NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

Contents:

The following documents are made available to consultees and commentators:

Link to TA559 on the NICE website

The final scope and final stakeholder list are available on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Kite, a Gilead company
   a. Company submission
   b. Additional information submitted following the Committee meeting on 6 September 2022

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Anthony Nolan
   b. Public Health England SACT report

4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Dr Graham Collins – clinical expert, nominated by National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists
   b. Cerys Thompson – patient expert, nominated by Blood Cancer UK
   c. Patient expert, nominated by Anthony Nolan

8. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA559

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies (ID3980)

Company evidence submission for committee

May 2022

File name	Version	Contains confidential information	Date
ID3980 Axi-cel for 3L DLBCL_CDF review submission v1.0_REDACTED	**V1.0**	Yes	6 May 2022

Instructions for companies

This is the template you should use for your evidence submission to the National Institute for Health and Care Excellence (NICE) as part of the Cancer Drugs Fund (CDF) review process. This document will provide the appraisal committee with an overview of the important aspects of your submission for decision-making.

This submission should not be longer than 25 pages, excluding the pages covered by this template. If it is too long it will not be accepted.

If applicable provide any supportive and detailed methodological or investigative evidence (additional to the clinical trial and/or Systemic Anti-Cancer Therapy data) in an appendix to this submission.

When cross referring to evidence in the original submission or appendices, please use the following format: Document, heading, subheading (page X).

For all figures and tables in this summary that have been replicated, cross refer to the evidence from the main submission or appendices in the caption in the following format: Table/figure name – document, heading, subheading (page X).Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Tables and figures

Cancer Drugs Fund review submission

A.1 Background

As per the terms of engagement document:

- Axicabtagene ciloleucel is recommended for use within the Cancer Drugs Fund (CDF) as an option for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after two or more systemic therapies, only if the conditions in the managed access agreement are followed
- Incremental cost-effectiveness ratios (ICERs) presented to the Committee included a [redacted] This equates to an overall discount of [redacted]
- The Committee's preferred ICER was between the company's base case of [redacted] per quality-adjusted life year (QALY) gained and the Evidence Review Group (ERG) upper-bound base case of [redacted] per QALY gained versus salvage chemotherapy. The ERG ICER used the ERG's alternative analysis and the combined costing approach (considering the use of higher proportion of post-treatment autologous stem cell transplants, a cure assumption at 5 rather than 2 years, intravenous immunoglobulins [IVIG] use for 3 years and the use of the intention-to-treat population) with a generalised gamma distribution for overall survival (OS) for salvage chemotherapy
- The Committee agreed that axicabtagene ciloleucel met end-of-life criteria and therefore is plausibly cost-effective. The Committee accepted that, although there was significant uncertainty in the cost-effectiveness estimates, many of the assumptions in the company's base case appear plausible and might be verified through further data collection
- The Committee's key uncertainties were the OS estimates for axicabtagene ciloleucel, the convergence of OS and progression-free survival (PFS), and post-treatment intravenous immunoglobulin use. The Committee agreed that more mature trial data would reduce uncertainty in these factors. It was anticipated at the start of data collection that Medical Data Solutions and

Services (MDSAS) would provide data for IVIG use in the National Health Service (NHS). Subsequently, it was established that IVIG use in the NHS would be provided by the NHS Blueteq System

A.2 Key committee assumptions

Table 1: Key committee assumptions as per the terms of engagement

Area	Committee-preferred assumptions
Population	The final scope stated the population as adults with relapsed or refractory DLBCL, PMBCL or transformed follicular lymphoma. The Committee acknowledged that the marketing authorisation for axicabtagene ciloleucel (axi-cel) specifies its use after two or more systemic therapies so agreed it could not consider people whose disease had relapsed after one systemic therapy, including those who are unable to have an ASCT as axi-cel would not be used as an alternative to ASCT. The Committee concluded that axi-cel would be positioned as a treatment option for people: • Whose disease did not respond after two systemic therapies or • Whose disease relapsed after one systemic therapy and who would be able to have an ASCT as part of a second treatment, but whose disease does not respond to salvage chemotherapy or • Whose disease has relapsed after one systemic therapy, and who have had chemotherapy and ASCT but whose disease has relapsed again Since ZUMA-1 began (the key trial) the World Health Organization's definition of follicular lymphoma has been expanded to include the transformed follicular lymphoma population. The Committee concluded that patients in ZUMA-1 were representative of the various subgroups who would be eligible for the technology in the NHS. **Adults with relapsed or refractory DLBCL, PMBCL or transformed follicular lymphoma who have had two or more systemic therapies are the relevant population for the CDF review.**
Comparator	The Committee noted that salvage chemotherapy is the available treatment option for the three positions in the treatment pathway where axi-cel would most likely be used. The company had

Area	Committee-preferred assumptions
	excluded pixantrone as a comparator and clinical experts agreed that it is rarely used in clinical practice. **The company should present clinical and cost-effective evidence for axi-cel compared with salvage chemotherapy, excluding pixantrone.**
Indirect treatment comparison	As ZUMA-1 is a single-arm study, an indirect treatment comparison was needed to establish the relative effectiveness of axi-cel. The company used SCHOLAR-1, a retrospective study with pooled data from four datasets (N = 636), to compare axi-cel with salvage chemotherapy. There were differences in study populations between ZUMA-1 and SCHOLAR-1. The Committee noted that SCHOLAR-1 included patients with primary refractory disease and had less advanced disease. The Committee also noted the relatively high proportion of people who had SCT post-treatment in SCHOLAR-1. These patients would not be eligible for axi-cel and are likely to have better outcomes than people who are only receiving salvage chemotherapy. This makes the comparison between the two studies uncertain. The company adjusted the SCHOLAR-1 dataset to be more reflective of ZUMA-1 and UK practice. This analysis excluded patients with an ECOG performance status of 2–4 (patients must be performance status 0–1 in UK practice), patients with an unknown ECOG status and patients with primary refractory disease. This reduced the sample size from 562 to 133. The company also adjusted for the high rate of SCT and assumed 10% of people had a transplant after salvage chemotherapy. The Committee recognised the limitations given the reduced sample size but concluded it would consider this adjusted SCHOLAR-1 data in its decision-making. **The company should fully explore the most appropriate approach for establishing the relative effectiveness of axi-cel, utilising any data that has become available during the period of managed access.**
Sources of comparator data	The Committee considered alternative data sources to inform the salvage chemotherapy comparison. These included a subpopulation of the ORCHARRD study, standard of care data from the Haematological Malignancy Research Network, the CORAL study, and the Oxford audit dataset. The first two were not available to use in the appraisal because data was either owned by another company or the data would not be available within the appraisal timeframe.

Area	Committee-preferred assumptions
	CORAL was disregarded due to its similarity to SCHOLAR-1 and the Committee said the Oxford audit dataset was small and limited. **The Committee should use SCHOLAR-1 and any additional data that has become available during the period of managed access to inform the comparator arm.**
Subsequent treatments	Results from ZUMA-1 showed that only a small number of patients needed IVIG treatment for B-cell aplasia. B-cell aplasia is a likely consequence of treatment with axi-cel due to a decrease in serum immunoglobulin levels that is typically associated with CD19-targeted CAR T therapy. Experts explained that infection rates had been low in ZUMA-1 suggesting not all patients would need IVIG. The Committee concluded that the need for IVIG treatment remained unknown, so the effect of B-cell aplasia on mortality risk was uncertain. **The company should use more mature data from ZUMA-1, any data that has become available during the period of managed access, and data collected through Blueteq to inform the proportion of people who subsequently have IVIG, and the length of time this is required.**
Extrapolation of OS and PFS	Median OS was not reached in ZUMA-1 and survival data were immature. Using single parametric curves to model OS meant the curve for axi-cel crossed the curve for salvage chemotherapy and the Committee deemed this implausible because it did not reflect the trial data. The company's base case was a mixture cure model that included long-term remission for 50% of people having axi-cel and their exploratory analyses provided a cure fraction for OS of between 1% and 53%. Their preferred approach to model PFS was a single parametric curve and exploratory analyses using a mixture cure model for PFS produced cure fractions of 40% to 43%. The Committee deemed these uncertain. The ERG provided an analysis which incorporated post-progression treatment data from the company's model. This also suggested that the OS and PFS curves would converge. Experts said it was clinically plausible that a small proportion of people could have long-term survival if they relapsed after axi-cel. However, the difference in PFS and OS is more likely a result of the immature data. The company stated that a later data cut of ZUMA-1 supported their base case model and the curves had not converged. However, without seeing these data the Committee agreed that uncertainty remained.

Area	Committee-preferred assumptions
	The company provided updated data on the 10 patients who had retreatment with axi-cel. The Committee concluded that retreatment adds to the uncertainty around the long-term survival for people who had axi-cel. The Committee acknowledged that future data cuts are planned for ZUMA-1 and that these may provide more certainty in the survival extrapolation modelling. **The company should use the latest data cut from ZUMA-1 to inform the survival outcomes and SACT dataset to validate the trial outputs.**
Cure assumption	The company's original model assumed people who were alive after 2 years in the pre-progression state were functionally cured and they reverted to age-matched general population mortality. The Committee recalled the ERG's hybrid approach which assumed that people reverted to age-matched general population mortality only after the crossing of the OS and PFS curves at around 52 months. The Committee concluded that the company's cure assumption at 2 years was optimistic and the assumption of no excess mortality risk for functionally cured patients compared with the general population was not appropriate. However, it had little effect on the cost-effectiveness results. **The company should fully explore assumptions of cure using the more mature ZUMA-1 data and other updated data that has become available during the period of managed access.**
Most plausible ICER	The company's base case ICER was [redacted] per QALY gained compared with salvage chemotherapy. The ERG's upper-bound base case ICER was [redacted] per QALY gained compared with salvage chemotherapy. The ICERs in all the company's scenario analyses were lower than £50,000 per QALY gained. Of the ERG's scenario and exploratory analyses, some ICERs fell above and some below the £50,000 per QALY gained. The Committee agreed that the most plausible ICER is between the company's and the ERG's revised base case estimates. This is because of the uncertainty around OS and PFS of axi-cel, the correct incorporation of costs for post-treatment SCTs, the cure assumptions and the use of the intention-to-treat population. **The Committee agreed that axi-cel demonstrated plausible potential to be cost-effective.**

Area	Committee-preferred assumptions
End of life	Axi-cel meets the end-of-life criteria.

Key: ASCT, autologous stem cell transplant; CAR T, chimeric antigen receptor therapy; CDF, Cancer Drugs Fund; CORAL, Collaborative Trial in Relapsed Aggressive Lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; IVIG, intravenous immunoglobulins; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; QALY, quality-adjusted life year; SACT, Systemic Anti-Cancer Therapy; SCT, stem cell transplant.

A.3 Other agreed changes

As per the terms of engagement document:

- The company should not alter the decision-problem, submit additional evidence or make further alterations to the model during the CDF review period unless NICE requests or agrees to this in advance

A.4 The technology

Table 2: Technology being reviewed

UK approved name and brand name	Axicabtagene ciloleucel (axi-cel) (Yescarta®)
Mechanism of action	Axi-cel is an autologous anti-CD19 CAR T-cell product, that recognises and eliminates all CD19-expressing target cells, including B-cell malignancies and normal B-cells. To produce axi-cel, patient T-cells are extracted via leukapheresis and activated with IL-2 and an anti-CD3 monoclonal antibody (mAb), and then transduced with the anti-CD19 CAR transgene-containing γ-retroviral vector. The anti-CD19 CAR construct comprises the following domains: an anti-human CD19 single-chain variable region fragment (scFv); the partial extracellular domain and complete transmembrane and intracellular signalling domains of human CD28, a lymphocyte co-stimulatory receptor that plays an important role in optimising T-cell survival and function; and the cytoplasmic portion, including the signalling domain, of human CD3ζ, a component of the T-cell receptor complex.[1] The transduced T-cells are then expanded for

	several days in the presence of IL-2, washed, and cryopreserved to generate the anti-CD19 CAR T-cell product. Following infusion of axi-cel into the patient, the anti-CD19 region of axi-cel binds to CD19, an antigen expressed on the cell surface of the target B-cell malignancies as well as normal B-cells. Following engagement with CD19-expressing target cells, the CD3ζ domain activates the downstream signalling cascade that leads to T-cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. The intracellular signalling domain of CD28 provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including IL-2 production.[2] Together, these signals act in concert resulting in proliferation of the axi-cel CAR T-cells and apoptosis and necrosis of the CD19-expressing target cells. In addition, activated T-cells secrete cytokines and other molecules that can recruit and activate additional anti-tumour immune cells.[3]
Marketing authorisation/CE mark status	Axi-cel received a marketing authorisation valid throughout the EU on 23 August 2018.This states that axi-cel 'is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy'.
Indications and any restriction(s) as described in the summary of product characteristics	As above.
Method of administration and dosage	A single dose of axi-cel contains 2 x 10^6 CAR-positive viable T-cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T-cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag. The availability of axi-cel must be confirmed before starting the lymphodepleting regimen. <u>Pre-treatment (lymphodepleting chemotherapy)</u> • A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m2 intravenous and fludarabine 30 mg/m2 intravenous should be administered on the 5th, 4th, and 3rd day before infusion of axi-cel <u>Pre-medication</u> • Paracetamol 500–1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour before axi-cel infusion is recommended • Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of axi-cel

	Monitoring • Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities. Physicians should consider hospitalisation for the first 10 days post-infusion or at the first signs or symptoms of CRS and/or neurological events • After the first 10 days following the infusion, the patient should be monitored at the physician's discretion • Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion Administration • For autologous use only • At least 1 dose of tocilizumab for use in the event of CRS and emergency equipment must be available prior to infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Medicines & Healthcare products Regulatory Agency (MHRA) Central Alerting System, suitable alternative measures to treat CRS instead of tocilizumab must be available before infusion takes place • A leucodepletion filter must not be used • Central venous access is recommended for the administration of axi-cel • Verify the patient ID again to match the patient identifiers on the axi-cel bag • Prime the tubing with 0.9% sodium chloride solution (0.154 mmol sodium per mL) prior to infusion • Infuse the entire contents of the axi-cel bag within 30 minutes by either gravity or a peristaltic pump • Gently agitate the bag during axi-cel infusion to prevent cell clumping • After the entire contents of the bag is infused, rinse the tubing at the same infusion rate with 0.9% sodium chloride solution (0.154 mmol sodium per mL) to ensure all axi-cel is delivered
Additional tests or investigations	No additional tests or investigations are needed.
List price and average cost of a course of treatment	£280,451 is the average price of a course of treatment.
Commercial arrangement (if applicable)	A PAS has been conditionally approved and comprises a simple discount of [redacted] to the axi-cel list price.

Date technology was recommended for use in the CDF	December 2018
Data collection end date	February 2022
Key: CAR, chimeric antigen receptor; CDF, Cancer Drugs Fund; CRS, cytokine release syndrome; PAS, patient access scheme.	

A.5 Clinical effectiveness evidence

Table 3: Primary source of clinical effectiveness evidence

Study title	**ZUMA-1**	**SACT data cohort study**
Study design	ZUMA-1 is an ongoing Phase I/II multicentre, open-label study.	SACT data cohort study.
Population	Adults with aggressive B-cell NHL (DLBCL, PMBCL, and TFL) that was either refractory to treatment or had relapsed ≤ 12 months after ASCT.	Adults with relapsed or refractory DLBCL and PMBCL, after two or more lines of systemic therapy, and TFL after one or more lines of systemic therapy.
Intervention(s)	Axicabtagene ciloleucel. A single infusion of CAR-transduced autologous T-cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg.	Axicabtagene ciloleucel.
Comparator(s)	Not applicable.	Not applicable.
Outcomes collected that address Committee's key uncertainties	• **Overall survival** • **Progression-free survival** • IVIG usage	• Overall survival • IVIG usage*
Key: CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; IVIG, intravenous immunoglobulin; NHS, National Health Service; PMBCL, primary mediastinal B-cell lymphoma; SACT, Systemic Anti-Cancer Therapy; TFL, transformed follicular lymphoma. **Notes:** *Real-world IVIG usage data not available at the time of submission. To be provided post-submission.		

