure models [re-produced from Figure 27, Document B of the CS]

Different models lead to substantial variability in expected LYGs, ranging from [redacted] (worst case, likely implausible: exponential) to [redacted] (best case, likely implausible: gompertz). The company base case analysis generates [redacted] LYGs (generalised gamma, which the ERG considers to be the more optimistic of the two clinically plausible extrapolations – generalised gamma and log-logistic). Table 25 of the company submission shows that all curves fit approximately equally well to the KM data. The ERG notes that the company's base case generalised gamma has the worst statistical fit according to BIC score amongst all considered standard parametric MCMs. The log-logistic model has the lowest AIC and BIC. Given the similarity of

statistical fits to the KM data, a decision on the most plausible extrapolation curve (or range of plausible curves) rests on an assessment of face validity. In response to clarification queries, the company explained that the most pessimistic log-normal and exponential curves are not appropriate because they provide OS extrapolations that lie below the long-term (5-year) follow up from ZUMA-1 where axi-cel was used as 3rd line plus treatment. The ERG agrees that such extrapolations would lack face validity and further notes that they would generate cure fractions which are lower than the EFS cure fractions, which is clearly implausible. The four remaining curves (Weibull, Gompertz, Log-logistic and generalised gamma) all have acceptable statistical fits (AIC / BIC) and generate OS extrapolations with acceptable face validity. The ERG clinical expert's view is that any of these four curves could be considered clinically plausible. In response to a clarification query (B1), the company provided additional information, illustrating the OS extrapolations for the axi-cel and SOC uncured fractions. The ERG is satisfied that OS tends quite quickly towards 0 for the uncured fraction and so any four of the standard parametric selections for the mixture cure models could be considered reasonable. Given the substantial residual uncertainty in long-term extrapolations due to immature data, the ERG considers it more appropriate to use the log-logistic curve for MCM because it has the best statistical fit to KM data and it also generates clinically plausible, if slightly conservative OS extrapolations for axi-cel.

<u>SOC OS (cross over analysis)</u>

CAR-T therapies were used widely post event for patients randomised to the SOC arm of the ZUMA-7 study, with [redacted]% expected to receive CAR-T therapy 3rd line. Axi-cel is only available in England through the CDF and according to NICE's position statement on CDF treatments requires that the base case analysis should exclude the OS effect of axi-cel treatment post-event in the SOC arm of the model.[32] The company base case therefore uses cross-over analysis, specifically rank preserving structural failure time (RPSFT) models following the methods outlined in NICE DSU TSD 16.[33] Full details of the methods and analyses carried out for the crossover analysis are provided in Appendix S of the company submission. The company's base case analysis uses a RPSFT model with full re-censoring of all control arm patients, which generates a HR (95% CI) of [redacted]). This HR is then applied directly to the axi-cel OS for the company base case analysis. Alternative

RPSFT specifications re-censoring switchers only and no re-censoring generate HRs of [redacted] and [redacted] respectively. Other models including IPCWs were explored, and details provided in Appendix S. The company explore the use of ITT analyses assuming that axi-cel is available as 3rd line treatment in a scenario analysis.

The ERG agrees that the company's decision to use cross-over analysis is consistent with NICE's guidance and that the investigations conducted by the company in terms of exploring alternative models is comprehensive. Nonetheless, the ERG notes that different HRs applied to the OS axi-cel arm generate substantially different ICERs, and this is a key area of uncertainty for decision making. The ERG was concerned that the company submission did not provide details of the OS HRs or associated impact on the ICER of using alternative crossover analysis approaches such as IPCW. On initial inspection of Appendix S, it was unclear to the ERG as to why the RPSFT models had been chosen in preference to the IPCWs. It was also unclear why the independently fitted OS MCMs were not applied and why a HR approach was used instead.

In response to clarification queries (B2) the company provided further justification in support of their base case HR approach using RPSFT models with full re-censoring of the control arm. First, the decision not to use independently fitted cross-over adjusted MCMs for the SOC arm was that most independently fitted mixture cure models lay above the SOC ITT curve, which was deemed to be clinically implausible. The HR approach was therefore preferred. The most appropriate HR for the base case analysis was also based primarily on an assessment of clinical plausibility. The RPSFT model with full re-censoring generated OS curves that lie between ORCHAARD and SCHOLAR-1 predictions and was also the only model where the proportional hazards assumption appeared to hold true. All other explored cross-over models generated OS curves that lie above the ORCHAARD study. This is demonstrated in Figures 2-5 of the company's response to clarification queries. The ERG's clinical expert agrees that it is reasonable to select an OS projection from the SOC arm of the model (in the absence of axi-cel availability 3rd plus line) that lies between ORCHARRD and SCHOLAR-1 because SCHOLAR-1 could be considered a worst-case scenario whereas ORCHARRD could be considered a more optimistic set of extrapolations.[12, 15]

In summary, the ERG considers the long-term extrapolations of the SOC arm to be highly uncertain. This uncertainty is driven in part by the immature data from ZUMA-7 which would be reduced with further longer term follow up data. It is also driven by the requirement for cross-over analysis because 3rd line plus use of axi-cel is only available through the CDF in England and is not considered standard care in England. The upcoming review of 3rd line plus use of axi-cel on the CDF may have implications for the ICER. On balance the ERG considers the company's approach to be reasonable, and notes that additional scenario analyses were provided to illustrate the uncertainty in modelling in response to clarification queries.

TTNT

TTNT curves are used to model the time at which the cohort receive subsequent therapy costs. The approach to selecting TTNT mixture cure models was similar to that described for EFS above, with further details provided in appendix O of the company submission. KM data for TTNT are plotted in Figure 22 of the CS and the alternative mixture cure models explored are illustrated in Figures 30 and 31 of the CS, with little difference between the alternative curves explored. As with the modelling of EFS, the implied cure fractions are similar across all six explored parametric survival models used in the MCM, ranging from [redacted] to [redacted] for axi-cel and approximately [redacted] for all SOC curves explored.

The ERG is satisfied that the approach to modelling TTNT is reasonable, and that the choice of parametric curve has little impact on the ICER.

4.2.7 Health related quality of life

Model health state utility values for the company base case analysis were obtained from the ZUMA-7 study (pre-event), the literature (post-event), and based on assumptions / literature review for the disutilities associated with adverse events. It was further assumed that the proportion of the cohort event free after 5 years would incur general population age and sex-adjusted utilities beyond 5 years for those remaining in the event free state.

Event free utilities

Event free health state utility values were obtained from analysis of EQ-5D-5L data collected in the ZUMA-7 study pre-event. Out of 359 patients enrolled in ZUMA-7, 296 (82%) provided EQ-5D-5L data and at least one follow-up time point (from data collection points in 3-monthly intervals up to 24 months post-randomisation). EQ-5D-5L responses were cross-walked to EQ-5D-3L using the van Hout algorithm and valued using UK general population tariffs to generate the EFS utilities.[34] Utility data were analysed using mixed effects repeated measures models to account for multiple observations per participant.

The proportion of the cohort who remained in the event free state beyond five years, were assumed to be cured and thus would no longer experience a reduction in quality of life due to r/r DLBCL. The proportion remaining in the event free state beyond 5 years were therefore assigned age and sex adjusted UK general population norm utilities for the remainder of time in the event free state.