The primary data source for informing the long-term OS estimates in the model was the updated 60-month data cut from ZUMA-1. The generalisability of these data is supported by the OS data collected from Systemic Anti-Cancer Therapy (SACT).

To inform the long-term PFS estimates in the model, the 24-month data cut from ZUMA-1 data was used.

Per the terms of engagement, real-world IVIG usage data from Blueteq will become available to inform the proportion of people who have IVIG following axi-cel, and the length of time this is required. As this is not available in time for the submission, IVIG data from ZUMA-1 were used in the model instead; this was consistent with real-world experience and validated by clinical expert opinion.

The ZUMA-1 OS, PFS and IVIG usage data informing the economic model are discussed in more detail in Section A.6.1 and the SACT OS data are discussed in Section A.6.2

A.6 Key results of the data collection

A.6.1 ZUMA-1

The latest data cut of the ZUMA-1 study (11 August 2021) includes 60 months' minimum follow-up.[4] Herein, this is referred to as the 60-month data cut. Consistent with the original submission, TA559[5], all survival analyses for axi-cel were conducted using the modified intent-to-treat (mITT) population from combined Phase I and II of ZUMA-1 (N = 108; i.e. those patients who received at least 1 x 10^6 anti-CD19 CAR T-cells/kg body weight).

From the 60-month data cut, in the Phase I (N = 7) and Phase II (N = 101) populations, the median potential follow-up duration from axi-cel infusion was [redacted] months and [redacted] months, respectively. The median actual follow-up, defined as the time from axi-cel infusion to the date of death or the last date known alive, was [redacted] months in Phase I and [redacted] months in Phase II. OS and OS by objective response were collected to address key uncertainties raised in the original submission.

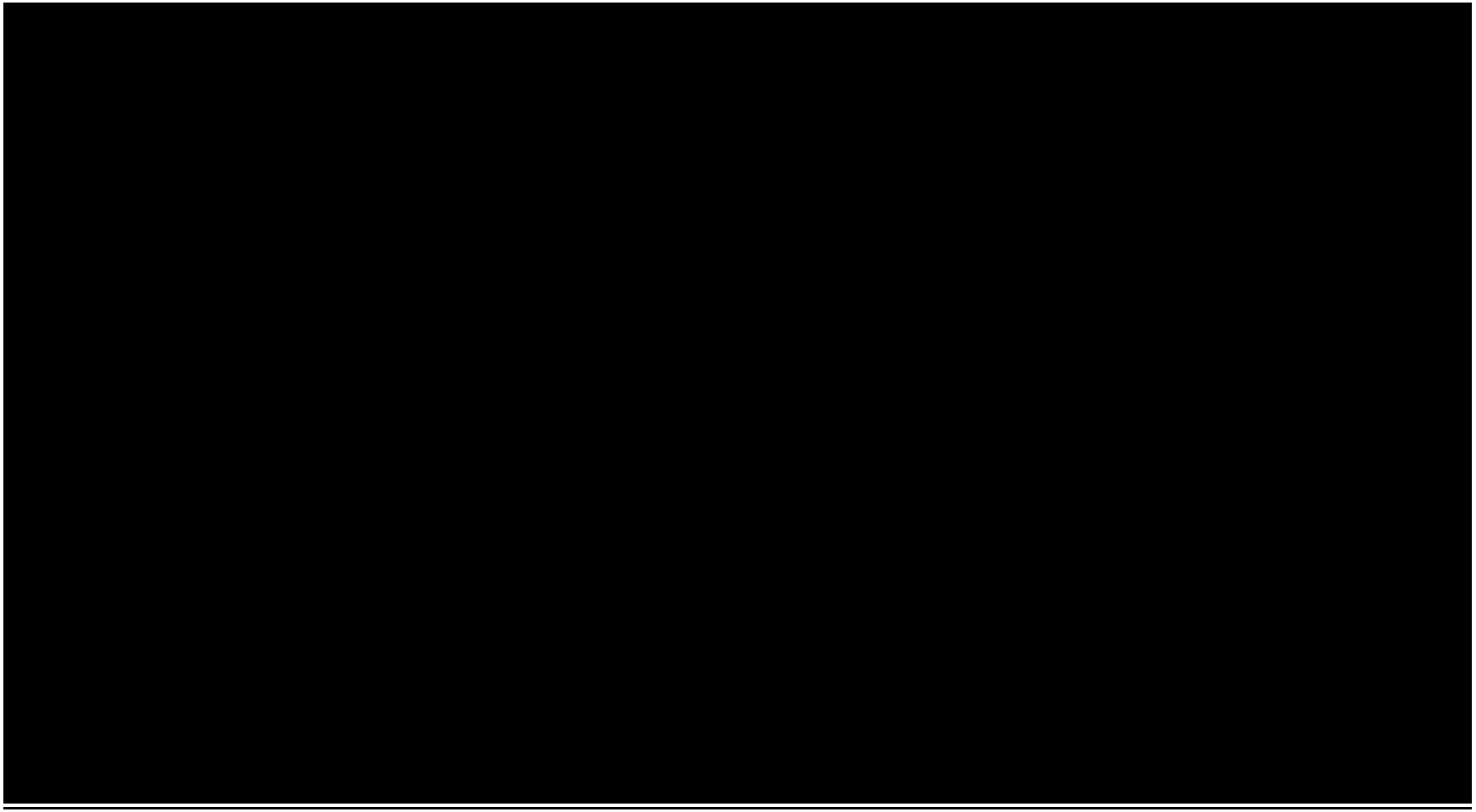
Overall survival

Figure 1 presents the Kaplan–Meier curve for OS, with a median OS of [redacted] months (95% confidence interval [CI], [redacted]). At the time of data cut-off providing a

maximum actual follow-up of [redacted] months, [redacted] patients ([redacted]%) had died. Estimated OS rates at specific time points are presented in Table 4.

The longer-term data continues to support the hypothesis that a proportion of patients receiving axi-cel will experience long-term remission and survival. This is evidenced by the plateau observed in Figure 1 and is expected based on the mechanism of action of axi-cel and expert opinion from clinicians, provided in the original submission.[6]

Figure 1: ZUMA-1 overall survival in the Phase I and II modified intent-to-treat population (N = 108, 11 August 2021 data cut)



Key: CI, confidence interval.
Source: ZUMA-1 60-month data cut.[4]

Table 4: ZUMA-1 survival rate by Kaplan–Meier estimation in the Phase I and II modified intent-to-treat population (N = 108, 11 August 2021 data cut)[4]

Time point	Survival rate by Kaplan–Meier estimation	
	Phase I (N = 7)	Phase II (N = 101)
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]

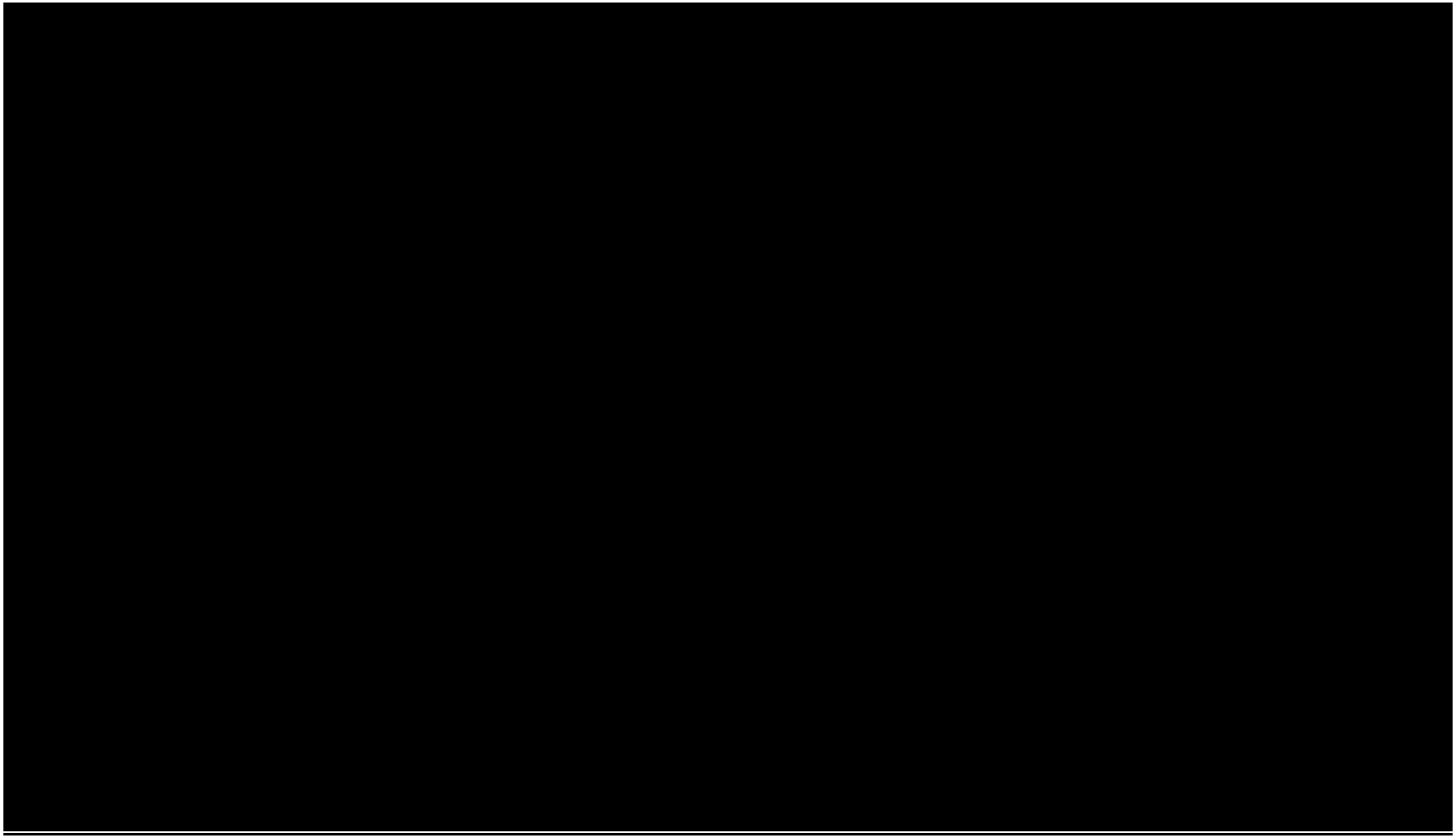
Among patients who achieved a complete response (CR) (N = [redacted]), the estimated 60-month survival rate was [redacted]% in Phase I and [redacted]% in Phase II.

Overall survival by best objective response

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

Figure 2 presents OS by best objective response and shows a substantial extension to life for patients experiencing a CR to axi-cel treatment (compared with patients experiencing a partial response [PR]).

Figure 2: ZUMA-1 overall survival by best overall response group in the Phase I and II modified intent-to-treat population (N = 108, 11 August 2021 data cut)



Key: CI, confidence interval.
Source: ZUMA-1 60-month data cut.[4]

Progression-free survival

Per the ZUMA-1 study protocol, there was no protocol-defined mandate to collect progression data beyond 24 months. Instead, this assessment was done per institutional standard of care. Therefore, any PFS data collected beyond 24 months may not be consistent with the criteria applied in ZUMA-1. For this reason, PFS data collected up to month 24 is presented here and used in the economic model.[7]

Figure 3 shows that the median PFS for the mITT population was [redacted] months after a median potential follow-up of [redacted] months in Phase I and [redacted] months in Phase II, using investigator assessment as defined by IWG criteria. Median actual follow-up was [redacted] months in Phase I and [redacted] months in Phase II.

Consistent with the latest ZUMA-1 OS data, the observed PFS curve plateaus and continues to support the hypothesis that a proportion of patients receiving axi-cel will experience long-term remission. Although the follow-up is limited, it is anticipated that patients remaining progression-free for 2 years are likely to remain progression-free in the long-term.[8] This was validated by UK clinical expert opinion and is also supported by UK real-world data from 298 CAR T-cell therapy infused patients (N = 222 axi-cel, N = 76 tisagenlecleucel) treated between February 2019 – January 2021, which found that 97.5% of progressions occurred by month 6.[9]

Figure 3: ZUMA-1 progression-free survival in the Phase I and II modified intent-to-treat population (N = 108, 11 August 2018 data cut)

Key: CI, confidence interval.
Source: ZUMA-1 24-month CSR.[7]

Intravenous immunoglobulins use

Data collected through Blueteq to inform the proportion of patients who have IVIG following axi-cel, and the length of time this is required is not available in time for the submission. Therefore, data from ZUMA-1 were considered.

ZUMA-1 is a controlled clinical trial environment where investigations/interventions are strictly adhered to according to defined protocol based on clinical management that is determined at the time of the study; this is therefore not necessarily entirely reflective of real-world clinical practice. Given the increased understanding of how to manage B-cell aplasia, which has evolved over time, and the advent of best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) on IVIG usage whereby IVIG is recommended only in patients with hypogammaglobulinemia and recurrent infections with encapsulated bacteria[10], the proportion of patients receiving IVIG is anticipated to be very low in NHS England clinical practice.

Considering the above, the proportion of patients receiving IVIG that was used in the original submitted economic model for TA559, [redacted], was used. This is consistent with the expected low rates in today's clinical practice, as confirmed by expert clinical opinion.[8] Furthermore, real-world data from Kings College Hospital on patients being treated with axi-cel or tisagenlecleucel for relapsed/refractory high-grade B non-Hodgkin lymphoma further supports the expectation of low IVIG usage in clinical practice, with three out of 53 patients (6%) reported to have received IVIG post-chimeric antigen receptor (CAR) T-cell therapy.[11]

Summary

The outcomes of the 60-month ZUMA-1 data cut remain consistent with those previously presented in the original submission and continue to demonstrate that patients receiving axi-cel have clinically meaningful OS and PFS.

The latest OS and PFS data continue to show an observed plateau, indicative of long-term, durable survival. No such survival curve plateau is observed with conventional immunochemotherapy treatment in this setting.

The depth of response in ZUMA-1 further supports an expectation of longer-term treatment benefit from axi-cel.

A.6.2 Systemic Anti-Cancer Therapy dataset

Systemic Anti-Cancer Therapy patient cohort

Two CDF applications are required for axi-cel. The initial application is made at the point of leukapheresis and manufacture of the CAR T-cells, and a subsequent application is required at the point of infusion of the CAR T-cells. It was not possible to collect reasons why any subsequent infusion application was not made following a leukapheresis application.

There were 507 CDF funding applications for leukapheresis between 7 December 2018 and 31 October 2021, relating to 501 unique patients. There were 358 CDF funding applications for axi-cel infusion for treating diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) between 7 December 2018 and 31 October 2021 in the NHS England and Ireland Blueteq database.[12] This relates to 336 unique patients after the exclusion of four duplicate applications and 18 patients who were registered at GP practices in either Scotland,

Wales or Northern Ireland. No patients received axi-cel infusion before the CDF start date.

Of the 336 new applications for CDF funding for axi-cel infusion in DLBCL and PMBCL, seven patients died before treatment started and 11 were missing from SACT, leaving 318 patients with a treatment record in SACT.

A summary of patient characteristics included in the SACT cohort is presented in the Appendix (Section A.16.1) alongside the ZUMA-1 population.