The ERG is satisfied that the use of pre-event utility data from the ZUMA-7 study is the most appropriate source for modelling event-free utility. The company's cross-walking is in line with the NICE recommendations and the analysis methods undertaken are appropriate. Company exploratory analyses tested the impact of assigning on and off-treatment utilities separately for axi-cel and SOC to capture the impact of the disutility of adverse events (as opposed to the base case which used 'off-treatment' utility for the EFS state and assigned specific adverse event disutilities). Whilst either approach could be considered reasonable, the ERG is satisfied that the choice of approach is not an important determinant of the ICER, and the company's base case can be considered appropriate. In response to a clarification query, the company also explored the use of treatment specific health state utilities in the model. However, as the company describe in their response to queries B4 and B5, the approach would substantially reduce the sample available for analysis and would generate potentially inconsistent combinations of pre and post event utility in the model that would lack face validity (i.e., some post-event utilities higher than pre-event utilities). For these reasons, the company's source and methodology for deriving pre-event utilities up to 5 years is appropriate.

It is plausible to assume that the longer one is event-free, the closer their quality of life would trend to that of the general population. However, it is unclear whether QoL would fully return to age- and sex- adjusted general population utility norms and whether it is appropriate to assume this would happen at 5 years. The ERG notes that the company appropriately assumes a long-term excess mortality risk, with an SMR = 1.09 in long-term survivors. It may therefore be optimistic to assume that there is no long-term decrement in quality of life. The ERG therefore conducts a less optimistic scenario analysis where it is assumed that patients do not revert to general population QoL, with pre-event utilities applied to all in the event-free state for the full model time horizon. The assumption has a small upward effect on the ICER.

Post-event utilities

Base case post-event utilities were obtained from the JULIET study, where SF-36 utilities were mapped to EQ-5D and were used in previous NICE assessment for TA567. The company explored a scenario analysis where EQ-5D data collected from the ZUMA-1 study (3rd line plus use of axi-cel) were applied in the model, showing a modest increase in the ICER. In response to a clarification query regarding how many observations were available from ZUMA-7 on post-event utility, and why these were not used in the base case analysis, the company clarified that data were not systematically collected post-event in the ZUMA-7 study and were only collected at disease assessment visits, in some trial sites. The company therefore justify the decision not to use ZUMA-7 utilities because:

1) The sample size was small (<[redacted]% of total observations were post-event)
2) Completion at disease assessment visits leads to selection bias
3) ZUMA-7 utilities would not capture end-of-life utility decrements

The ERG accepts that there are limitations with using the ZUMA-7 data. In addition to those raised by the company, it would appear that post-event utility is only slightly worse than pre-event (0.785 compared to 0.779), a substantially smaller magnitude of difference when compared to other studies and technology appraisals, as outlined in Table 28 of the company submission. Nonetheless, there may be possible advantages of using the ZUMA-7 data:

1) *ZUMA-7 used a quality-of-life measurement tool (EQ-5D) that is consistent with the NICE reference case*
2) *The sample are obtained from ZUMA-7 which is directly relevant to the current assessment and may reduce uncertainty associated with assuming comparability of patient groups to other NICE technology appraisals (TA559 of TA567)*[22, 29]

The ERG also considers the company's scenario analysis using ZUMA-1 data, from third line plus disease applied to the model for pre- and post-event states to be questionable because patients have more advanced disease and lower QoL would be expected. The company's suggestion, provided during clarification (B6), that using ZUMA-1 (pre-progression) utilities (0.72), applied to the post-event state for the current assessment would be a reasonable approach. Despite small sample size, this approach would at least ensure that the same quality of life measure is used (EQ-5D) and the disease populations could be considered comparable. The impact of this change in utility source on the ICER is minimal.

A summary of company base case, plausible alternative, and ERG preferred utility data and sources is outlined in Table 15 below.

Table 15 Summary of plausible health state utility values for the economic model

	Company base case analysis	Company scenario analysis	ERG base case analysis
Pre-event (up to 5 years)	0.785 (ZUMA-7, EQ-5D, off treatment)	0.72 (ZUMA-1, EQ-5D)	0.785 (ZUMA-7, EQ-5D, off treatment
Pre-event (beyond 5 years)	General population utilities	General population utilities	General population utilities, but notes uncertainty
Post event	0.710 (JULIET study SF-36 mapped to EQ-5D)	0.65 (ZUMA -1 EQ-5D)	0.72 (ZUMA-1, EQ-5D, 3rd line plus pre-progression

Abbreviations: ERG: Evidence review group; EQ-5D: EuroQol-5 Dimension; SF-36: Short Form 36

Adverse event disutilities

The following criteria were used for inclusion of adverse events in the economic model:

1) Severe adverse events (Grade 3 or 4) +
2) Occurring in at least 10% of axi-cel or SOC patients or events which were likely to have a particularly severe impact on QoL or incur substantial cost (i.e. CRS and B-cell aplasia)

Details of modelled adverse events and associated disutilities applied are provided in Tables 29 and 30 of the company submission. Adverse event utility decrements range from -0.09 for Neutropenia to -0.78 for CRS, with an assumption that B-cell aplasia does not incur any disutility.

Whilst some of the utility decrements are substantial, particularly for CRS, and are likely to impact on patient quality of life, they are assumed to be incurred over very

short durations, ranging from 6 days for febrile neutropenia to 64 days for decreased lymphocyte counts. Duration of adverse events was sourced from a patient level analysis of data from the ZUMA-1 study, which informed NICE TA559. Whilst the company has not detailed how the durations of adverse events were derived from ZUMA-1, the ERG's clinical expert considers it reasonable that most adverse events associated with axi-cel or SOC can be quickly resolved. Furthermore, the ERG notes that the company has not clarified if disutility sources use EQ-5D or other disutility measures. However, the ERG does not consider this to be an important determinant of the ICER due to the negligible impact that adverse events have on QALYs in the economic model. The ERG, therefore, accepts the company's base case analysis as reasonable.

4.2.8 Resources and costs

Axi-cel treatment acquisition and administration costs

Full details of the company approach to calculating axi-cel treatment acquisition and administration costs are provided in Section B.3.5.2.1, including details of unit costs in Tables 33 to 36 of the company submission. In brief, axi-cel may compose of the following treatment components: leukapheresis, bridging therapy, conditioning chemotherapy and axi-cel infusion/monitoring.

For the proportions receiving each resource use (treatment), the corresponding unit costs applied in the model and the ERG's critique of the approach to costing each component are provided in Table 16. The ERG preferred:

A) *Axi-cel treatment acquisition and administration costs that include re-treatment as described in the company's clarification response to query B7.*
B) *Leukapheresis costs are slightly higher than in the company's base case model because the ERG prefers to include the costs of re-treatment with axi-cel as per the ZUMA-7 trial to maintain consistency between the modelled treatment costs and benefits.*

Table 16 Summary of treatment acquisition costs included in the company base case analysis

	Proportion receiving in Zuma-7	Proportion receiving in company base case	Unit cost (Company base case)	*ERG preferred proportion*	*ERG preferred unit cost*	*ERG comments*
Leukapheresis	[redacted]	[redacted]	£2,014 (Total HRGs, weighted average SA34Z and SA18Z)	[redacted]	*As per company base case* [A]	*The ERG is satisfied with the proportion receiving Leukapheresis. The ERG was able to reproduce the company's use of total HRGs for code SA18Z, but not SA43Z. The ERG believes this may be a typo in the company submission (Table 33) and that the costed code is SA34Z rather than SA43Z. The ERG considers the use of Total HRGs, weighted according to different settings to be appropriate, and in line with the ERG clinical expert's view that many will be performed as 'day case' procedures, some will be performed as outpatients, whilst others that require temporary femoral lines may require inpatient admission. It is not clear to the ERG why the specific HRG code for Leukapheresis (HRG code SA43Z) was not used in the company base case analysis and would appreciate further clarification.*
Bridging therapy	[redacted]	66.7%	£6,025[B]	*66.7%*	£6,025	*The ERG's clinical expert notes that the majority of patients in the UK will receive RBP (Rituximab, Bendamustine and*