The patient characteristics are generally consistent across ZUMA-1 and the SACT cohort; in particular, the median age is very similar. One notable finding is the level of missing data from SACT on the Eastern Cooperative Oncology Group (ECOG) performance status. In the ZUMA-1 population, 58% of patients had an ECOG performance status of > 0; in the SACT cohort, this was 39%, but 37% had missing outcomes. The missing outcomes from SACT make a comparison to ZUMA-1 difficult.

A further limitation of the SACT data is that, in the initial period when axi-cel first became available, there was a trend towards consideration of CAR T-cell therapy for patients with heavily relapsed, very bulky and aggressive disease as a last-resort treatment option. Over time, however, the UK clinical community has learned to: (1) optimise patient selection through a positive evolution in the understanding of appropriate CAR T-cell therapy patients; (2) improve patient referrals and benefit from efficiencies in company manufacturing times for patients approaching their CAR T-cell therapy infusion; (3) benefit from the availability of better bridging therapy options for patients during the apheresis to infusion period; and (4) better understand toxicity management, which in turn allows for improved confidence in patient selection. A combination of these, among other factors, has led to an improvement in outcomes as reflected in the real-world evidence collected through the National CAR-T Clinical Panel.[13] Of note, however, the consolidated SACT data relates to patients treated both before and after these learnings were embedded into UK practice and, therefore, may not be truly representative of the overall current situation in today's UK clinical practice. It is therefore possible that in today's clinical practice, key determinants of patient selection for CAR T-cell therapies, such as

ECOG performance status, are likely to be more closely aligned with ZUMA-1 than the SACT data currently suggest.

Overall survival

Of the 318 patients with a treatment record in SACT, the minimum follow-up was four months (121 days) from the last CDF application. Patients were traced for their vital status on 3 March 2022; this date was used as the follow-up date (censored date) if a patient was still alive. The median follow-up time in SACT was 11.2 months (340 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 4 provides the Kaplan–Meier curve for OS, censored at 3 March 2022. The median survival was 28.5 months (N = 318).

Survival at 12 months was 64% [95% CI: 58%, 69%], survival at 24 months was 52% [95% CI: 45%, 58%] and 36-month survival was 45% [95% CI: 34%, 55%]. A comparison of survival from the SACT cohort with the modelled ZUMA-1 population is provided in Table 5.

Figure 4: Kaplan–Meier survival plot of overall survival from Systemic Anti-Cancer Therapy (N = 318)

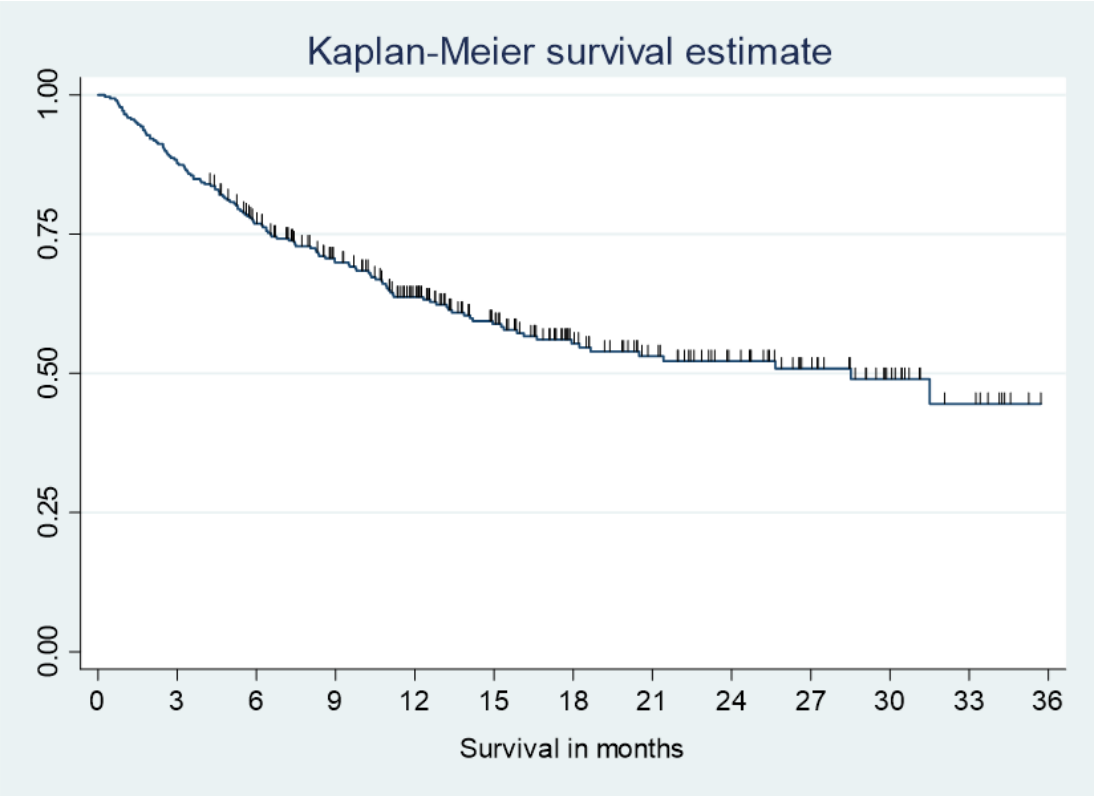


Table 5: Comparison of ZUMA-1 and SACT survival, at specified time intervals

Time point	ZUMA-1 survival rate by Kaplan–Meier estimation		SACT dataset overall survival
	Phase I (N = 7)	Phase II (N = 101)	
6 months	[redacted]	[redacted]	77%
12 months	[redacted]	[redacted]	64%
18 months	[redacted]	[redacted]	55%
24 months	[redacted]	[redacted]	52%
30 months	[redacted]	[redacted]	49%
36 months	[redacted]	[redacted]	45%
Key: SACT, Systemic Anti-Cancer Therapy. **Notes:** Comparison made with ZUMA-1 Phase I and II modified intent-to-treat population (N = 108, 11 August 2021 data cut)[4]			

Summary

In general, comparing the patient characteristics supports the view that the patients treated in ZUMA-1 are reflective of patients eligible for CAR T-cell therapy in NHS England clinical practice.

When comparing the OS for the SACT cohort with the OS from ZUMA-1, although the follow-up from SACT is much more limited, it is evident that the outcomes are similar. Comparing median survival for SACT (28.5 months) and ZUMA-1 ([redacted] months), the outcomes for the SACT cohort are slightly better. As discussed above, these findings may be due to differences such as the use of bridging therapy in clinical practice, which is anticipated to reduce tumour burden and thus improve patient outcomes[8], and an improved understanding of appropriate patient selection and toxicity management over time.

A.7 Evidence synthesis

A.7.1 SCHOLAR-1

ZUMA-1 was conducted as a single-arm study, which makes comparison to salvage chemotherapy difficult. The Committee previously identified SCHOLAR-1 as the most relevant source of comparator data for decision-making. Given the heterogeneity between the patient populations for relevant comparator treatments (where the majority of patients have received only one prior line of therapy), as outlined in the original submission, the availability of patient-level data to account for differences between patient characteristics and key prognostic factors was considered more rigorous and allowed a more appropriate comparison.

The SCHOLAR-1 study was conducted using data from four sources for which patient-level data were available: MD Anderson Cancer Centre (MDACC) database; Mayo Clinic and University of Iowa (MC/IA) Specialized Programs of Research Excellence (SPORE) database; the National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) randomised Phase III study LY.12; and the French Lymphoma Academic Research Organisation (LYSARC) randomised Phase III Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study. The availability of patient-level data allowed for patients to be included that more closely

matched the patient population of ZUMA-1 and for adjustments to be made to account for any differences.

The approach to modelling outcomes for the salvage chemotherapy arm has not changed given: 1) the strengths of the SCHOLAR-1 study; 2) the Committee consensus previously on the study being the most appropriate source, and the approach used to analyse the data from the source and; 3) that, via the CDF, use of CAR T-cell therapies for DLBCL after two or more treatment lines has become so established that trying to find a newer data source to model the counterfactual of a 'world' without these therapies being available is unfeasible.

Acknowledging, however, the uncertainties around the indirect comparison and comparator data source that were highlighted by the Committee in the terms of engagement document, a targeted PubMed search using keyword searches was conducted to identify additional sources of comparative data published since September 2018. The search identified three publications that provided outcomes of salvage chemotherapy in the relapsed or refractory setting. Of these studies, only one (Radford et al. 2019) was based in the UK. Given this was published as an abstract only, the available information to allow a comparison to SCHOLAR-1 was extremely limited. However, in the third-line setting, a median OS of 195 days (6.4 months) was reported, further supporting the extremely poor outcomes in patients treated with salvage chemotherapy. A comparison of the baseline characteristics across the identified studies with ZUMA-1 and SCHOLAR-1 is presented in Appendix A.16.2

Modelled salvage chemotherapy: adjustment of the SCHOLAR-1 cohort

As described in Gilead's appraisal consultation document (ACD) response, SCHOLAR-1 was adjusted to ensure comparability with the ZUMA-1 population. The following steps were taken to do this:

- Patients with an ECOG 2–4 and an unknown ECOG status were excluded, consistent with the ERG-preferred approach
- Primary refractory patients were excluded, consistent with the marketing authorisation

- The resulting OS curve was adjusted to reflect outcomes for a population in which 10% of patients underwent subsequent stem cell transplant (SCT)

Regarding the adjustment for SCT, the 10% estimate was based on clinical opinion (CDF discussions and tisagenlecleucel appraisal meeting) that approximately 10% of patients would receive SCT in clinical practice after undergoing two or more lines of systemic treatment.[14, 15]

To adjust the OS for SCT, separate survival curves were used to generate a weighted survival estimate based on whether or not patients had received an SCT. This approach was consistent with the ERG's approach outlined in the NICE ACD slides for tisagenlecleucel-T DLBCL appraisal (TA567).[14]

Figure 5 presents the Kaplan–Meier and selected parametric curves (generalised gamma) for the non-SCT and SCT populations (SCHOLAR-1 with ECOG 2–4 and unknowns and primary refractory patients excluded) and the derived curve fit for the base case 10% SCT population.

The generalised gamma model was selected based on the Committee's commentary in the final appraisal determination (FAD): 'The Committee concluded that a single parametric survival model applying a generalised gamma distribution curve to OS data was the most clinically plausible extrapolation and was appropriate to model salvage chemotherapy'.[16]

Figure 5: Overall survival of salvage chemotherapy: SCHOLAR-1 (ECOG 0–1 only and excluding primary refractory) with 10% stem cell transplant

Key: ECOG, Eastern Cooperative Oncology Group; SCT, stem cell transplant.

A.8 Incorporating collected data into the model

A.8.1 Overall survival

In the initial NICE submission FAD[16], the Committee noted that using single parametric survival curves to model OS for axi-cel produced clinically implausible results. Therefore, mixture cure models were used in the original submission base case as an alternative, more flexible approach that better accounted for the complex hazard functions observed in the data.

Since the original NICE submission, the NICE Decision Support Unit (DSU) has published the Technical Support Document 21 (TSD 21) with guidance on the use of flexible methods for survival analysis.[17] The document notes that, given the advent of immunotherapy treatments in oncology, there is an increase in complex survival models and complex hazard functions due to the delayed response to treatment and the existence of long-term survivors. The document therefore discusses a variety of survival modelling approaches that may be more appropriate to use (than standard parametric models) when hazard functions are complex.

Of the model types discussed in TSD 21 and based on the modelling approaches used in CAR T-cell therapy submissions to date, the mixture cure models and flexible parametric models (i.e. spline-based models) are considered the most appropriate. Therefore, both approaches have been included in the current economic model and are discussed further below. Detail around the standard parametric models is included in Appendix A.16 , for completeness; however, consistent with the Committee's conclusions in the TA559 FAD, these are not considered to be an appropriate method for modelling axi-cel OS.

A recent study by Vadgama et al. (2021)[18] looked at applying different survival extrapolation methods to four ZUMA-1 data snapshots with increasing follow-up data. The aim of the study was to empirically test which methods most accurately predicted long-term survival data when fitted with early data cuts (e.g. 12 month data cut). Consistent with the conclusions in the TA559 FAD, the study found that the standard parametric models generally did not fit the ZUMA-1 data well, across each data snapshot, and the models were shown to consistently, and in some cases considerably, underestimate OS even with more mature data from ZUMA-1. Conversely, relative to the standard parametric models, the spline-based models provided a better visual fit to the Kaplan–Meier estimates. However, the ability of these models to accurately project survival based on later data snapshots was limited; the models did not reflect the expected plateau, which was not fully established in the earlier data snapshots of ZUMA-1. The study found that the cure-based models provided the best fit to the observed data, both visually and empirically using a variety of metrics. This is also supported by more recent findings, reported in a poster, showing that the mixture cure models continued to produce similar ICERs at earlier ZUMA-1 data cuts when compared with mixture cure models fitted to the 60-month ZUMA-1 data.[19]

A further recommendation from TSD 21 is that background mortality should be incorporated into survival models to avoid 'extremely implausible' projections. Therefore, to account for background population mortality consistently across the models, a relative survival framework has been adopted, which considers the age- and sex-matched hazard rate of the general population when extrapolating survival.[17]

Mixture cure models

As discussed above, mixture cure models represent a flexible approach to modelling OS for axi-cel that can potentially account for more complex hazard functions. These models were used in the original submitted base case and can be beneficial over alternative options where there is evidence to support that a proportion of patients have more favourable outcomes (i.e. experience long-term survivorship) following treatment, and a proportion do not. The observed continued plateau in OS from the 60-month ZUMA-1 data is strong evidence to support this.

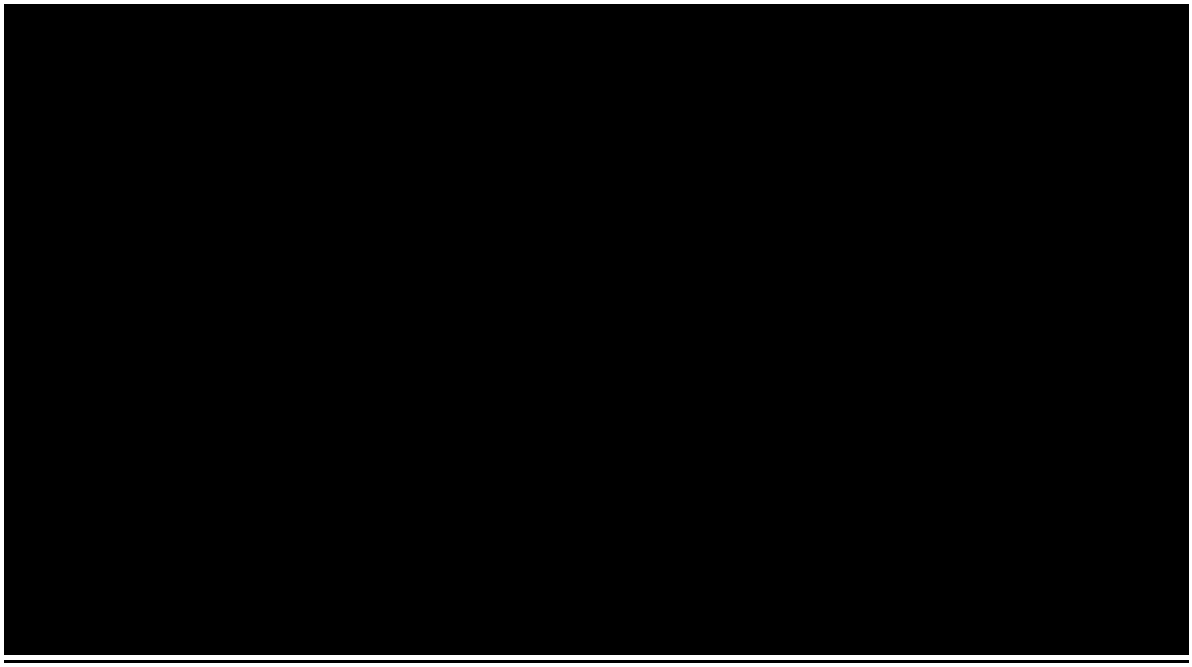
Combining the estimated long-term survivor fraction (Table 6), age- and gender-matched mortality for the proportion of patients who experienced long-term survivorship, and the fitted parametric patients for the proportion of patients who did not, Figure 6 presents the overall estimated OS for each mixture cure model compared with the ZUMA-1 OS Kaplan–Meier data. Additionally, corresponding smoothed hazard plots are presented in Figure 7, while Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics and landmark estimates are presented in Table 7.

By assessing the visual fit of the mixture cure models, all appear to provide a good fit to the observed data, and all models produce similar long-term survival projections. These projections capture the observed and anticipated plateau in the OS Kaplan–Meier plot. Due to the visual similarities of the models, the base case model was selected based on providing the best statistical goodness-of-fit; this was the log-logistic model and was therefore selected for the base case.

Table 6: Axi-cel overall survival: mixture cure model cure fractions

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

Figure 6: Axi-cel overall survival: mixture cure models



Key: MCM, mixture cure model; OS, overall survival.

Figure 7: Axi-cel overall survival: mixture cure model smoothed hazard plots

Key: MCM, mixture cure model.

Table 7: Axi-cel overall survival: mixture cure model AIC and BIC statistics

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

Key: AIC Akaike information criterion; BIC, Bayesian information criterion.
Note: Bold values represent statistical best fit.

Spline-based models

In TSD 21, spline-based models are referred to as flexible parametric models which 'use restricted cubic splines to enable hazard and survival functions with complex shapes to be accurately modelled'.[17] As discussed above, the strong biomedical rationale, good statistical fit and clinical plausibility of the long-term projections associated with the mixture cure model renders the approach suitable for use in the model base case. Between the simplicity of the standard parametric models and the flexibility of the mixture cure models, the cubic spline models were not considered to add value to the analysis. However, in recognition of the guidance in TSD 21[17], these have been modelled as a scenario.

Figure 8 presents the axi-cel survival curves for one, two, and three knots. Additionally, corresponding smoothed hazard plots are presented in Figure 9, while AIC and BIC statistics and landmark estimates are presented in Table 8.

By assessing the visual fit of the spline-based models, all appear to provide a good fit to the observed data, and all models produce similar long-term survival projections. These projections capture the observed and anticipated plateau in the OS Kaplan–Meier plot, albeit to a lesser extent compared with the mixture cure models. Based on combined AIC and BIC scores, the two knot(s) normal spline was the best fitting, and therefore tested in a scenario analysis.

Figure 8: Axi-cel overall survival: spline-based models

Figure 9: Axi-cel overall survival: spline-based model smoothed hazard plots

Table 8: Axi-cel overall survival: spline-based model AIC and BIC statistics

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

Key: AIC Akaike information criterion; BIC, Bayesian information criterion.
Note: Bold values represent statistical best fit.

A.8.2 Progression-free survival

In the original submission, a standard Gompertz parametric model was used in the base case for axi-cel PFS. This was also the model selected in the ERG base case. Given this, standard parametric models fitted to the 24-month PFS data are explored and presented in this section.

However, noting the TSD 21 guidance around the use of flexible modelling approaches to better capture complex hazards, as discussed in Section A.8.1 , mixture cure models and spline-based models have also been explored. These are provided in Appendix A.16.4.

Consistent with the approach for OS, a relative survival framework has been used for each of the PFS model approaches.[17]

Standard parametric curves

The standard six parametric models are graphically represented alongside ZUMA-1 PFS Kaplan–Meier data in Figure 17, with corresponding smoothed hazard plots presented in Figure 18. AIC and BIC statistics are presented in Table 9.

The standard parametric models all appear to provide varying levels of visual fit to the observed data, and all models produce differing long-term survival projections. Consistent with the original submitted model, only the Gompertz distribution captures

the observed and anticipated plateau in the PFS Kaplan–Meier plot. Based on statistical goodness-of-fit, this was also the best-fitting model. The Gompertz model was therefore selected for the base case.

Figure 10: Axi-cel progression-free survival: standard parametric curves

Key: PFS, progression-free survival.

Figure 11: Axi-cel progression-free survival: standard parametric model smoothed hazard plots

Table 9: Axi-cel progression-free survival: standard parametric curve AIC and BIC statistics

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

Key: AIC Akaike information criterion; BIC, Bayesian information criterion.
Note: Bold values represent statistical best fit.

A.8.3 Final model overall survival and progression-free survival projections

Following model selection, Figure 12 presents the selected base case models used for estimating OS and PFS for axi-cel; these were the log-logistic mixture cure models and the Gompertz standard parametric model, respectively.

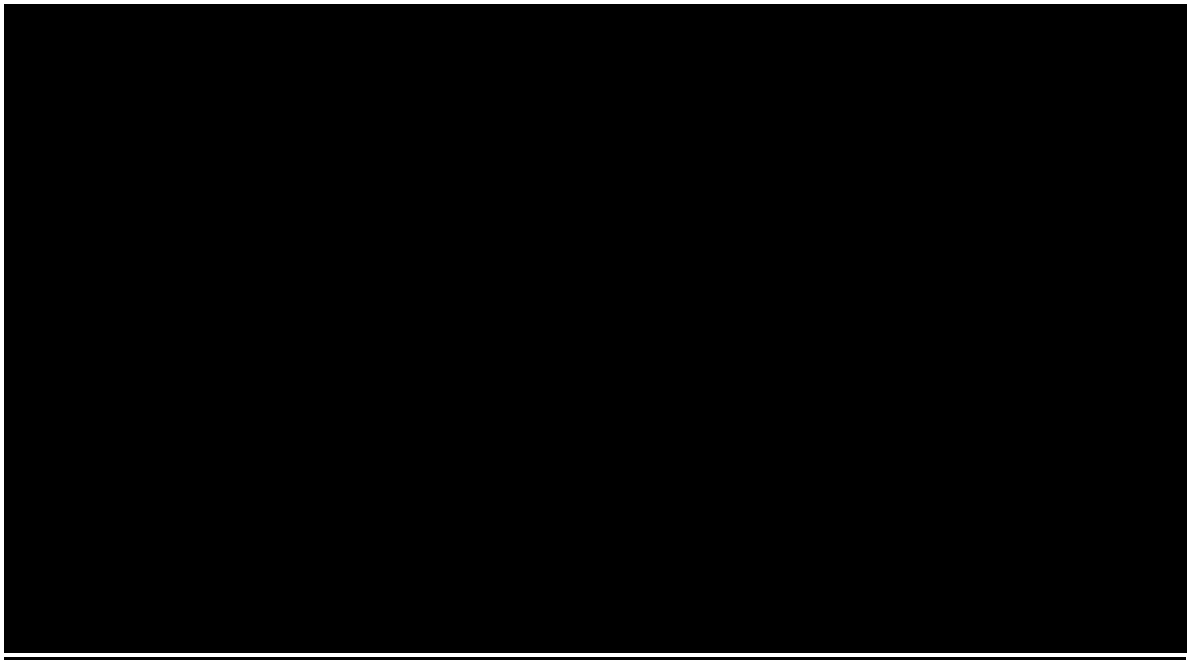
Figure 13 summarises lifetime base case projections of OS and PFS, across model arms, using the selected data and assumptions described throughout Sections A.7 and A.8.

Consistent with the Committee's preferred base case[16], standardised-mortality-ratio-adjusted general population mortality is applied to patients in both treatment arms who were alive after 60 months. This is therefore reflected in the OS curves for axi-cel and salvage chemotherapy.

These figures illustrate the data-driven expectations of patient benefit offered by axi-cel versus salvage chemotherapy are indicated for relapsed or refractory DLBCL and PMBCL after two or more lines of systemic therapy.

It is plausible that this long-term survivorship is largely attributable to the [redacted]% of patients receiving allogeneic SCT following axi-cel in ZUMA-1. This is consistent with UK real-world data, which found that 11 out of 298 (3.7%) patients received allogeneic SCT as treatment post CAR T-cell infusion, resulting in >90% survival at 12 months post-progression.

Figure 12: Base case overall survival and progression-free survival projections for axi-cel, alongside ZUMA-1 Kaplan–Meier data



Key: K-M, Kaplan Meier; OS, overall survival; PFS, progression-free survival.

Figure 13: Base case lifetime overall survival and progression-free survival projections for axi-cel and salvage chemotherapy

Key: K-M, Kaplan Meier; OS, overall survival; PFS, progression-free survival.

A.8.4 Intravenous immunoglobulins use

Per the original submitted model, it was assumed that [redacted]% of patients receiving axi-cel infusion would require IVIG treatment for a duration of 12 months. This was based on the ZUMA-1 clinical study report and assumptions.

A.9 Key model assumptions and inputs

Analyses were conducted using the Committee's preferred assumptions from the original submission but using the more mature ZUMA-1 OS and PFS data. The 'original' assumptions, provided in Table 10, describe the latest model that was considered by the Committee and discussed in Gilead's ACD response.

The more mature (60 month) data from ZUMA-1 provide additional evidence that the assumptions and survival extrapolations used in the original submission were appropriate.

Table 10: Key model assumptions and inputs

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Overall survival [B.4.2.6.2 (pg77)]	Survival analysis followed TSD 14 guidance	Relative survival framework used in updated survival analysis, per TSD 21.	Following updated guidance, as per TSD 21
Progression-free survival [B.4.2.6.3 (pg84)]			
Overall survival [B.4.2.6.2 (pg77)]	The Weibull mixture cure model was used in the base case analysis of OS for axi-cel	The log-logistic mixture cure model is used in the updated base case analysis of OS for axi-cel.	With the 60-month ZUMA-1 data, the goodness-of-fit statistics identified log-logistic as the best fitting curve. Note, overall variance across predicted survival was small
	The Gompertz model was used in the base case analysis of OS for salvage chemotherapy	The generalised gamma model is used in the base case analysis of OS for salvage chemotherapy.	This is consistent with the ERG and Committee-preferred base case, outlined in the FAD.[16]
Overall survival [B.4.2.6.2 (pg77)]	No SMR applied	SMR of 1.09 applied to patients in both treatment arms who were alive after 60 months to address the uncertainty of excess mortality for long-term survivors.	This is consistent with the ERG and Committee-preferred base case, outlined in the FAD.[16] The approach used is the same as that provided in the updated model, submitted after the first Appraisal Committee meeting
Progression-free survival [B.4.2.6.3 (pg84)]	PFS for axi-cel modelled based on ZUMA-1 August 2017 cut-off	PFS for axi-cel modelled based on ZUMA-1 August 2018 cut-off ('24-month' data)	As noted in Section A.6.1 , 60-month ZUMA-1 PFS data is not modelled because beyond 24 months, this assessment was done per institutional standard of care (rather than using investigator assessment as defined by IWG criteria).
Population life tables	Based on ONS 2017 published data	Based on ONS 2021 published data.	Life tables have been updated to the latest source year, given these data impact the survival analysis updates that have been implemented for the latest ZUMA-1 data cut

Model input and cross reference	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Key: FAD, final appraisal determination; IWG, International Working Group; ONS, Office for National Statistics; OS, overall survival; PFS, progression-free survival; SMR, standardised mortality ratio; TSD, technical support document.			

A.10 Cost-effectiveness results (deterministic)

Table 11 outlines the deterministic results for:

- The original submitted base case
- The company's updated base case, given the new ZUMA-1 data cut and guidance since the original submission.

Changes to the company's updated base case are outlined in the previous section (Section A.9). This also includes a correction made to the application of the SMR, such that it is applied to the mortality rate rather than the probability of death. The impact of each individual change on the ICER is reported in Section A.1.1.

For the original submitted base case, [redacted] was used.

The cost-effectiveness results for the updated base case uses the updated simple PAS discount of [redacted].

Table 11: Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER change from analysis 1
Cost-effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry [redacted]								
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,917	N/A
Cost-effectiveness analysis 3: New company base case ([redacted] PAS)								
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–	–
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£49,159	+£3,243

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

A.11 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was carried out to explore the sensitivity in the deterministic base case model results when all model parameters were varied simultaneously. Each parameter was varied according to its associated distribution (as presented in the TA559 company submission, B.3.6) 1,000 times, and mean model results were recorded.

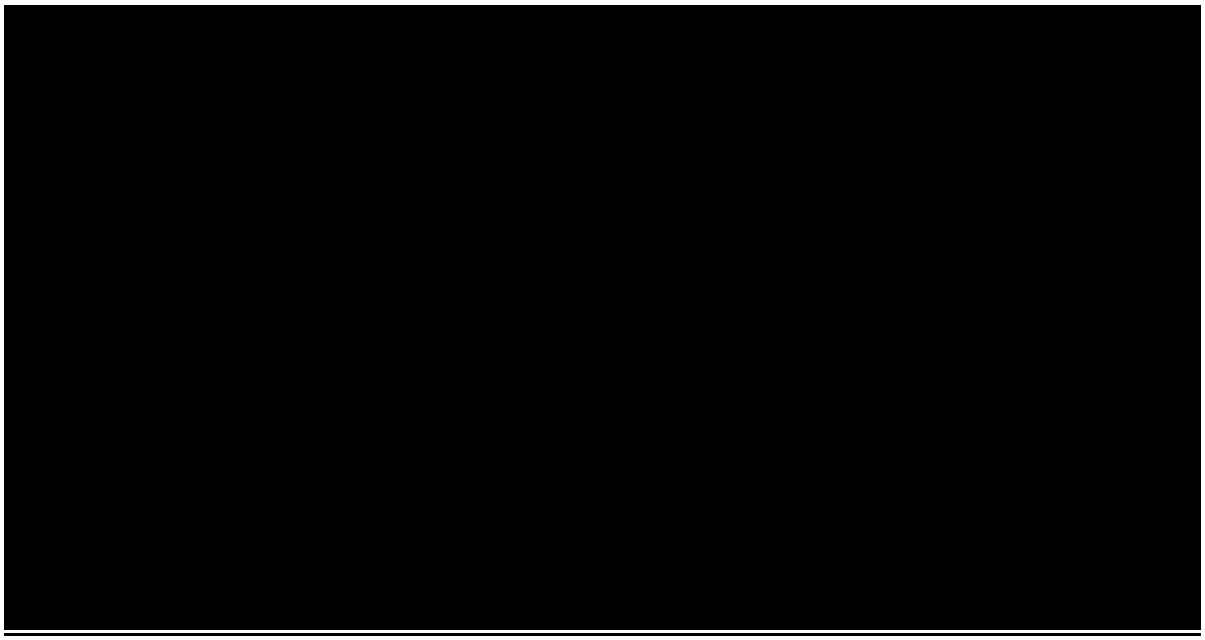
The mean incremental QALYs gained from axi-cel with the PAS applied across the 1,000 iterations are displayed in Table 12. These were also used to inform a PSA scatter plot (Figure 14). Figure 15 also shows a PSA scatterplot where survival analysis parameters have been excluded from the PSA, to illustrate the independent importance of uncertainty around these parameters for the shape and size of the PSA scatterplot.