	Proportion receiving in Zuma-7	**Proportion receiving in company base case**	**Unit cost (Company base case)**	***ERG preferred proportion***	***ERG preferred unit cost***	***ERG comments***
	(oral dexa - methasone)	(2 cycles of outpatient R-GDP)				*Polatuzumab) as bridging with some receiving radiotherapy and a small number receiving steroids or no bridging. From this point, the company's assumed reduction in dexamethasone compared to ZUMA-7 seems reasonable, but the choice of alternative treatment may not reflect clinical practice. Whilst there is some uncertainty, the ERG notes that the costs of different bridging therapies are broadly similar. The ERG is also satisfied that differing use of bridging therapy between the trial and the model, or the use of different treatments as bridging therapy would not impact EFS or OS and so impact on QALYs is minimal. Therefore, net impact of uncertainty in this parameter on the ICER is minimal.*
Conditioning chemotherapy	[redacted]	[redacted]	£1,476[C]	[redacted]	£1,476	*The ERG considers the company approach to be appropriate and reflective of UK clinical practice.*

	Proportion receiving in Zuma-7	**Proportion receiving in company base case**	**Unit cost (Company base case)**	***ERG preferred proportion***	***ERG preferred unit cost***	***ERG comments***
Axi-cel infusion costs	[redacted]	[redacted]	[redacted], including [redacted] PAS	[redacted]	[redacted], including [redacted] PAS	*The ERG is satisfied with the company's approach to costing the first infusion of axi-cel. The company confirmed during clarification that the NHS would not incur treatment acquisition costs for whom axi-cel has not been infused, regardless of whether leukapheresis and production of axi-cel had taken place.*
Axi-cel infusion re-treatment costs	[redacted]	0%	[redacted], including [redacted] PAS	[redacted]	[redacted], including [redacted] PAS	*The ERG notes that re-treatment is unlikely in UK clinical practice but believes the full re-treatment costs (acquisition and administration) should be included as per the ZUMA-7 study as re-treatment may have contributed to the modelled OS estimates. Applying consistency between treatment costs and effectiveness reduces the potential for bias.*
Axi-cel infusion and monitoring costs (1st treatment)	[redacted]	[redacted]	£8,709 (ZUMA-7 LOS: [redacted] days; HRG: SA31A-F elective long stay	[redacted]	£8,709 (ZUMA-7 LOS: [redacted] days; HRG: SA31A-F elective long stay for 16.08 days +	*The ERG is satisfied that the approach to costing hospital resource and monitoring is appropriate*

	Proportion receiving in Zuma-7	**Proportion receiving in company base case**	**Unit cost (Company base case)**	***ERG preferred proportion***	***ERG preferred unit cost***	***ERG comments***
Axi-cel infusion and monitoring costs (re-treatment)	[redacted]	0%	for 16.08 days + £468.12 per day for [redacted] days	[redacted]	£468.12 per day for [redacted] days	*The ERG considers it appropriate that the hospital costs would be incurred for each subsequent round of treatment.*

[A] Weighted average of elective HRGs (SA18Z: 98; cost: £3,460 and SA34Z: 226, cost £5,238) = £4,700.21, inflated to 2021 values: £4,844.98 (as per the company's approach).
[B] Calculated as two cycles of R-GDP (See table 34 of the company submission)
[C] Composed of IV Fludarabine 30mg/m^2 and IV Cyclophosphamide 500 mg/m^2 , 3 administrations in total
[D] Excess bed days above the trim-point of 16.08 days

SOC treatment acquisition and administration costs

SOC treatment costs are mostly informed by the resource usage incurred in the standard care arm of the ZUMA-7 study, and include:

- Platinum based chemotherapy.
- High dose chemotherapy (BEAM) in responders
- Stem cell harvest and auto-SCT in responders

The proportion of patients receiving treatment, sourced from ZUMA-7, company adaptions based on UK clinical expert opinion, and associated treatment acquisition/administration costs are provided in detail in Section B.3.5.2.2 of the company's submission.

The ERG considers the treatments sourced for the SOC arm of the model to be reasonable and consistent with UK clinical practice. However, the ERG raises concerns regarding A) the company's decision to apply salvage chemotherapy costs to 100% of patients in the SOC arm, when only 93.9% received salvage chemotherapy in the SOC arm of the ZUMA-7 study. Moreover, the ERG considers the costs of autologous SCT to have been substantially overestimated and prefers the use of NHS reference costs where possible and appropriate. For these reasons, the ERG's preferred SOC treatment cost (treatment acquisition and administration) is [redacted]*, compared to the company base case estimate of* [redacted]*. Further description and critique of the SOC costing approach, including a comparison of company and ERG preferred model parameter inputs is provided in Table 17.*

Table 17 ERG and company preferred SOC costing assumptions

	Proportion receiving in Zuma-7	**Proportion receiving in company base case**	**Unit cost (Company base case)**	***ERG preferred proportion***	***ERG preferred unit cost***	***ERG comments***
Salvage chemotherapy	168/179 (93.9%) R-DHAP (21%) R-ESHAP (3%) R-ICE (47%) R-GDP (23%)	100% R-DHAP (0%) R-ESHAP (0%) R-ICE (50%) R-GDP (50%)	**Total chemo cost:** £8,179*100% = **£8,179**	*93.9%; distribution of type as per company base case.*	***Total chemo cost:*** *£8,179*93.9%* = ***£7,680***	*The ERG prefers to use the proportion of patients who received platinum chemotherapy (93.9%) from the ZUMA-7 trial as opposed to the 100% assumed in the economic model. The justification for the ERG's preference is that applying the proportions receiving platinum-based chemotherapy from the trial ensures that the modelled costs are consistent with the resource use required to generate the modelled benefits (obtained from the trial ITT analyses).* *The ERG's clinical expert confirms that it is reasonable to assume all chemotherapy régimes are equally effective. Whilst some centers may also use R-DHAP, there is a more general move to outpatient use of R-GDP and on balance the company's re-distribution assumption is reasonable.*

	Proportion receiving in Zuma-7	**Proportion receiving in company base case**	**Unit cost (Company base case)**	***ERG preferred proportion***	***ERG preferred unit cost***	***ERG comments***
						The ERG further notes that different distributions of chemotherapy regiments have only minimal impact on the ICER. The ERG is satisfied that the number of treatment cycles and unit costs for chemotherapy regimens are appropriate.
BEAM high dose chemotherapy	62/179 (35.8%) [A]	62/179 (35.8%) [A]	Total cost per cycle: **£2,684.70**	*35.8% as per company base case*	Total cost per cycle: **£2,684.70**	*The ERG's clinical expert considers the treatment regimen to be appropriate and reflective of UK clinical practice.* *There is some uncertainty regarding the most appropriate unit cost of carmustine (100mg vial for injection) as unit costs are not available from either eMIT or BNF. The company have inflated a quoted cost from NG52, based on expert opinion, though expert opinion provided for that guideline appears to provide costs ranging from £358.80 to £1,000 per unit[35]. The ERG therefore notes that the company's approach to costing may be conservative, though the impact on the ICER is minimal.*

	Proportion receiving in Zuma-7	**Proportion receiving in company base case**	**Unit cost (Company base case)**	***ERG preferred proportion***	***ERG preferred unit cost***	***ERG comments***
Stem cell harvest	41.3% [A]	41.3%	£3,021.82 (HRG: SA34Z, stem cell harvest, outpatient) [B]	*As per company base case.*	*As per company base case*	*The company submission suggests that only those who receive SCT would receive high dose chemotherapy (34.6%) though the model uses data directly from the ZUMA-7 study which the ERG considers to be the most appropriate approach to costing.* *The ERG was unable to reproduce the HRG costings for stem cell harvest as stated in the company submission and used in the economic model, however it is stated that average HRGs are used. Whilst it is unclear which HRG code was applied in the model, the costs appear reasonable, and the ERG's clinical expert considers a range of settings to be appropriate as described for leukapheresis for axi-cel above. The ERG would appreciate further clarification on the costing approach applied by the company.*