Table 12: Updated base case results (probabilistic) – B.3.8 (page 148)

Technologies	Incremental. costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Salvage chemotherapy			
Axi-cel	[redacted]	[redacted]	£49,700

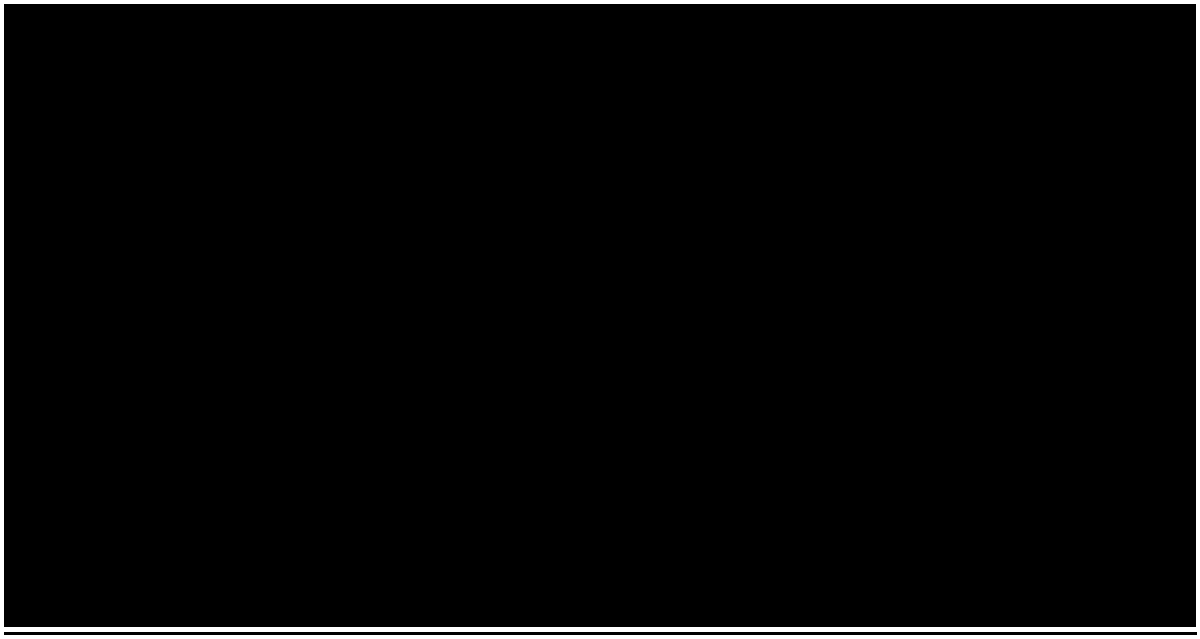
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.
Notes: [redacted] simple PAS applied.

Figure 14: Scatterplot of probabilistic results – B.3.8 (page 148)



Key: QALYs, quality-adjusted life years.
Notes: [redacted] simple PAS applied.

Figure 15: Scatterplot of probabilistic results, excluding survival analysis parameters

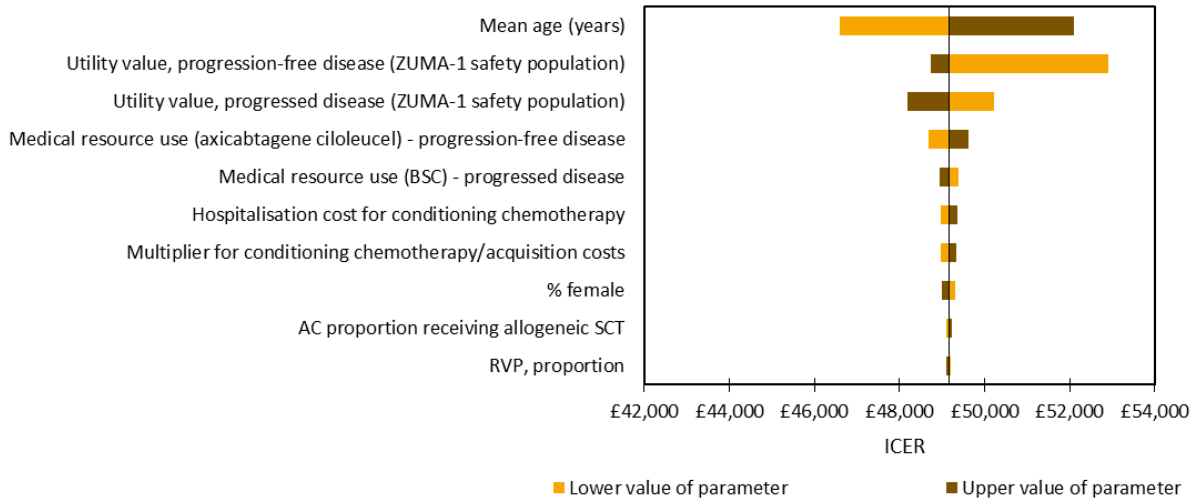


Key: QALYs, quality-adjusted life years.
Notes: [redacted] simple PAS applied.

A.12 Key sensitivity and scenario analyses

One-way sensitivity analysis (OWSA) was conducted to explore the sensitivity in the deterministic base case model results when one parameter is varied at a time. Each parameter was set to its lower and upper bound, and the deterministic model results were recorded. The top 10 influential parameters on the ICER are presented as a tornado diagram in Figure 16.

Figure 16: Tornado diagram – B.3.8 (page 150)



Key: AC, axicabtagene ciloleucel; BSC, best supportive care; MCM, mixture cure model; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; RVP, rituximab, vincristine and prednisolone; SCT, stem cell transplant; WTP, willingness to pay.
Notes: [redacted] simple PAS applied.

Scenario analysis was performed to analyse the effect of varying a given model parameter on the base case model results. The key scenarios that were explored are listed below:

Table 13: Key scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			£49,159

Axi-cel overall survival – alternative extrapolation	Best fitting spline model used for axi-cel overall survival (two knots, normal)	A splines model is explored based on new NICE guidance outlined in TSD 21, as discussed previously	£49,415 [+£255]
Axi-cel progression-free survival – alternative extrapolation	MCM (log-logistic) used for axi-cel PFS	PFS MCM used to match the preferred model used for overall survival	£49,802 [+£642]
No standard mortality ratio	The standard mortality ratio (1.09 after 60 months) is not applied	This is consistent with the original submitted model	£46,493 [-£2,667]
Key: ERG, Evidence Review Group, FAD, final appraisal determination; IVIG, intravenous immunoglobulin; MCM, mixture cure model; PFS, progression-free survival; TSD, technical support document. **Notes:** [redacted] simple PAS applied.			

A.13 End-of-life criteria

Per the FAD and terms of engagement document, axi-cel meets both criteria to be considered a life-extending treatment at the end-of-life. As such, this topic is no longer considered an area of uncertainty.

Table 14: End-of-life criteria – B.2.13 (page 83)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Outlined in the original appraisal, based on the revised base case comparator data and preferred extrapolation for overall survival, and clinical expert opinion
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Based on both the company and ERG modelling in the original submission; this is further supported by the updated ZUMA-1 60 months data cut included in the cost-effectiveness model

A.14 Key issues and conclusions based on the data collected during the CDF review period

The additional data now available from ZUMA-1 provide further evidence of the long-term benefit of axi-cel for treating relapsed or refractory DLBCL or PMBCL in adults after two or more systemic therapies. This is supported by considerable reduction in the variance of the long-term survival estimates of all MCM and spline models.

The updated data cut (60 months) continues to demonstrate a significant OS improvement for axi-cel compared with salvage chemotherapy. Furthermore, the continued follow-up demonstrates the existence of a plateau that illustrates a substantial number of patients experience extended long-term survival.

Data from the SACT cohort study were collected mainly to address the uncertainty associated with generalisability of ZUMA-1 to NHS England clinical practice. Patient characteristics are generally consistent across ZUMA-1 and the SACT cohort. With improvements in CAR T-cell therapy patient selection that have occurred since the

SACT data collection commenced, it is possible that baseline characteristics, such as the ECOG performance status are likely to be closer aligned with ZUMA-1 than the SACT data currently suggest. Furthermore, the SACT OS data is consistent with, and slightly better than the latest ZUMA-1 OS.

As real-world IVIG usage and duration data were not available at the time of submission, ZUMA-1 data were used instead, per the original submission. The modelled IVIG usage was consistent with the expected low rates in today's clinical practice, and backed up by real-world data from Kings College Hospital.[11]

In conclusion, the new analysis validates the results of the previous submission: axi-cel demonstrates improved survival outcomes compared with salvage chemotherapy; it is a cost-effective treatment for the NHS at a willingness to pay threshold of £50,000; and it should be available to patients in England through routine commissioning.

A.15 References

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A.16 Appendices

A.16.1 Comparison of ZUMA-1 and SACT baseline characteristics

Table 15: Summary of baseline characteristics – ZUMA-1 and Systemic Anti-Cancer Therapy cohort

Patient characteristic	SACT cohort (N = 127)	ZUMA-1 mITT population (N = 101)
Median age, n (range)	59.5 (not reported)	58 (23–76)
Age category, n (%)		Age ≥ 65 years: 24 (24%)
< 40	34 (11%)	
40–49	43 (14%)	
50–59	82 (26%)	
60–69	124 (39%)	
70–79	35 (11%)	
80+	0 (0%)	
Sex, n (%)		
Male	191 (60%)	68 (67%)
Female	127 (40%)	33 (33%)
ECOG Performance Status, n (%)		
0	75 (24%)	42 (42%)
1	111 (35%)	59 (58%)
2	13 (4%)	0 (0%)
Missing	119 (37%)	0 (0%)
Disease type, n (%)		
DLBCL	136 (43%)	77 (76%)
TFL	45 (14%)	16 (16%)
PMBCL	18 (6%)	8 (8%)
Not currently captured	119 (37%)	0 (0%)
Refractory subgroup, n (%)		
Primary refractory	0 (0%)	2 (2%)
Refractory to second or later therapy	132 (42%)	78 (77%)
Relapsed	58 (18%)	21 (21%)
Not currently captured	128 (40%)	0 (0%)
SCT status, n (%)		Has not had autologous SCT: 76 (75%)
Has not had SCT	158 (50%)	
Has had autologous SCT	38 (12%)	

Patient characteristic	SACT cohort (N = 127)	ZUMA-1 mITT population (N = 101)
Has had allogeneic SCT Not currently captured	3 (1%) 119 (37%)	Has had autologous SCT: 25 (25%)
Key: DLBCL, diffuse large B-cell lymphoma; n, number; PMBCL, primary mediastinal large B-cell lymphoma; SACT, Systemic Anti-Cancer Therapy data; SCT, stem cell transplant; TFL, transformed follicular lymphoma.		

A.16.2 Comparator data sources for salvage chemotherapy

	ZUMA-1	SCHOLAR-1		Radford et al. [20]	Fuji et al. [21]	Nakaya et al. [22]
	ZUMA-1 mITT (N = 108)	**All patients (N = 593)**	**ECOG 0-1 (N = 188)**	**All patients (N = 89)**	**All patients (N = 189)**	**All patients (N = 131)**
Age (years)						
Median (Min, Max)	59 (23, 76)	56 (20, 83)	54 (20, 69)	66 (58, 72)	63 (24, 70)	68 (35, 87)
<65 Years, n (%)	81 (75)	509 (86)	181 (96)	NR	NR	NR
≥65 Years, n (%)	27 (25)	84 (14)	7 (4)	NR	NR	NR
IPI Score						
0 – 1, n (%)	27 (25)	69 (12)	69 (37)	NR	NR	Low, 29 (22%) Low-Int, 23 (18%)
2, n (%)	33 (31)	61 (10)	54 (29)	NR	NR	High-Int, 29 (22%)
≥3, n (%)	48 (44)	80 (13)	54 (29)	NR	NR	High, 50 (38%)
2-3, n (%)	N/A	N/A	N/A	NR	NR	N/A
4-5, n (%)	N/A	N/A	N/A	NR	NR	N/A
Not Assessed, n (%)	0	383 (65)	11 (6)	NR	NR	N/A
Disease Stage						
I-II, n (%)	18 (17)	69 (12)	62 (33)	NR	NR	35 (27)
III-IV, n (%)	90 (83)	149 (25)	119 (63)	57 (64)	NR	96 (73)
IIIS, n (%)	0	0	0	NR	NR	0
IE, n (%)	0	0	0	NR	NR	0
Not Assessed, n (%)	0	375 (63)	7 (4)	NR	NR	0
Total Number of Lines of Chemotherapy & ASCT Received						
1, n (%)	2 (2)	89 (15)	44 (23)	89 (100)*	189 (100)*	NR
2-3, n (%)	65 (60)	464 (78)	143 (76)	63 (71)*	189 (100)*	NR
≥4, n (%)	**35 (33)**	**37 (7)**	1 (1)	41 (46)*	NR	NR
Outcomes						

	ZUMA-1	SCHOLAR-1	Radford et al. [20]	Fuji et al. [21]	Nakaya et al. [22]
OS	Median OS of 23.5 months, 41% survival at 73 months.	0% SCT, median OS of 4.0 months, 10.4% survival at 60 months. 100% SCT, median OS of 9.7 months, 27.3% survival at 60 months.	44% survival in patients who received 3 or more lines of chemotherapy at 3 years.	Median OS in all patients who received third-line therapy: 195 days. Median OS in refractory patients who received third-line therapy: 126.5 days.	25 patients underwent ASCT after 2L salvage therapy. OS was 75.6 months for these patients compared with 33.5 months for patients who did not undergo ASCT.
Key: ASCT, autologous stem cell transplant; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; OS, overall survival. *Patients followed up over time, and therefore received multiple treatment lines.					

A.16.3 Standard parametric curves for axi-cel overall survival

A range of standard parametric survival models were fitted to axi-cel OS data. As specified in NICE TSD 14, the following parametric models were explored:

- Exponential
- Weibull
- Log-logistic
- Log-normal
- Gompertz
- Generalised gamma

These models are graphically represented alongside ZUMA-1 OS Kaplan–Meier data in Figure 17, with corresponding smoothed hazard plots presented in Figure 18. AIC and BIC statistics are presented in Table 16.

Figure 17: Axi-cel overall survival: standard parametric curves

Key: OS, overall survival.

Figure 18: Axi-cel overall survival: standard parametric model smoothed hazard plots

Table 16: Axi-cel overall survival: standard parametric curve AIC and BIC statistics

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

Key: AIC Akaike information criterion; BIC, Bayesian information criterion.
Note: Bold values represent statistical best fit.

A.16.4 Flexible parametric curves for axi-cel progression-free survival

Mixture cure models

As discussed previously, mixture cure models represent a flexible approach to modelling PFS for axi-cel that can potentially account for more complex hazard functions.

Combining the estimated long-term survivor fraction (Table 17), age- and gender-matched mortality for the proportion of patients who experienced long-term survivorship, and the fitted parametric patients for the proportion of patients who did not, Figure 19 presents the overall estimated OS for each mixture cure model compared with the ZUMA-2 OS Kaplan–Meier data. Additionally, corresponding smoothed hazard plots are presented in Figure 20, while AIC and BIC statistics and landmark estimates are presented in Table 18.

By assessing the visual fit of the mixture cure models, all appear to provide a good fit to the observed data, and all models produce similar long-term survival projections. These projections capture the observed and anticipated plateau in the PFS Kaplan–Meier plot. Based on AIC and BIC, the log-normal was the best fitting, and therefore tested in a scenario analysis.

Table 17: Axi-cel progression-free survival: mixture cure model cure fractions

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

Figure 19: Axi-cel progression-free survival: mixture cure models

Key: PFS, progression-free survival.

Figure 20: Axi-cel overall survival: mixture cure model smoothed hazard plots

Table 18: Axi-cel progression-free survival: mixture cure model AIC and BIC statistics

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

Key: AIC Akaike information criterion; BIC, Bayesian information criterion.
Note: Bold values represent statistical best fit.