	Proportion receiving in Zuma-7	**Proportion receiving in company base case**	**Unit cost (Company base case)**	***ERG preferred proportion***	***ERG preferred unit cost***	***ERG comments***
Auto-SCT	34.6%	34.6%	£37,735.95 (inflated from £34,000 used in NG52)	*As per company base case*	*£16,668 inflated to 2020/21 values*	*The ERG is concerned that the unit cost applied for Auto-SCT, sourced from NG52 is substantially higher than the most appropriate HRG (SA26A: Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over) for an elective procedure of £16,668.* *The company has not justified the use of NG52 costs instead of NHS reference costs and the ERG believes the NG52 costs were based on the opinion of one clinical expert, with no corresponding tariff code quoted (See appendix A page 16 of the NG52 guideline document).*[35] *The ERG was unable to verify the NG52 auto-SCT costs.* *Unless there is a strong justification as to why they are inappropriate, the ERG prefers the use of NHS reference costs wherever possible.*

[A] NR in company submission, sourced from company economic model, sheet "costs" cell: H94

[B] Source as stated in the company submission: NHS reference costs from 2019/20 (HRG: SA34Z, outpatient), which were then inflated to 2021 values for use in the model.

Health state resource use and monitoring costs:

Additional health state costs are included in the economic model to account for routine follow-up and monitoring of patients and include primary and secondary care attendances, as well as scans and tests. The frequency of resource usage is obtained from TA559 (axi-cel third line plus)[29] and is assumed to be health state-dependent, with more frequent monitoring in secondary care for patients following an event. Patients who are event free for five years are assumed to have a six-monthly GP visit. Full details are provided in Table 43 of the company submission.

The ERG agrees that the company's approach to modelling monitoring and follow up is reasonable and that it is appropriate to apply costs separately to health states, as opposed to treatment specific monitoring. Despite applying resource use frequencies from the assessment of axi-cel third line plus (TA559)[29] to second-line patients, the ERG's clinical expert is satisfied that the resource use estimates are a fair reflection of UK clinical practice, though there may be some heterogeneity in practice across centers. The ERG is also aware that monitoring and resource use costs are minimal in the context of treating r/r DLBCL and therefore assumptions about resource use frequency have only a negligible impact on the ICER.

Adverse event costs:

As with the incorporation of adverse event disutilities (See Section 4.2.7), adverse event costs were applied for Grade 3 and above AEs occurring in at least 10% of either arm of the ZUMA-7 trial, in addition to the costs of high resource use events (CRS and B-cell aplasia). Adverse event management costs were obtained from a previous NICE assessment of tisagenlecleucel for r/r DLBCL (TA567)[22] and NHS reference costs (2019-20),[36] inflated to 2021 values throughout. Details of the AE costs are provided in Table 45 of the company submission.

The ERG considers the types and rates of adverse events obtained from the ZUMA-7 study to be reflective of the AEs that might be expected in clinical practice and is inclusive of the events that would likely generate the greatest cost impact in terms of treatment. It was not possible for the ERG to directly verify the appropriateness of AE costs for CRS or B-cell aplasia because the level of detail included in the company submission and economic model was not sufficient to fully replicate the costs applied in the model. However, the ERG was

able to cross check the costs against un-redacted information from TA567 and notes the following uncertainties:

- *The ERG is aware of substantial uncertainty surrounding the management of B-cell aplasia in UK clinical practice, and the most appropriate duration of IVIg treatment, as noted in the FAD for TA567 (page 17).[22] The company submission appears to apply costs based on a median treatment duration of 11.4 months (sourced from page 128 of TA567 company submission), but this is substantially shorter than the ERG and committee preferred duration of 36 months noted in the FAD. Currently, in the UK, there is a restriction on immunoglobulin use due to supply issues. This means that patients with low immunoglobulin levels after treatment (secondary hypogammaglobulinaemia) will only receive immunoglobulin replacement if they develop infections despite antibiotic prophylaxis. In practice, this is a small subset of patients with low secondary hypogammaglobulinaemia, although this may increase once the UK manufacturer of immunoglobulins re-starts as is planned. Given the uncertainty around current and future IVIg usage, the ERG retains the company base case assumption but explores scenario analyses varying the duration of IVIg from an average of 0 (assuming lack of supply) to 36 months (as per the FAD for TA567). The magnitude of impact on the ICER is small because the cost implications, although substantial, are small in comparison to the overall treatment acquisition costs in the model.*
- *The ERG notes that the company assumes an average ICU stay for managing CRS of 4 nights for all patients. This is stated to follow the same approach as TA567, however, the costs in TA567 are substantially higher than in the current assessment and would appear to be driven by an assumption of 10 nights in ICU.[22] The ERG's clinical expert notes that the median time to resolution of CRS is ~7-8 days for axi-cel, though not all patients will require ICU admission. Whilst the company duration of ICU stay of 4 days is too short for those that require ICU care, the company may have over-estimated the proportion requiring an ICU stay (although this is unclear from the submission document). On balance, the ERG is satisfied that a mean of 4 days may be reasonable, but again notes substantial uncertainty and explores scenario analyses where the costs of treating CRS are varied by +/- 50% in the model.*

- *The ERG considers the company base case assumption that Grade 3 and above neurological events would not incur any resource use to be inappropriate. The assumption that these costs were not included in the economic models for other CAR-T therapies does not seem to be sufficient justification for their exclusion. The ERG's clinical expert confirms that neurological events would always be investigated in secondary care. Many would be treated as inpatients as part of their hospitalization for axi-cel treatment, but some would require intensive care admission (approximately 50% of Grade 3 and all Grade 4). The ERG believes that the company should have included the costs of investigating / treating neurological events, even if they occur during initial hospitalization and should have explored the resource use associated with ICU care. The ERG considers a minimum resource requirement that all neurological AEs would receive at least an additional consultation with a neurologist (assumed consultant lead outpatient clinic) and explores the impact of requiring ICU admission on the ICER.*

The ERG is satisfied that the remaining adverse event costs, as included in the economic model are appropriate and reflect anticipated resource use in UK clinical practice. There remains uncertainty surrounding the most appropriate costs to apply for CRS, B-cell aplasia and neurological adverse events. The ERG therefore conducts further scenario analyses illustrating the impact of alternative adverse event management costs and assumptions on the ICER.

Subsequent (post-event) treatment costs:

Subsequent treatment costs were included in the model, for the proportion of the cohort who transition into the post-event state of the model and are on active treatment post event (i.e. based on the predictions of TTNT extrapolation curves fitted to ZUMA-7 data as described in Section 4.2.6). The company report a distribution of different post-event therapies as per the ZUMA-7 study and as per advice sought from UK clinical experts in Tables 47 and 48 respectively.

The ERG accepts that some of the treatments used in the ZUMA-7 study may not currently be available for use in routine NHS practice (e.g., Nivolumab and Pembrolizumab). The ERG is also aware of NICE's methods preference to assume that treatments currently only available on the CDF should not be considered available for routine NHS practice (i.e. axi-cel, liso-cel

and tisagenlecleucel). The ERG notes that the effectiveness of CAR-T therapies has been removed through the company's cross-over analysis for OS, and therefore considers it appropriate, within the current NICE recommendations to also remove the post-event costs of these treatments. However, it is less clear whether the removal of the costs of nivolumab and pembrolizumab is appropriate because the corresponding impact on OS has not been accounted for in the model. It is also unclear how clinical experts consulted by the company decided to re-allocate the cohort to different treatments and the approach does not seem to be consistent between axi-cel and SOC. The ERG would have preferred an analysis where the distribution for axi-cel remained as reported in the ZUMA-7 study, including nivolumab and pembrolizumab to maintain consistency between the costs of treatments required to generate OS estimates, despite the treatments not being available in the UK clinical practice. The ERG would also prefer that, for the SOC arm, patients receiving CAR-T therapies are re-distributed to the other reported SOC post-event therapies using the weightings between treatments as observed in the ZUMA-7 study. The ZUMA-7, company base case and ERG preferred subsequent treatment distributions are summarised in Table 18 below.

Table 18 Comparison of company and ERG preferred distributions of subsequent treatments

Subsequent treatment	ZUMA-7		Company base case		ERG base case	
	Axi-cel	SOC	Axi-cel	SOC	Axi-cel	SOC
R-chemotherapy	68%	19%	25%	30%	68%	35%
Nivolumab	11%	3%	0%	0%	11%	6%
Pembrolizumab	5%	4%	0%	0%	5%	7%
Pola-BR	20%	13%	10%	26%	20%	24%
R-lenalidomide	14%	13%	25%	10%	14%	24%
Radiotherapy	20%	25%	40%	20%	20%	46%
Allo-SCT	8%	4%	5%	5%	8%	7%
Axi-cel	0%	56%	0%	0%	0%	0%
Liso-cel	0%	4%	0%	0%	0%	0%
Tisagenlecleucel	0%	12%	0%	0%	0%	0%
Auto-SCT	11%	4%	11%	8%	11%	7%

At the clarification stage, the ERG requested further details of the sources used to decide on the number of cycles for each post-event treatment. The company responded that treatment duration was in line with guidelines and provided full details in response to clarification query B9. The ERG's clinical expert reviewed the company's response and confirms that the duration and dosage of subsequent treatments are appropriate and consistent with UK clinical practice.

The ERG is also satisfied that the company's unit cost sources are accurate and appropriate, though notes that some subsequent treatments are subject to confidential prices, which are detailed in a separate confidential appendix to this report.

5 COST-EFFECTIVENESS RESULTS

Section 5.1 and 5.2 summarise the company provided cost-effectiveness results, including sensitivity, scenario and probabilistic analyses provided in the company submission and in response to ERG clarification queries. Section 5.3 describes the company and ERG model validation and face validity checks.

5.1 Company's cost-effectiveness results

Figures 33 and 34 of the company's submission illustrate the health state occupancy probabilities for 'event free', 'post-event' and 'death' over time under the company's base case modelling assumptions. Disaggregated QALYs and costs accrued in each model health state, are provided in Table 30 and 31 of appendix J of the company submission, respectively.

The health state occupancy from the company's base case model is largely consistent with the ERG preferences as described in Chapter 6. The graphs illustrate that the model predicts a higher proportion of axi-cel patients to remain event-free over a longer period compared to SOC, driven mostly by the larger proportion of the cohort considered to be statistically cured through mixture cure modelling. The majority of modelled axi-cel QALY gains (73%) are therefore accrued in the event free state. QALY gains (27% of incremental QALYs) are also derived from OS benefits post-event. These post-event benefits are largely driven by the company's crossover adjustment (RPSFT models) to remove the OS benefit of 3rd line CAR-T therapies from the SOC arm of the model. The ERG appreciates that the company's base case approach is appropriate because it complies with NICE's position statement on the modelling of treatments that are only available in England through the CDF and notes that an ITT analysis was conducted as a scenario analysis (See Appendix Q of the company submission and Section 5.2 below).

The company's preferred base case deterministic and probabilistic ICERs are re-produced in Table 19. The company's preferred base case assumptions remained unchanged following clarification queries.

Table 19 Company base case deterministic and probabilistic ICERs [reproduced from Tables 51 of the CS and from the company's economic model]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case analysis (deterministic)							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,996
Company base case analysis (probabilistic)							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,669

The scatter plot of incremental costs and QALYs and the cost-effectiveness acceptability curve (CEAC) from the company's base case probabilistic analysis are re-produced from the company submission in Figures 10 and 11 respectively.

Figure 10 PSA scatter plot for the company base case probabilistic analysis [reproduced from Figure 35, Document B of the CS]

Figure 11 CEAC for the company base case probabilistic analysis [reproduced from Figure 36, Document B of the CS]

The CEAC shows that the probability that axi-cel (with a [redacted] PAS discount applied) is cost-effective at a £50,000 per QALY threshold is [redacted].

The ERG has reviewed the company's probabilistic analysis and is satisfied that it has been implemented correctly and includes variation in the most important model parameters. Where standard errors are available for parameter inputs, these are used to sample from appropriate distributions. Where SEs are not available, a SE = 20% of the mean was assumed. There is some uncertainty around how appropriate this decision may be, but in general the ERG is satisfied that the company's approach is reasonable.

The ERG notes that the £50,000 threshold may be applicable for decision making if the company's case for claiming end-of-life is accepted by the committee. However, the ERG is not convinced that the end-of-life criteria are definitively met for this submission (see the ERG's critique of the company's end-of-life case in Chapter 7). It may therefore be appropriate to also consider that the company base case PSA suggests a [redacted]% probability of cost-effectiveness at a £20,000 to £30,000 threshold value of willingness to pay per QALY gained.

5.2 Company's sensitivity analyses

The company conducted a range of deterministic one-way sensitivity analyses varying key parameter inputs between the upper and lower bounds of their confidence intervals, or by assuming a margin of error of 20% where standard error information was not available. The results of the deterministic analyses are illustrated using a tornado diagram in Figure 38 of the company submission, which illustrates that the ICER is most sensitive to assumptions about the proportion of people receiving axi-cel, as well as assumptions about the proportions receiving different post-event treatments in the respective model arms.

Whilst the ERG considers the deterministic analyses to be useful indicators of important model parameters, they do not capture key uncertainties in the choice of data inputs or modelling assumptions. The ERG, therefore, considers the scenario analyses conducted by the company, both in the company submission and in response to clarification queries to be more useful indicators of the key uncertainties surrounding the base case ICER.

The company conducted a range of scenario analyses around key modelling assumptions in the company submission and in response to the ERG's clarification queries. The findings of these analyses are collated and reproduced in Table 20.

Table 20 Company conducted scenario analyses [reproduced from Table 53 of the CS and Tables 3, 7, 8, 12, 14, 16 and 17 of the company's clarification response]

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change from base case ICER[A]
Base case	-	[redacted]	[redacted]	**£51,996**	-
Scenario analyses conducted in the company submission					
Time horizon = 10 years	50 years	[redacted]	[redacted]	£111,183	113.83%
Time horizon = 20 years		[redacted]	[redacted]	£66,249	27.41%
Discount rates = 1.5%	3.5%	[redacted]	[redacted]	£40,631	-21.86%
Axi-cel OS = Weibull (MCM)	Generalised gamma (MCM)	[redacted]	[redacted]	£51,882	-0.22%
Axi-cel OS = Log-logistic (MCM)		[redacted]	[redacted]	£53,075	2.08%
Axi-cel EFS = Generalised gamma (MCM)	Log-logistic (MCM)	[redacted]	[redacted]	£51,705	-0.56%
SOC EFS = Weibull (MCM)	Exponential (MCM)	[redacted]	[redacted]	£52,012	0.03%
SOC OS convergence with EFS at 5 years applied	No convergence applied	[redacted]	[redacted]	£49,792	-4.24%
Utility values based on ZUMA-1	Based on ZUMA-7 and JULIET study	[redacted]	[redacted]	£54,144	4.13%
No AE disutilities applied and on-treatment specific utilities applied	AE disutilities included and no on-treatment specific utility applied	[redacted]	[redacted]	£51,973	-0.04%
Cure time point = 2 years	5 years	[redacted]	[redacted]	£50,770	-2.36%
Cure time point = 7 years		[redacted]	[redacted]	£52,557	1.08%
Use of ZUMA-7 estimates for SOC distribution	UK clinical expert estimates	[redacted]	[redacted]	£51,953	-0.08%