Spline-based models

Again, in recognition of the guidance in TSD 21[17], spline-based models have been included as a model scenario.

Figure 21 illustrates the survival axi-cel PFS curves for one, two, and three knots. Additionally, corresponding smoothed hazard plots are presented in Figure 22, while AIC and BIC statistics and landmark estimates are presented in Table 19.

By assessing the visual fit of the spline-based models, all appear to provide a good fit to the observed data, and all models produce similar long-term survival projections. These projections capture the observed and anticipated plateau in the PFS Kaplan–Meier plot to a lesser extent, compared with the mixture cure models. Based on combined AIC and BIC scores, the two knot(s) normal spline was the best fitting, and therefore tested in a scenario analysis.

Figure 21: Axi-cel progression-free survival: spline-based models

Key: PFS, progression-free survival.

Figure 22: Axi-cel progression-free survival: spline-based model smoothed hazard plots

Table 19: Axi-cel overall survival: spline-based model AIC and BIC statistics

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

Key: AIC Akaike information criterion; BIC, Bayesian information criterion.
Note: Bold values represent statistical best fit.

A.16.5 Scenario analysis: impact of each individual model change

Table 20: Individual impact of each model change (original submitted base case to updated base case)

	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER	ICER difference
Base-case	[redacted]	[redacted]	£45,917	0%	-
ZUMA-1 data cut (OS). Re-submission 60M	[redacted]	[redacted]	£50,547	10.1%	£4,630
ZUMA-1 data cut (PFS). Re-submission 24M	[redacted]	[redacted]	£48,813	6.3%	£2,896
BSC, OS parametric curve: Generalised Gamma	[redacted]	[redacted]	£39,988	-12.9%	-£5,928
Axi-cel, OS parametric curve: Log-logistic	[redacted]	[redacted]	£51,870	13.0%	£5,954
Axi-cel, PFS parametric curve: Log-logistic	[redacted]	[redacted]	£45,917	0.0%	£0
Use updated life tables: Yes	[redacted]	[redacted]	£46,046	0.3%	£130
Use correct SMR method: Yes	[redacted]	[redacted]	£45,917	0.0%	£0
SMR cut-off (months): 60; SMR applied: 1.09	[redacted]	[redacted]	£46,493	1.3%	£576
Axi-cel discount percentage: [redacted]	[redacted]	[redacted]	£47,767	4.0%	£1,851
Key: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; SMR, standardised mortality ratio.					

Table 21: Incremental impact of each model change (original submitted base case to updated base case)

	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER	ICER difference
Base-case	[redacted]	[redacted]	£45,917	0%	-
ZUMA-1 data cut (OS). Re-submission 60M	[redacted]	[redacted]	£50,547	10.1%	£4,630
ZUMA-1 data cut (PFS). Re-submission 24M	[redacted]	[redacted]	£52,466	14.3%	£6,549
BSC, OS parametric curve: Generalised Gamma	[redacted]	[redacted]	£44,885	-2.2%	-£1,032
Axi-cel, OS parametric curve: Log-logistic	[redacted]	[redacted]	£44,812	-2.4%	-£1,105
Axi-cel, PFS parametric curve: Log-logistic	[redacted]	[redacted]	£44,812	-2.4%	-£1,105
Use updated life tables: Yes	[redacted]	[redacted]	£45,005	-2.0%	-£912
Use correct SMR method: Yes	[redacted]	[redacted]	£45,011	-2.0%	-£906
SMR cut-off (months): 60; SMR applied: 1.09	[redacted]	[redacted]	£47,606	3.7%	£1,690
Axi-cel discount percentage: [redacted]	[redacted]	[redacted]	£49,159	7.1%	£3,243

Key: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; SMR, standardised mortality ratio.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

Additional information request

20 September 2022

1. **Training cost**
    a. **Company approach: Cost per patient = Cost per centre / (Annual number of patients per centre * Years before retraining) = £93**
    b. **The brackets may be causing an error in the model, Cost per patient = Cost per centre / Annual number of patients per centre * Years before retraining = £371. Please could you check this?**

The calculations in the model are correct and are the same as those used in the model provided by NICE for the resubmission: *ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC ACIC*.

A breakdown of the calculations and rationale is given below:

- Cost per centre = £1,853
- Annual number of patients per centre (10) * years before retraining (2) = 20
- Cost per patient = £1,853 / 20 = £93

The calculation could also be written as cost per patient = (cost per centre / annual number of patients) / years before retraining, which also equals £93.

Dividing the cost per centre by the annual number of patients gives the annual cost per patient. However, because retraining is done every 2 years rather than annually, the annual cost per patient is then divided by 2.

2. **Axi-cel hospitalisation cost for administration**
    a. **With the cost update during technical engagement, there may be a discrepancy between approaches used in TA559 and ID3980 relating to cell E69 in Cost data and New cost data. In TA559 the company accounted for excess hospitalisation bed days in the analysis. It appears these excess bed days may not be accounted for in the analysis for ID3980. Please could you check this?**
    b. **In addition, is there any updated data from ZUMA-1 on the mean length of stay? If so, could the calculations be updated to use this figure?**

Thank you for bringing this to our attention.

In the 'Cost data' sheet, the administration cost of axi-cel was calculated using the weighted average HRG costs for malignant lymphoma (£3,716) plus the excess bed days (7.2) multiplied by the excess bed day costs (£422) from the 2015/2016 reference costs. The reported mean length of stay associated with this HRG (from the Hospital Episode Statistics) was 10.4 days. This was 7.2 days shorter than the mean length of stay observed in ZUMA-1, hence the addition of the excess bed days. The total cost for cell infusion and monitoring was therefore calculated to be £6,760.37 (i.e. 3716.28 + [7.2 x 422.79]).

In the 'New cost data' sheet, you are correct that the excess bed days were erroneously missed out of the calculation. We have now updated the model to correct for this and have included a switch in the 'Key results' sheet (cell J121) to apply this change.

In the 2019/2020 NHS references costs used in the 'New cost data' sheet, no excess bed day costs are reported, meaning that the same method to calculate hospitalisation costs was not possible. Therefore, in the updated model, we have taken a similar approach to that used in *ID1685 Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma*. Here, the cost per day in hospital was calculated as the weighted average cost for malignant lymphoma, including Hodgkin lymphoma and non-Hodgkin lymphoma from NHS reference costs 2019/2020 (£7,303.97; Table 1) divided by the mean length of stay from Hospital Episode Statistics 2019/2020 (Codes C81-C96) of 8.1 days, to

provide a cost per day of £903.51. This was then multiplied by the mean length of stay from the trial.

Table 1: Malignant lymphoma elective inpatient HRGs (NHS reference costs 2019/2020)

Description	Number of cases	Cost	Code / Setting
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 15+	323	£35,245,33	SA31A / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 10-14	482	£12,834.36	SA31B / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 6-9	1,070	£7,423.28	SA31C / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 4-5	998	£7,128.60	SA31D / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 2-3	1,554	£4,923.93	SA31E / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 0-1	1,817	£2,931.50	SA31F / elective inpatient
Weighted average		£7,303.97	Calculated

There is no updated length of stay following axi-cel infusion from ZUMA-1. Therefore, considering the duration of 17.6 days used in the original model, this resulted in a hospitalisation cost of £15,901.73 (i.e. 903.51 x 17.6). When applying the updated hospitalisation cost, this results in an ICER increase from £50,480 to £52,589.

Evidence obtained from the Adelphi Real World DLBCL DSP™, a real-world point-in-time survey of haematologists, haem-oncologists, and medical oncologists and their patients with DLBCL in the UK, Germany, Spain, Italy, France and Canada in 2021, would suggest that the length of stay observed in ZUMA-1 is an overestimate. The real-world analysis considered the 100 days following CAR-T administration. A total of 19 patients received CAR-T at 3rd line in the DSP UK sample, and the analysis found that 11 of the 19 patients in the UK who received CAR-T were hospitalised as an inpatient for an average of 14 (SD: 7.9) nights within the first 100 days of administration.

When applying the hospitalisation cost for 14 days rather than 17.6 days, this results in an ICER of £51,791.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund review

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

Clarification questions

June 2022

File name	Version	Contains confidential information	Date
ID3980 axi-cel ERG Clarification letter to PM for company ACIC_v1.0	1.0	Yes	06/06/2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

A1. Priority question: The terms of engagement (ToE) states that in addition to using SCHOLAR-1 data, the submission should use *"any additional data that has become available during the period of managed access to inform the comparator arm"*.

On page 28 of the company evidence submission (CES), it states that *"a targeted PubMed search using keyword searches was conducted to identify additional sources of comparative data published since September 2018"*.

Please provide full details of the search strategy used.

A basic literature search (via PubMed) was undertaken to review any additional data pertaining the use of conventional chemotherapy within the 3L DLBCL setting which may further inform our assumptions around the comparator arm. This was based on suitable keyword MeSH term searches, for example, related to "DLBCL" OR "diffuse large B cell lymphoma" AND "chemotherapy" AND "relapsed/refractory", and search criteria were further refined to datasets published since 2018 (following the last appraisal of axi-cel in this setting). Whilst acknowledging the absence of high rigour that one would typically expect of a conventional SLR approach, this search revealed a very limited number of datasets, which we have referred to and commented on in Section A.7 of the company evidence submission (CES). The outcome of this search

is not unexpected since the establishment of CAR T-cell therapy for DLBCL after two or more prior therapies in the last few years has meant that a counterfactual 'world' without CAR T is expected to have significantly limited the use of chemotherapy for patients treated with curative intent in this setting. Therefore, nothing of any further scientific rigour than the original SCHOLAR-1 dataset has been identified in which to inform the comparator arm in this appraisal. This conclusion was deemed very reasonable by UK clinical expert validation when reviewing the economic modelling and clinical assumptions part of this resubmission.[1]

A2. Priority question: The CES has provided a clear description of the one-arm ZUMA-1 and SACT results. However, the ToE states that *"the company should present clinical and cost-effective evidence for axicabtagene ciloleucel compared to salvage chemotherapy, excluding pixantrone"*.

Therefore, the Evidence Assessment Group (EAG) is more interested in the results of the indirect analyses performed in conjunction with patient-level data from the SCHOLAR-1 studies (used as the comparator cohort), which are not presented clearly nor fully.

Please present combined ZUMA-1/SACT and SCHOLAR-1 results in a clear way, e.g. with appropriate statistical adjustments, to facilitate a more meaningful interpretation of clinical effectiveness.

Given we do not have access to the SACT patient level data, presenting a combined analysis of ZUMA-1 and SACT is not possible. As described in the CES, the survival data from the SACT cohort provided validation of the ZUMA-1 outcomes, showing that these are similar. As discussed in the CES, it is worth noting that SACT as a data source is arguably inferior to ZUMA-1 given both: a) the shorter follow-up; and b) the initial sub-optimal allocation of certain patients to treatment with axi-cel/CAR T during early experience in the UK as their understanding around appropriate patient selection for CAR T-cell therapy continued to evolve in clinical practice.

Regarding the indirect comparison of axi-cel and salvage chemotherapy, 'adjusted' SCHOLAR-1 data was used to ensure comparability with the ZUMA-1 population (necessary due to ZUMA-1 being a single-arm trial). This was possible because the company had access to the SCHOLAR-1 patient level data. In the original company

submission (TA559), the SCHOLAR-1 dataset was adjusted by removing patients with an ECOG score of 2-4, to better align with the ZUMA-1 inclusion criteria. The ERG-preferred approach differed to this; therefore, in response to the NICE ACD, Kite/Gilead revised the SCHOLAR-1 dataset as requested. These revisions are summarised in Table 1.

Table 1:Summary of SCHOLAR-1 adjustments

SCHOLAR-1 adjustments	Justification for adjustment	Resulting population size
No adjustments	N/A	636
Refractory subgroup classified as “last refractory categorisation”	This was based on the refractory status at the last time in the treatment course the subject was determined to be refractory and is most consistent with how analyses in ZUMA-1 were conducted.	593
Patients evaluable for survival only		562
Patients with an ECOG score of 2-4 and unknown removed	Consistent with the ERG-preferred approach.	188
Primary refractory patients removed	Consistent with the axi-cel EMA label.	133
Weighted to reflect an expected subsequent SCT rate of 10%	Based on clinical opinion.	Patients who underwent SCT: 67 Patient who did not undergo SCT: 66
Key: ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; N/A, not applicable; SCT, stem cell transplant.		

In the TA559 final appraisal determination (FAD), the committee concluded that the adjusted SCHOLAR-1 dataset is appropriate for decision-making. Hence, in the CES, the same adjusted SCHOLAR-1 dataset was used to inform salvage chemotherapy OS outcomes.

Section B: Clarification on cost-effectiveness data

Progression-free survival

B1. Priority question: Please answer the following questions regarding progression-free survival:

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

   Please clarify what the last sentence means.

As per the ZUMA-1 study protocol, progression data was collected by positron emission tomography–computed tomography (PET-CT) every 3 months and confirmed by blinded central review committee until 24 months. Beyond 24 months, there was no protocol-defined mandated PET-CT to collect progression data. Instead, the disease assessment was done per institutional standard of care every 6 months. Therefore, any PFS data collected beyond 24 months may not be consistent with the criteria applied in ZUMA-1 in the first 24 months, which may introduce bias into the survival analysis of time to event variables, like PFS.

b. **Page 21 of the CES continues as follows: *"Therefore, any PFS data collected beyond 24 months may not be consistent with the criteria applied in ZUMA-1. For this reason, PFS data collected up to month 24 is presented here and used in the economic model"*.**

   Please explain what criteria were used to establish consistency, determine whether the PFS data collected beyond 24 months are indeed consistent or not with the criteria applied in ZUMA-1, and explain the differences if any. Furthermore, please include the PFS data collected beyond 24 months (e.g., 60-month data) in the model and use it to run a scenario analysis.

Please see the above response to B1.a. for the criteria in collecting PFS data.

Although PFS is a reliable surrogate endpoint of OS, and meaningful to inform the clinicians about the value of the product on patient outcomes at an earlier stage compared to OS data, OS is the definitive and best-established primary efficacy end point to evaluate diffuse large B-cell lymphoma therapies that is meaningful to patients. Since we present at least 5 years of follow up of OS data in ZUMA-1, we believe it should be of ultimate interest in terms of pointing out potential cure with axi-cel.

Since the model is informed by mature survival data and survival estimates are stable (as demonstrated by the small variation in cure fractions in the cure models), further follow-up data on PFS will likely not change cost-effectiveness in a meaningful way. For these reasons, PFS data collected up to month 24 is presented and used in the economic model.

c. **The CES indicated that *"it is anticipated that patients remaining progression-free for 2 years are likely to remain progression-free in the long-term"*. Data beyond 24 months could be used to confirm such statement. The CES also indicated that the previous statement was validated by UK clinical expert opinion and is also supported by UK real-world data from 298 CAR T-cell therapy infused patients (N=222 axi-cel, N=76 tisagenlecleucel) treated between February 2019 to January 2021, which found that 97.5% of progressions occurred by month 6.**

   Please use the PFS data collected beyond 24 months for validation purposes. Furthermore, please explain how the statement above was validated by clinical experts and clarify why the company consider that it was supported by the real-world data.

   Secondly, Please clarify at what point in time the PFS plateau is observed. Note that there is substantial censoring around month 24. Please explain the reasons for the censoring. Note that due to the censoring, the plateau assumption for PFS could be deemed as uncertain. As mentioned above, please consider using long-term data to resolve this uncertainty.

Clinical expert validation was sought on the assumption of a sustained PFS plateau beyond 24 months in the absence of routinely collected PFS data. This was in addition to long-term ZUMA-1 data demonstrating few progression events between 2 and 4+ years, and real-world evidence confirming the majority of progression events occurring within the first 6 months.[2]

Regarding censoring events, Figure 1 shows the censoring reasons for the 24-month PFS data.