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change from base case ICER[A]
Base case	-	[redacted]	[redacted]	**£51,996**	-
OS: ITT analysis	OS: Crossover adjusted	[redacted]	[redacted]	£79,034	52.00%
Additional scenarios in response to clarification queries					
RPSFTM, no recensoring [redacted]	Crossover adjustment approach for SOC OS: RPSFTM, re-censoring full analysis [redacted]	[redacted]	[redacted]	£74,750	27.41%
RPSFTM, recensoring switchers only [redacted]		[redacted]	[redacted]	£70,738	-21.86%
IPCW, robust SE, wide intervals [redacted]		[redacted]	[redacted]	£94,604	-0.22%
IPCW, robust SE, 2-day intervals [redacted]		[redacted]	[redacted]	£82,862	2.08%
Post-event utility = 0.779 (ZUMA-7 study)	0.710 (post-progression from JULIET study)[22]	[redacted]	[redacted]	£50,678	-0.56%
Post-event utility = 0.72 (pre-progression utility from 3rd line plus ZUMA 1)[29]		[redacted]	[redacted]	£51,801	0.03%
Include axi-cel re-treatment costs	No retreatment costs	[redacted]	[redacted]	£54,902	-4.24%
Subsequent treatment costs (ZUMA-7 study, except CAR-T to align with OS SOC cross-over analysis)	Clinical expert opinion	[redacted]	[redacted]	£51,099	4.13%
OS: ITT analysis Subsequent Tx: Clinical expert opinion (with CAR-T therapies included 3rd line)	OS: Crossover adjusted Subsequent Tx: Clinical expert opinion (No CAR-T therapy 3rd line)	[redacted]	[redacted]	£46,856	-0.04%

[A] Percentage change from base case ICER, calculated by the ERG to 2 decimal places. Any inconsistencies from the company submission likely due to rounding.

Abbreviations: EFS: Event free survival; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; IPCW: Inverse probability of censoring weighting; ITT: Intention to treat; MCM: Mixture cure model; OS: Overall survival; QALY: Quality adjusted life year; RPSFTM: Rank preserving structural failure time model; SOC: Standard of care; Tx: treatment.

The scenario analyses illustrate that the ICER is most sensitive to the modelled time horizon, alternative cross-over analysis approaches, the inclusion or exclusion of axi-cel re-treatment costs, and the decision whether to adopt a cross-over or ITT analysis for overall survival. The ERG's preferred assumptions are detailed in Chapter 6.

The appropriateness of using a cross-over analysis or ITT analysis depends on the outcome of the upcoming CDF review of axi-cel (and other CAR-T therapies) as third-line treatments for r/r DLBCL. The outcome of the review is anticipated to be available towards the end of 2022. It should be noted that modelled incremental QALY gains for the current appraisal (2nd line therapy) would be substantially lower if CAR-T therapies were recommended as SOC third line plus treatment of r/r DLBCL. This is demonstrated in the ITT OS analysis conducted by the company and reported in appendix Q of the company submission showing an ICER of £79,034 per QALY gained. However, an important observation about the analysis in Appendix Q is that whilst the analysis appropriately applies an ITT approach for estimating OS, it does not apply the corresponding post-event costs of CAR-T therapy, which would be incurred in the SOC arm if CAR-T therapies were available 3rd line (as was the case in the ZUMA-7 study).

The company's ITT analysis therefore substantially over-estimates the true incremental costs of axi-cel, a point which was acknowledged by the company in response to clarification queries (B8). The clarification response demonstrates that an ITT analysis of OS, combined with assuming the post-event distribution of subsequent therapies that includes CAR-T for the SOC arm, as per the ZUMA-7 study, leads to a reduced ICER of £46,856 per QALY gained. The ERG considers this latter analysis to be more appropriate for decision making in a world where CAR-T therapies are available for 3rd line plus treatment of r/r DLBCL.

5.3 Model validation and face validity check

The ERG has quality assessed the model against the black-box checklist described by Tappenden and Chilcott 2014.[37] The results of the checks conducted are detailed in Table 21.

Table 21 Summary of "black box" checks of the model carried out by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	No issues found.
	Sum expected health state populations at any model timepoint	Total probability equals 1.0	For the partitioned survival traces, data obtained from the extrapolations of the cohort distribution between pre-event, post-event (on and off treatment) and death all summed to 1.
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	No issues found.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No issues found.
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No issues found
Cost estimation	Set intervention costs to 0	ICER is reduced	No issues found.
	Increase intervention cost	ICER is increased	No issues found.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	No issues found.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	Total costs behave as expected, but it should be noted that the impact of

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
			varying the discount rate is minimal in the axi-cel arm because the majority of the costs are incurred in the first year of the model and are thus not impacted on through cost discounting.
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	Sample tested. No issues found.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	Difficult to completely achieve for the current model, though the ERG has no concerns.

Abbreviations: ICER: Incremental cost-effectiveness ratio; QALY: Quality adjusted life year.

The ERG black-box checks did not identify any modelling errors, and the ERG is satisfied that the company's model provides an appropriate representation of the care pathway.

The ERG considers the company's validity checks of model output are reasonable and it is reassuring that the model projections are broadly consistent, potentially conservative, when compared to the median OS and EFS data from the ZUMA-7 trial. As noted in Section 4.2.6, outcomes from the model lead to OS curves above those estimated from ZUMA-1 for axi-cel 3rd line plus, which indicates better outcomes from 2nd line treatment, which might be anticipated. The ERG is also satisfied that the company's approach to validating OS extrapolation models and choosing models that lie between the ORCHAARD and SCHOLAR1 studies is appropriate and is in line with the ERG clinical experts anticipated outcomes.

Further face validity checks of model outputs around survival extrapolations, cure fractions and cure timepoints (applied to utilities and costs) with the ERG's clinical expert did not identify any other major face validity concerns. Whilst the company's base case inputs may be clinically plausible, there are often more than one clinically plausible options available for the model, and these are tested by both the company and ERG in scenario analyses. It is important to acknowledge that, whilst the extrapolations may be broadly in line with expectations, the remaining uncertainty around long-term EFS and OS estimates, including the cure fractions from the mixture cure models should not be understated. This uncertainty could be mitigated in future through further data collection and follow up of the ZUMA-7 study participants.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG critique of the company submission from Chapter 4 has identified several issues of remaining uncertainty and differences between ERG and company preferred assumptions. The additional scenario analyses conducted by the ERG are described in Table 22, including the ERG's rationale for conducting each analysis.

Table 22 ERG's justification for additional exploratory and sensitivity analyses

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
	Treatment acquisition and administration costs for Axi-cel and SOC				
1	Axi-cel re-treatment costs	Excluded	**ERG base case:** Included	ERG preferred base case includes full re-treatment costs as per company clarification response scenario. Ensures consistency between the treatment delivered in the ZUMA-7 trial and the economic model. Maintains consistency between treatment costs required to generate modelled benefits	4.2.8
2	Proportion in the SOC arm that receive initial salvage chemotherapy	100%	**ERG base case:** [redacted]	Ensures consistency between the costs required to generate the modelled benefits, and maintains consistency between ZUMA-7 and the economic model.	4.2.8
3	Source of Auto-SCT unit costs	Based on clinical expert opinion sought as part of	**ERG base case:**	The ERG believes that the use of NHS reference costs is a more appropriate source unless a clear	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
		NG52,[35] and inflated to 2021 values	Obtained directly from NHS reference costs 2019/20[36]	justification can be provided as to why NHS reference costs are inaccurate.	
	AE treatment costs				
4 & 5	Duration of IVIg treatment for patients with b-cell aplasia AE	11.4 months	**ERG exploratory analysis:** Vary costs by 0 and 36 months to explore impact of uncertainty around duration of IVIg treatment to treat b-cell aplasia	The use of IVIg in clinical practice, and the duration of prophylaxis is uncertain. Restrictions on supply mean current use of IVIg is strictly controlled, but previous NICE guidance assumes 36 months of treatment duration	4.2.8
6 & 7	Number of nights in ICU for CRS	4	**ERG exploratory analysis:** Vary costs by +/- 50% to explore impact of uncertainty around the requirement for ICU care	The requirement for ICU is uncertain. ERG's clinical expert estimates that only a proportion would be treated in ICU for about 7-8 nights. TA567 FAD assumes 10 nights[22]	4.2.8
8 & 9	Costs of treating grade 3+ neurological AEs	No costs	**ERG base case:**	ERG clinical expert confirms that all neurological AEs of grade 3+	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
			Consultant lead neurology outpatient investigation **ERG exploratory analysis:** 50% of grade 3 and 100% of grade 4 neurological AEs would require ICU care	would be investigated. ERG scenario may be a conservative estimate of true costs in the absence of information on whether any AEs in ZUMA-7 required hospital admission/ ICU care. In UK clinical practice, the ERG believes that up to 50% of grade 3 and all with grade 4 AEs may require ICU care (assume: HRG code: XC06Z, 1 organ supported). Breakdown of grade of AEs were obtained from Table 36 and Table 14.3.1.4.1.2.1 in the ZUMA-7 CSR.	
	Subsequent (post-event) treatment costs				
10	Distribution of subsequent (post-event) treatments	Uses clinical expert opinion, excludes CAR-T treatments 3rd line and also other treatments unlikely to	**ERG base case:** Accepts removal of CAR-T treatments because OS curves are adjusted to	The ERG's analysis more closely maintains consistency between the costs and benefits of treatments used as post-event therapy and	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
		be used in UK clinical practice	reflect the associated effectiveness implications. Retains the remaining distribution from ZUMA-7, with CAR-T treatments re-distributed to other treatments from ZUMA-7.	retains the randomised proportions in each arm receiving treatment.	
	OS extrapolations				
11	Axi-cel OS mixture cure model	Generalised gamma MCM	**ERG base case:** Log logistic MCM	ERG considers the log-logistic scenario analysis provided by the company to be clinically plausible, the best fit to the data and generates a more conservative estimate of long-term projections	4.2.
	Utilities				
12	Event free utilities beyond five years	Revert to UK general population norms	**ERG scenario analysis:** Retain event-free utilities for the full time horizon in the event free state.	Quality of life is likely to improve the longer one is event-free. However, whether it fully reverts to general population norms is a	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
				questionable assumption, the impact of which is tested in this scenario analysis.	
13	Post-event utilities	JULIET study utilities based on mapping from SF-36 to EQ-5D. Utility = 0.71	**ERG base case:** Use pre-progression utilities (EQ-5D) from ZUMA-1 study (utility = 0.72)	Using ZUMA 1 pre-progression utilities from 3rd line plus treatment may be a reasonable proxy for post-event utilities and may be more appropriate because they allow use of EQ-5D data, maintaining consistency with the NICE reference case	4.2.7

Abbreviations: AE: Adverse events; Auto-SCT: Autologous stem cell transplant; CRS: Cytokine release syndrome; ERG: Evidence review group; ICU: Intensive care unit; IVIg: Intravenous immunoglobulins; QALY: Quality adjusted life year; SOC: Standard of care

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 23 provides the results of all the ERG's exploratory analyses applied to the company base case ICER.

Table 23 ERG scenario analyses applied to the company base case analysis

Analysis number	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Co BC	**Company preferred base case ICER**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,996
1	**Include axi-cel re-treatment costs (as per company clarification response scenario)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,902
2	**Proportion in SOC arm receiving initial salvage chemotherapy ([redacted]**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,119
3	**Auto-SCT cost source: NHS reference costs (HRG: SA26A)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,755
4	**Duration of IVIg treatment for b-cell aplasia: 0 months**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,755
5	**Duration of IVIg treatment for b-cell aplasia: 36 months**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,515

Analysis number	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
6	**Costs of treating CRS: -50%**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,941
7	**Costs of treating CRS: +50%**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,051
8	**Costs of treating Grade 3 and above neurological AEs (Outpatient consultation)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,001
9	**Costs of treating Grade 3 and above neurological AEs (50% of grade 3 and 100% of grade 4 AEs require ICU care)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,033
10	**Subsequent treatment distribution (as per ZUMA-7, with CAR-T treatments in SOC arm re-distributed)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,318
11	**Axi-cel OS extrapolation: Log logistic MCM**							
	SoC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,075
12	**Event free utilities after 5 years (EFS utility applied)**							

Analysis number	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
	SoC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£53,296
13	**Post-event utilities, ZUMA-1 pre-progression (0.72)**							
	SoC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,801

Abbreviations: AE: Adverse events; Auto-SCT: Autologous stem cell transplant; CRS: Cytokine release syndrome; ERG: Evidence review group; ICER: Incremental cost-effectiveness ratio; ICU: Intensive care unit; IVIg: Intravenous immunoglobulins; LYG: Life year gains; MCM: Mixture cure model; QALY: Quality adjusted life year; SOC: Standard of care.

6.3 ERG's preferred assumptions

The key differences between the company's and ERG's preferred base case analyses are:

Cost parameters:

- The company base case analysis did not include axi-cel re-treatment costs. The ERG prefers inclusion of axi-cel re-treatment costs because it ensures the model accurately reflects treatments in the ZUMA-7 study, with the implication that the resource use required to deliver modelled benefits is fully costed.
- The company assumed 100% of SOC patients would receive salvage chemotherapy. The ERG prefers to include the costs of salvage chemotherapy for the proportion of the standard care arm from ZUMA-7 who received it ([redacted]
- The company base case uses auto-SCT costs inflated from clinical expert opinion sought for the development of NG52 guidance. The ERG prefers to use the most recently available NHS reference costs.
- The company base case assumes no treatment costs would be incurred for neurological AEs (grade 3+). The ERG prefers an assumption that all neurological AEs would require outpatient investigation as a minimum.
- The company use clinical expert opinion sought from clinicians in England experienced in the treatment of r/r DLBCL, and exclusion of treatment costs for therapies not routinely available in UK clinical practice. The ERG prefers to use the distribution of subsequent treatments from the ZUMA-7 study, with CAR-T therapies removed and re-distributed to other therapies received in ZUMA-7. Whilst the ERG acknowledges that Nivolumab and pembrolizumab are not available in UK practice, it is still appropriate to include their costs to ensure that resource use is costed in a manner that matches the treatments used to derive OS benefits in the model.

Clinical parameters:

- The company uses a generalised gamma MCM for axi-cel OS, whilst the ERG prefers the company's scenario analysis using a log-logistic MCM because it is also clinically plausible, provides the best fit to the KM data, and provides a more cautious estimate of long-term OS gains for axi-cel in light of the considerable residual uncertainty.

Utility parameters:

- The company preferred source of post-event utility is the JULIET study, which uses SF-36 responses mapped to EQ-5D. The ERG prefers to assume that pre-progression EQ-5D utilities sourced from the ZUMA-1 trial (3rd line plus treatment) are a more appropriate source for 2nd line post-event in this assessment. The data are from a similar patient population, and utility measurement is more consistent with the NICE reference case.