Figure 1: Investigator PFS (24M) data

Kite Pharma, Inc. Confidential Protocol: KTE-C19-101

Table 14.2.6.1.1 Progression-free Survival (PFS) (Phase 1 and 2 Combined) using Investigator Assessment per Cheson 2007
All Treated Phase 1 and Phase 2

	Phase 1 and 2 Combined (N = 108)
Progression-free Survival (PFS)	
No. of subjects	108
Censored (%)	43 (40)
KM Median (95% CI) PFS time (in month)	5.8 (3.3, 15.0)
Type of Events	
Disease Progression	59
Disease/treatment related Death	6
Censoring reason	
Response/SD Ongoing	42
Started new anti-cancer therapy	1
PFS (95% CI) at	
3 Month	66.5 (56.8, 74.6)
6 Month	48.7 (39.0, 57.8)
9 Month	45.0 (35.4, 54.1)
12 Month	44.0 (34.5, 53.2)
15 Month	41.2 (31.8, 50.3)
18 Month	40.2 (30.9, 49.3)
24 Month	39.2 (29.9, 48.3)

Note: Percentages are based on number of subjects treated.
PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause.
Disease assessment after initiation of new anti-cancer theapy (not including SCT) are not included in the PFS derivation.
Disease status used are investigator assessment of disease status per Cheson 2007.

Data Source: ADSL, ADEFF, ADTTE Data Cutoff: 11AUG2018 Program Name: t_pfs12 Output Generated: 20180926_08-32

Ref: 24-month follow-up analysis of zuma-1 cohorts 1 and 2 addendum to module 5.3.5.1 zuma-1 clinical study report: kte-c19-101 a phase 1/2 multi-centre study evaluating the safety and efficacy of kte-c19 in subjects with refractory aggressive non-Hodgkin lymphoma (zuma-1).

d. **Please clarify why for PFS cure models were not considered in the base case when the PFS curves show a similar shape (i.e., a plateau) as the overall survival (OS) curves. The CES indicated that *"these projections capture the observed and anticipated plateau in the PFS Kaplan–Meier plot"*. This would suggest the same approach as for OS. Note that by assuming standard parametric curves, the only distribution showing a plateau is the Gompertz.**

The Gompertz standard parametric model was selected as the base case option for modelling axi-cel PFS because it was consistent with both the company and ERG base case approach in TA559. This issue was explained at length in the TA559 ERG report; please refer to sections 4.2.6.3 for further details. The Gompertz model also remained the best-fitting, both in terms of visual and statistical goodness of fit, with the updated ZUMA-1 PFS data cut. Therefore, considering both the ability of the simple Gompertz parametric model to capture the observed and expected shape of the axi-cel PFS, and the agreed approach used for decision making in TA559, this was selected for the base case in the CES over the more complex, flexible models.

Of note, a scenario was provided in the CES whereby the log-logistic mixture cure model was used for axi-cel PFS. This had a minimal impact on the ICER (+£642), which shows that the Gompertz model resulted in similar projected outcomes for PFS as the mixture cure models.

e. **The CES indicated that *"consistent with the approach for OS, a relative survival framework has been used for each of the PFS model approaches"*.**

   Please confirm that in the model PFS is always smaller or equal than OS. If that is not the case, please modify the model to include that assumption.

The model has a logical cap in the estimation of long-term PFS and OS, in which the proportion of patients that remain in the PFS state cannot exceed that. This can be seen in the formulas within the Engine (patient flow) sheets, columns G:L.

Intravenous immunoglobulins use

B2. Priority question: Please answer the following questions regarding IVIG use:

a. **Page 22 of the CES indicates that *"ZUMA-1 is a controlled clinical trial environment where investigations/interventions are strictly adhered to according to defined protocol based on clinical management that is determined at the time of the study; this is therefore not necessarily entirely reflective of real-world clinical practice"*.**

   Please clarify whether IVIG use as observed in ZUMA-1 is expected to be higher or lower compared to clinical practice.

Per the CES, the observed IVIG rate of [redacted]% from ZUMA-1, which was used in the original company submission, TA559, and derived from an earlier data cut, is expected to be reflective of clinical practice. This was validated by input from a UK clinician, and by comparing the rate with real-world data from Kings College Hospital.

b. **The CES assumes the same proportion of patients receiving IVIG that was used in the original submitted economic model for technology appraisal (TA) 559 ([redacted]%). The CES indicates that *"this is consistent with the expected low rates in today's clinical practice, as confirmed by expert clinical opinion and backed up by real-world data from Kings College Hospital"*.**

   Please clarify how this was confirmed by clinical experts and backed-up by the real-world data.

As stated in Section A.6.1 of the CES, real-world data from Kings College Hospital on patients being treated with axi-cel or tisagenlecleucel for relapsed/refractory high-grade B non-Hodgkin lymphoma reported that three out of 53 patients (6%) received IVIG post-chimeric antigen receptor (CAR) T-cell therapy. This is supportive of the observed IVIG rate of [redacted]% from ZUMA-1, used in the economic model base case.

In addition, the IVIG rate of [redacted]% was validated by a UK clinician who noted that the value was reasonable and further added that he doesn't see many patients requiring long-term IVIG with axi-cel.

c. **The additional evidence provided by the company seems to focus on IVIG usage but not on the duration of treatment. Please confirm whether this was the case or not. If additional evidence on the duration of IVIG treatment were available, please provide a summary of these data and include it in the cost effectiveness model.**

Per the managed access agreement, real-world IVIG usage and duration data were expected to be available from NHS England for inclusion in the CES. Given delays to the data collection, these outcomes were not available.

To overcome this data gap in the CES, additional evidence was provided on IVIG usage to validate the IVIG rate observed in the ZUMA-1 trial. Appropriate duration data was not available from ZUMA-1, and we did not identify any literature to inform this; therefore, this was not updated from the assumptions used in TA559.

d. **Please run scenario analyses in which both the proportion of patients receiving IVIG treatment, and the treatment duration are varied within plausible values and justify the choices made for the scenarios.**

IVIG data within the SACT report was received on 30th May. Gilead still have follow-up questions for NHS England regarding the IVIG data, which will likely not be answered before the submission of this document. With this caveat, implementation of the proportion of patients receiving IVIG treatment (16%) and mean duration (6.5 months) outlined in the SACT report, results in an increased ICER: from £49,159 to £49,373.

Systemic Anti-Cancer Therapy dataset

B3. Priority question: Regarding the SACT dataset, the CES indicates that *"the consolidated SACT data relates to patients treated both before and after these learnings were embedded into UK practice and, therefore, may not be truly representative of the overall current situation in today's UK clinical practice. It is therefore possible that in today's clinical practice, key determinants of patient*

***selection for CAR T-cell therapies, such as ECOG performance status, are likely to be more closely aligned with ZUMA-1 than the SACT data currently suggest"*.**

Please clarify to what extent the SACT data may not be truly representative of the overall current situation in today's UK clinical practice and why the company consider that key determinants of patient selection for CAR T-cell therapies are likely to be more closely aligned with ZUMA-1 than the SACT data currently suggest.

When CAR-T first became available in the UK it was an entirely novel treatment option that clinicians had no clinical experience with. Therefore, it's not surprising that over time as clinicians have gained this experience, there has been a significant evolution and improvement in patient management (including patient selection, bridging, adverse event treatment etc.). The SACT dataset therefore reflects this natural heterogeneity over time and improvement from first use of a novel treatment option to the use of an established therapy, this is outlined in further detail in Section A.6.2 of the CES.

For example, in the ZUMA-1 population, 58% of patients had an ECOG performance status of > 0; versus in the SACT cohort this was only 39%. However, it is likely that the patient selection for ECOG performance status would now more closely mirror the ZUMA-1 population. This comparison is further confounded by the fact that performance status was not recorded in 37% of patients in the SACT dataset.

Adjustment of the SCHOLAR-1 cohort

B4. Priority question: In Table 1 of the CES, providing an overview of the *"key committee assumptions as per the terms of engagement"*, it is stated that *"the company [please note a typo in CES where Committee is mentioned instead] should use SCHOLAR-1 and any additional data that has become available during the period of managed access to inform the comparator arm"*.

a. **Please explain whether any additional data (e.g., standard of care data from the Haematological Malignancy Research Network, ORCHARRD or CORAL studies) have become available during the period of managed access to inform the comparator arm of the model.**

There have not been any pertinent datasets identified since the original appraisal that would provide further context on the comparator arm in the third-line relapsed/refectory setting.

b. Please justify that the assumptions made for the comparator arm are still representative of current clinical practice in the UK.

CAR T-cell therapies are now well embedded in UK clinical practice in the UK due to their potentially transformative outcomes and the access enabled via the CDF. As such the SCHOLAR-1 outcomes do not match those currently observed in UK practice. However, if for decision analytic reasons we consider the hypothetical outcomes that would be observed in the absence of CAR T-cell therapies such as axi-cel, there is every reason to believe they would match those observed in the adjusted SCHOLAR-1 data. This accords with the judgement raised by the committee previously.

Clinical expert-validated confirmation of such has been received given that availability of CAR T-cell therapy at third line, and its establishment as standard of care in this setting, has made it incredibly challenging to find newer data sources that would provide this information. This was addressed in Section A 7.1 of the CES. Please see the clinical expert email exchange below to validate this assumption.

Email exchange with Professor Gribben:

Recent comparator sources – please could we get clinical input on the following statement as to whether this is fair conclusion to make in our resubmission?: "Via the CDF, use of CAR T-cell therapies for DLBCL after two or more treatment lines has become so established that trying to find a newer data source to model the counterfactual of a 'world' without these therapies being available is unfeasible"

This statement is being made in our resubmission to support our modelling approach of continuing to focus on the SCHOLAR-1 data as the key source of comparative patient-level data on outcomes of 'salvage' chemotherapy in 3L DLBCL (as agreed by NICE committee consensus), in the absence of any additional appropriate comparative data sources since the original appraisal.

Professor Gribben's response:

I also agree that this is very reasonable. You can expect to get an answer back about bispecifics, but none are yet approached in this setting

B5. Please run scenario analyses in which the proportion of patients receiving stem cell transplant (SCT) is varied within plausible values and justify the choices made for the scenarios.

In the CES, an assumption that 10% of salvage chemotherapy patients had a subsequent stem cell transplant was used. This is consistent with the original company base case in TA559. The ERG's base case assumption, however, was 12.5%. In the FAD, the committee did not state a preference over the ERG's or company's base case assumption.

To account for the ERG's preferred assumption in TA559, we have provided a scenario that tests the impact of alternative subsequent SCT rates. This is presented in Table 2.

Table 2: Deterministic cost-effectiveness results, alternative assumptions used to model post-salvage chemotherapy SCT

Scenario	% patients receiving SCT	ICER
+2.0% to base case	12.0%	£49,316
+1.0% to base case	11.0%	£49,259
Base case	10.0%	£49,159
-1.0% to base case	9.0%	£49,061
-2.0% to base case	8.0%	£48,963
Key: ICER, incremental cost-effectiveness ratio; SCT, stem cell transplant.		

Utility/HRQoL

B6. Priority question: Please confirm that no changes were made regarding health-related quality of life (HRQoL)/utility data, and that no new data were available. In case that new data are available, please include them in the model.

No changes were made to the analysis of EQ-5D-5L data used to inform the economic model. Data used to inform the utility data from ZUMA-1 is derived from the 11th August 2017 data cut off.

Resource use/costs

B7. Priority question: The updated model is based on cost prices from the year 2015/2016. Please update the model using the most recent NHS Reference costs (i.e., version 2019/2020), and align the other cost inputs (e.g., sourced from the Personal Social Services Research Unit [PSSRU], electronic Market Information Tool [eMIT], British National Formulary [BNF], etc.) to the same cost year.

As requested, the model has been updated with the latest cost year. The impact that this change has on the ICER is presented in Table 3.

Table 3: Deterministic cost-effectiveness results, impact of using the latest cost year

Scenario	ICER
Base case	£49,159
Updated cost year	£50,251
Key: ICER, incremental cost-effectiveness ratio	

The EAG noted during the call on 24 May 2022 that there may be a costing error in the submitted economic model. Specifically, this was flagged for the costing of rituximab; in the latest version of MIMS, the rituximab price provided for the 100mg vial is for a pack size of two vials (i.e. 200mg in total). Given the pack size was not included in the costing calculations, the EAG's concern was that the cost for rituximab, and potentially other drugs, were being underestimated.

We are unable to decipher whether this was an error in the submitted model, given we cannot check the listing price or number of vials for costs in 2015/2016. We note that the salvage chemotherapy costing used in the submitted model had not been changed since the version submitted as part of TA559, which had undergone ERG review.

For the updated scenario provided in Table 3, the pack sizes provided in the latest versions of MIMS and eMIT have been considered in the drug costing calculations, as expected. Therefore, this concern has been addressed here.

Validation

B8. Priority question: Unlike the original company submission (CS), there is no validation specific section in this CES.

a. **Please provide all details of the validation efforts conducted in this CES.**

b. **Please explain whether the validation efforts included all steps (e.g., conceptual model validation, input data validation, model verification, validation of the model outcome) as explained for example in the 'Assessment of the Validation Status of Health Economic decision models' (AdvisHE) tool (https://advishe.wordpress.com/). If this was not the case, please include these steps as well.**

Regarding the overall modelling approach, the updated model used the cost-effectiveness model from the original appraisal and therefore has gone through all the validation processes as per the original company submission and ERG / NICE appraisal process. Consistent with the CDF resubmission process followed in this reappraisal process, minimal changes were made to the model, with the key focus being the inclusion of the updated OS, PFS and IVIG data, per the terms of engagement. As noted previously, real-world IVIG usage and duration data was not available at the time of submission.

Regarding the modelling of critical outcomes, various validation efforts were mandated within the CDF data collection agreement to validate the OS projections given its particular importance both in terms of its importance to patients and in terms of the impact it has on the cost-effectiveness results. Firstly, further OS data were collected from ZUMA-1. These data validated the extrapolations included in the initial model. The extrapolation approach used to model the OS projections with the latest ZUMA-1 data were also modelled to be consistent with the recommended approaches used in Vagdama et al. (2021), and a subsequent poster, which found that the cure-based models provided the best fit to the observed data, both visually and empirically using a variety of metrics.[3,4] Secondly, the SACT OS data, validated that the outcomes observed in ZUMA-1 were replicable in UK clinical practice.

Regarding the assessment tools, following the model updates, the model underwent an internal review and quality control checks, in line with Drummond, Phillips, and TechVER.[5,6,7]

B9. Priority question: Please provide a summary about how the new evidence and clinical expert opinion were used to validate assumptions in this CES. Please also explain whether any literature searches were performed to identify studies that were published since the initial appraisal, which could be used for validation purposes. For example, a study by Nastoupil et al. 2020 (J Clin Oncol 38:3119-3128) was published reporting the results of the US Lymphoma CAR T consortium on the use of axi-cel in the standard-of-care setting.

As noted in the response to A1, a targeted search was undertaken to identify if any further data of relevance had been published on the comparator arm since the initial appraisal. This confirmed that there were no further data to supplant the SCHOLAR-1 study (previously identified by the committee as suitable for decision making). The study by Nastoupil et al. (2020) provides supportive evidence of the excellent outcomes of patients treated with axi-cel in the US. This is encouraging but arguably of less relevance than the data on UK patients collected within SACT as mandated by the CDF data collection agreement (which similarly confirms that the outcomes achieved in ZUMA-1 are realisable in the 'real world' context).[8]

Model assumptions

B10. Priority question: Please provide a table showing all changes made to the company's model (also those after clarification, if any) indicating the new and old values, and justifications for the changes.