The cumulative impact of the ERG's preferred assumptions on the base case ICER is illustrated in Table 24. Under the ERG's preferred base case assumptions, the probabilistic analysis shows that the probability axi-cel is cost-effective is [redacted] at threshold values of £20,000, £30,000, and £50,000 respectively.

Table 24 ERG's preferred model assumptions

		Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Co BC	**Company preferred base case ICER**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,996
+ 1	**Include axi-cel re-treatment costs (as per company clarification response scenario)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,902
+2	**Proportion in SOC arm receiving initial salvage chemotherapy ([redacted]**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£55,026
+ 3	**Auto-SCT cost source: NHS reference costs (HRG: SA26A)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,784

		Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
+ 8	**Costs of treating Grade 3 and above neurological AEs (Outpatient consultation)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,789
+ 10	**Subsequent treatment distribution (as per ZUMA-7, with CAR-T treatments in SOC arm re-distributed)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,071
+ 11	**Axi-cel OS extrapolation: Log logistic MCM**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,338
+ 13	**Post-event utilities, ZUMA-1 pre progression (0.72)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,205

		Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
ERG BC (det)	**ERG preferred base case analysis (deterministic)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,205
ERG BC (prob)	**ERG preferred base case analysis (probabilistic)**							
	SOC	[redacted]	[redacted]	[redacted]				
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,767

Abbreviations: AE: Adverse events; Auto-SCT: Autologous stem cell transplant; CRS: Cytokine release syndrome; ERG: Evidence review group; ICER: Incremental cost-effectiveness ratio; ICU: Intensive care unit; IVIg: Intravenous immunoglobulins; LYG: Life year gains; QALY: Quality adjusted life year; SOC: Standard of care

Figure 12 Scatter plot of the cost-effectiveness plane for the ERG's preferred base case probabilistic analysis

Figure 13 CEAC for the ERG's preferred base case probabilistic analysis

Table 25 Selected scenario analyses applied to the ERG's preferred base case

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
ERG preferred base case analysis							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,205
1. OS ITT analysis (efficacy only)							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£345,437
2. ZUMA-7 subsequent treatment distribution (including CAR-T therapies)							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,965
3. (1+2)							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£115,379
4. 3 + company preferred axi-cel OS extrapolation (generalised gamma)							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,732
5. Cure time point (2 years)[A]							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,894

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
6. Cure time point (7 years)[A]							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£58,825
7. SOC OS cross-over (RPSFTM, no re-censoring [redacted]							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£84,703
8. SOC OS cross-over (RPSFTM, re-censoring switchers only [redacted]							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£80,169
9. SOC OS cross-over (IPCW, robust SE, wide intervals [redacted]							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£107,227
10. SOC OS cross-over (IPCW, robust SE, 2-day intervals [redacted]							
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£93,882

[A] The time point at which health care resource use in the pre-event state reverts to zero, and pre-event utilities are assumed to be equal to general population utility norms.

Abbreviations: ERG: Evidence review group; HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; ICU: Intensive care unit; IPCW: Inverse probability of censoring weights; IVIg: Intravenous immunoglobulins; LYG: Life year gains; QALY: Quality adjusted life year; RPSFTM: Rank preserving structural failure time model; SE: Standard error; SOC: Standard of care

6.4 Conclusions of the cost-effectiveness section

The company have developed a comprehensive submission, including a robust and flexible economic model to assess the cost-effectiveness of axi-cel versus soc for people with r/r DLBCL. The ERG is satisfied that the cost-effectiveness case is in line with the NICE scope for the assessment, uses the best available clinical data from the ZUMA-7 study where possible and generally adheres to the NICE reference case. The ERG notes that the main residual area of uncertainty relates to the use of immature data from the ZUMA-7 study to extrapolate long term EFS, and especially OS for both the axi-cel and soc arms. The company acknowledges this uncertainty and consider axi-cel to be an appropriate treatment for inclusion on the cancer drugs fund (CDF). The ERG agrees that further follow-up of the ZUMA-7 study will provide more robust estimation of long-term OS which would in turn substantially reduce remaining uncertainty surrounding the most appropriate base case ICER.

The company have conducted cross-over analysis to remove the OS benefit of using axi-cel as a third line treatment post-event in the SOC arm of the model. Whilst the ERG agrees that the company base case cross-over model is plausible, it is important to note that different cross-over methods produce substantially higher ICERs. The ERG notes that the decision to conduct a cross-over analysis is in line with NICE's position statement on CDF treatments. However, the outcome of the upcoming review of axi-cel as 3rd line plus treatment on the CDF would likely have implications for the ICER in the current assessment.

The ERG considers most of the company's base case assumptions to be plausible, and long-term extrapolations for EFS and OS to be plausible, though highly uncertain. The ERG preferred base case ICER assumes a more conservative, but clinically plausible log-logistic MCM for axi-cel OS, includes axi-cel re-treatment costs, prefers use of ZUMA-7 data over clinical assumptions where feasible, and prefers post-event utilities sourced from the ZUMA-1 study (pre progression).

7 End of life

To meet the NICE criteria for end-of-life designation, the company needs to demonstrate that axi-cel is a life-extending treatment (normally an additional life expectancy of at least three months compared to SOC) at the end-of-life (where the treatment is indicated for patients with a short life expectancy, normally less than 24 for people treated with SOC).

Section B.2.13.5 of the company submission outlines the company's case for axi-cel to be considered as an end-of-life treatment. The company quote data from the ORCHARRD (primary refractory or early relapse patients intended for transplant),[15] SCHOLAR 1 (primary refractory patients)[12] and axi-cel model for this appraisal (without CAR-T therapy available 3rd line plus), where the median OS is 9, 7.1 and [redacted] months, respectively. Additionally, the company preferred base case model configuration predicts that axi-cel is associated with [redacted] LYGs compared to SOC, in world where CAR-T therapies are not available for 3rd line treatment of r/r DLBCL.

The ERG agrees that axi-cel is a life extending treatment, with mean incremental life year gains ranging from [redacted] in the company's ITT analysis (for a scenario where CAR-T therapies are available as third line treatment) to [redacted] in the company and ERG preferred cross-over analysis (where CAR-T therapy is assumed to not be available third line). In both cases, the ERG is satisfied that the company's case for axi-cel as a life-extending treatment is robust.

Whether patients with r/r DLBCL can be considered to normally have a life expectancy of less than 24 months when treated with SOC is less clear, and dependent in part on whether axi-cel is available as a third line treatment for those experiencing an event post 2nd line SOC. The range of mixture cure model OS curves explored in the company submission for the crossover analysis (i.e. assuming 3rd line CAR-T therapy is not available) predict between [redacted] and [redacted] of the cohort to be alive at 2 years, but it should be noted that mixture cure modelling predicts long tails to the OS survival curves, and there is thus a substantially left-skewed distribution of OS, where a decision must be made as to whether the mean or the median should be considered the most appropriate measure by which to assess end-of-life criteria. Assuming that axi-cel is not available 3rd line for SOC patients, the company and ERG preferred base case economic models both predict mean (discounted) and median LYs

for SOC of [redacted] and [redacted] respectively. Given that the company's use of mixture cure modelling is clinically plausible in the SOC arm, and given that means, rather than medians are used to calculate ICERs, the ERG does not consider axi-cel to strictly meet the second of NICE's end of life criteria. The decision will ultimately depend on the committee's view of whether mean or median should be considered the most appropriate statistic by which to assess the criteria and the ERG is aware that both have been considered in previous technology appraisals.

8 References

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