Table 4 details the model updates and changes made since the original submission (model version ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC]), in addition to the base case changes listed in Section B11.

Table 4: Model updates since the original submission

Update / Change made to the economic model	Model location	Justification
Option to select OS (60M) and PFS (24M) data update from ZUMA-1	Clinical data – Progression, and Clinical data – Mortality sheets	New ZUMA-1 data added as per the CDF review process

Splines and knots survival modelling for axi-cel OS and PFS added	Splines – Progression and Splines – Mortality sheets	Recommendations as per TSD21
Mixture cure modelling for axi-cel PFS added	Clinical data – Progression	Option to be consistent with OS modelling approach
Option to select to use updated lifetables	Clinical data – Mortality sheet	An updated version of the lifetables was available since the original appraisal
Option to select the method to apply the SMR	Clinical data – Mortality sheet	The added functionality has been preferred by the ERG in previous appraisals
Option to select updated costs as per Section B7	Cost data sheet	Priority question from Section B7
Update to scenarios included in the scenario analysis	Sensitivity analysis and Control sheets	Aligned with updates to the survival data and analysis
Updated formulae to allow for relative survival framework to be used for the updated ZUMA-1 data cut	Health states sheet	Recommendations as per TSD21
Inclusion of the updates to the Control sheet	Control sheet	Functionality updates

Cost effectiveness results

B11. Priority question: The EAG could not reproduce the incremental cost effectiveness ratio (ICER; without discount and rebate) from the original CS in the updated model, after reverting to the original company settings as outlined in Table 10 of the CES.

a. **The ToE specifies that "The economic model submitted by the company in response to the ACD consultation named "[ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC]" should be used be used as the basis for the CDF review". Please confirm that this was the model used for the CDF review.**

We can confirm that the economic model submitted by the company in response to the ACD consultation named "[ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC]" was used for the CDF review. The ICER in the aforementioned model is £45,917.

b. Please provide a complete list of all the changes that need to be applied to the updated model in order to reproduce the results from the original CS.

A complete list of model changes needed to be applied to the updated model in order to reproduce the results from the "[ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC]" model is provided in Table 5. This is also included as an automated model scenario.

Table 5: Model changes needed to replicate the original submission base case

Sheet and cell reference	Name	ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC]	Updated model
'Key results'!J28	ZUMA-1 data cut (OS)	Original	Re-submission (60M)
'Key results'!J29	ZUMA-1 data cut (PFS)	Original	Re-submission (24M)
'Key results'!J46	BSC OS distribution (PSM)	Gompertz	Gen.Gamma
'Key results'!J40	AC OS distribution (MCM)	Weibull	Loglogistic
'Key results'!J42	AC PFS distribution (PSM)	Gen.Gamma	Loglogistic
'Key results'!J49	Use updated lifetables?	No	Yes
'Key results'!J62	Axi-cel Discount %	[redacted]	[redacted]
'Key results'!J67	Rebate %	[redacted]	[redacted]
'Key results'!J79	SMR	1	1.09
'Key results'!J80	SMR cut-off	999	60
'Key results'!J50	Use corrected method to apply SMR?	No	Yes

c. The ToE explicitly mentions that NICE expects the following functionality to be available within the model at the CDF review: replication of the key cost-effectiveness results used in committee's decision-making at the point of CDF entry. If possible, please include this functionality in the cost

effectiveness model and provide this model version as a separate version.

The functionality to replicate the cost-effectiveness results as per the ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC] model is included within the scenario analysis of the updated model (run in the Sensitivity analysis sheet). This can be performed manually following the above table.

d. Please indicate from where the base case ICER (at CDF entry) in Table 11 can be sourced, as this is not the same ICER as in the original CS.

The base case ICER at CDF entry (£45,917), which is provided in Table 11, is the same as the ICER for ID1115 axicabtagene ACD Kite-Gilead CE model v0.2 210918 SC [ACIC].

e. Please explain what changes were made to the comparator arm to reduce both life years/quality-adjusted life years (QALYs) and costs and what changes were made to the intervention arm to reduce life years/QALYs and to increase costs.

- The use of the updated ZUMA-1 data cut for OS (60M) and PFS (24M). This slightly increased the costs and reduced the LYs/QALYs for the axi-cel arm.
- The use of a generalised gamma single parametric model for SoC OS, rather than Gompertz reduces the LYs/QALYs and costs for the SoC arm.
- Updates to the life tables and standard mortality ratio, values and functionality increases costs for SoC and axi-cel arms. LYs/QALYs for SoC and axi-cel arms are also increased.

B12. Priority question: In the ToE, the reported ERG base case ICER is £[redacted] per QALY gained versus salvage chemotherapy, whereas in the CES, the company refers to the ERG's upper-bound base case ICER of £[redacted] per QALY gained compared with salvage chemotherapy. Please clarify which of these two values represents the ERG base case ICER and from where it can be sourced.

In the ERG's commentary on the response submitted by the company to the ACD, a range of ICERs was presented, with £[redacted] being the highest. This was presented in Table 13 of the document, where the following scenarios were combined:

- 87.5% autologous transplant and 12.5% allogeneic transplant for BSC

- IVIG use for 3 years
- Cure assumption of 5 years
- ITT population
- 12.5% SCT rate

The ERG then went on to conclude that the generalised gamma may provide a more appropriate choice than the Gompertz distribution for BSC OS. When using a generalised gamma distribution for BSC OS, in addition to the combined scenario detailed above, the upper bound ICER reduced from £[redacted] to £[redacted].

The ERG's analysis using the generalised gamma distribution for BSC OS was also referred to in the TA559 FAD: "using the ERG's alternative analysis and the combined costing approach (taking into account the use of higher proportion of post-treatment autologous stem cell transplants, a cure assumption at 5 rather than 2 years, IVIG use for 3 years and the use of the intention-to-treat population) with a gamma distribution for overall survival for salvage chemotherapy, the ICER was above £50,000 per QALY gained." Therefore, we considered this to reflect the ERG's base case approach.

Sensitivity/scenario analyses

B13. Priority question: please clarify the following points regarding the probabilistic sensitivity analysis (PSA):

a. Please provide a cost-effectiveness acceptability curves (CEAC) plot.

Please see Figure 3, which presents the CEAC for axi-cel.

Figure 2: CEAC for axi-cel

b. **According to the CES, *"Figure 15 shows a PSA scatterplot where survival analysis parameters have been excluded from the PSA, to illustrate the independent importance of uncertainty around these parameters for the shape and size of the PSA scatterplot"*.**

   Please explain the rationale for this scenario and how the results should be interpreted.

The inclusion of survival parameters in the one-way sensitivity analysis is not considered best practice given it does not allow the correlation between the parameters to be considered. Therefore, as an alternative to capturing uncertainty in the survival parameters in the OWSA, an option to exclude them from the probabilistic sensitivity analysis was provided in the updated economic model. This allows the impact with and without these parameters to be considered.

c. **Based on Figure 14 and 15 of the CES, it seems that the model is always estimating incremental costs of at least £[redacted], while at the same time the majority of simulations are relatively closely above incremental costs of approximately £[redacted].**

Please explain why this is the case and justify that these results are an accurate representation of the uncertainty surrounding the incremental costs.

Axi-cel drug acquisition costs and the percentage discount applied are not varied in the PSA. The discounted acquisition cost for axi-cel is [redacted]; therefore, the incremental costs cannot be below this value, and is why the incremental costs lies around [redacted].

B15. Priority question: Please provide additional scenario analyses results to cover at least the three key uncertainties highlighted in the submission (OS, PFS and IVIG), or provide a rationale for not conducting such scenarios.

Scenarios to reflect the uncertainty surrounding OS and PFS are listed in Table 6. These scenarios are also presented in Table 13 of the CES. The third scenario, which explores key uncertainties around IVIG data, is given in response to Section B2 above.

Table 6: Additional scenario analysis

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Base case			£49,159
Axi-cel overall survival – alternative extrapolation	Best fitting spline model used for axi-cel overall survival (two knots, normal)	A splines model is explored based on new NICE guidance outlined in TSD 21, as discussed previously	£49,415 [+£255]
Axi-cel progression-free survival – alternative extrapolation	MCM (log-logistic) used for axi-cel PFS	PFS MCM used to match the preferred model used for overall survival	£49,802 [+£642]

Section C: Textual clarification and additional points

C1. Please provide a new version of Figure 4 of the CES including the number of patients at risk. Since there seems to be substantial censoring over time, please explain the reasons for censoring.

The following text and tables, listed in Figure 3, are copied from the SACT report, pages 23-25. No further information is given regarding censoring in the SACT report.

Figure 3: Text and tables from the SACT report

Of the 318 patients with a treatment record in SACT, the minimum follow-up was four months (121 days) from the last CDF application. Patients were traced for their vital status on 3 March 2022. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 11.2 months (340 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 38.8 months (1,180 days), all patients were traced on 3 March 2022.

Table 8. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Number at risk	318	279	232	188	148	110	79	62	47	32	18	9

Table 9 shows that for all patients who received treatment, 186 were still alive (censored) at the date of follow-up and 132 had died (events).

Table 9. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Censored	186	186	173	149	125	97	72	58	44	30	17	9
Events	132	93	59	39	23	13	7	4	3	2	1	0

C2. In Figure 7 of the CES, the plotted hazard for background mortality seems to be constant. Please confirm whether this is the case or not, as it is expected that this should increase over time.

Survival models are fitted in a relative survival framework; hence background mortality is taken into account. See Figure 4 (axi-cel OS smooth hazard plot for mixture cure models) with a longer time horizon as an example:

Figure 4: OS smooth hazard plot for MCM

As you can see, hazards are increasing over time. PFS is also fitted in a relative survival framework.

C3. Figure 8 of the CES presents the axi-cel survival curves for one, two, and three knots. Please explain the rationale for selecting knots in spline-based models.

Regression analysis of the survival data was performed in R. For estimation of the spline models, the package *flexsurv* as used.[9] Knot points were not specified, and therefore determined by the default settings in the package. That is, knot points are chosen as equally spaced quantiles of the log uncensored survival times. Knot points are as described in Table 7.

Table 7: Spline and knots boundaries

Knots	Knot point (percentiles of log uncensored survival time)
1	50%
2	33.33, 66.66%
3	25%, 50%, 75%

C4. Please provide the source used to estimate an standardised mortality ratio (SMR) of 1.09 applied to patients in both treatment arms who were alive after 60 months.

An SMR of 1.09 for 60 months was used by the ERG in the Tisagenlecleucel-T (tis-T) DLBCL NICE appraisal (TA567), as noted in the original appraisal. The original source for this value is from Maurer et al (2014).[10] This was the source suggested by the evidence review group in both the tis-T and axi-cel appraisals.

C5. On page 39 of the CES, it is mentioned that *"It is plausible that this long-term survivorship is largely attributable to the [redacted]% of patients receiving allogeneic SCT following axi-cel in ZUMA-1. This is consistent with UK real-world data, which found that 11 out of 298 (3.7%) patients received allogeneic SCT as treatment post CAR T-cell infusion, resulting in >90% survival at 12 months post-progression"*.

Please explain how these sentences relate to the information shown in Figures 12 and 13.

Figures 12 and 13 show a very small but persisting difference between the OS and PFS projections for the axi-cel arm. These figures relate to the figure of 3-4% of patients going on to receive SCT as a number of these patients would be expected to experience long term survival. In other words, a small but persisting gap between the OS and PFS curves is plausible.

C6. Please explain the differences observed in the shapes of the OS and PFS curves for axi-cil in Figures 12 and 13 of the CES. For example, in Figure 12 the

curves seem to be rather parallel and flat between 60 and 100 months parallel and flat, whereas in Figure 13 this does not seem to be the case.

This is due to the difference in x-axis scale: Figure 12 of the CES is 100 months, and Figure 13 is 500 months. Please see below a replicated Figure 12 with an x-axis scale up to 500 month compared to CES Figure 13 (Figure 5).

Figure 5: OS and PFS curves for axi-cel with the same x-axis

C7. Please confirm that the following text on page 57 of the CES refers to PFS and not OS: *"Combining the estimated long-term survivor fraction (Table 17), age- and gender-matched mortality for the proportion of patients who experienced long-term survivorship, and the fitted parametric patients for the proportion of patients who did not, Figure 19 presents the overall estimated OS for each mixture cure model compared with the ZUMA-2 OS Kaplan–Meier data. Additionally, corresponding smoothed hazard plots are presented in Figure 20, while AIC and BIC statistics and landmark estimates are presented in Table 18"*.

Yes, this is a typo and should refer to PFS.

C8. Please confirm whether there is an error in Table 20: Two of the scenario analyses lead to the exact same ICER as the base case ICER (£). Also, in section A.16.4 the company mentions that *"based on AIC and BIC, the log-normal was the best fitting, and therefore tested in a scenario analysis"* for the mixture cure models of the PFS. This scenario is currently not included in Table 13, in which only the log-logistic model option of the mixture cure models for PFS is tested.

For the scenario “Axi-cel, PFS parametric curve: Log-logistic” in Table 20 of the CES, this is not relevant. The updated model uses the Gompertz single parametric model for axi-cel OS, consistent with the original model. We apologise for this confusion.

For the scenario “Use correct SMR method: Yes” in Table 20 of the CES, this is not an error. The original submission base case uses an SMR of 1 and a cut-off of 999 months. Therefore, when selection the option to use the correct SMR method individually, there is no impact on the ICER. This only occurs when the SMR is set to 1.09 and the cut-off is set to 60 months.

Updated versions of Table 20 and 21 of the CES are provided in Table 8 and Table 9, respectively.

Table 8: Updated Table 20 from the CES

	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER	ICER difference
Base-case	[redacted]	[redacted]	£45,917	0.0%	
ZUMA-1 data cut (OS). Re-submission 60M	[redacted]	[redacted]	£50,547	10.1%	£4,630
ZUMA-1 data cut (PFS). Re-submission 24M	[redacted]	[redacted]	£48,813	6.3%	£2,896
BSC, OS parametric curve: Generalised Gamma	[redacted]	[redacted]	£39,988	-12.9%	-£5,928
Axi-cel, OS parametric curve: Log-logistic	[redacted]	[redacted]	£51,870	13.0%	£5,954
Use updated life tables: Yes	[redacted]	[redacted]	£46,046	0.3%	£130
SMR cut-off (months): 60; SMR applied: 1.09	[redacted]	[redacted]	£46,493	1.3%	£576
Use correct SMR method: Yes	[redacted]	[redacted]	£45,917	0.0%	£0
Axi-cel discount percentage: [redacted]%; rebate: [redacted]%	[redacted]	[redacted]	£47,767	4.0%	£1,851
Key: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; SMR, standardized mortality ratio.					

Table 9: Updated Table 21 from the CES

	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER	ICER difference
Base-case	[redacted]	[redacted]	£45,917	0%	-
ZUMA-1 data cut (OS). Re-submission 60M	[redacted]	[redacted]	£50,547	10.1%	£4,630
ZUMA-1 data cut (PFS). Re-submission 24M	[redacted]	[redacted]	£52,466	14.3%	£6,549
BSC, OS parametric curve: Generalised Gamma	[redacted]	[redacted]	£44,885	-2.2%	-£1,032
Axi-cel, OS parametric curve: Log-logistic	[redacted]	[redacted]	£44,812	-2.4%	-£1,105
Use updated life tables: Yes	[redacted]	[redacted]	£45,005	-2.0%	-£912
SMR cut-off (months): 60; SMR applied: 1.09	[redacted]	[redacted]	£47,656	3.8%	£1,739
Use correct SMR method: Yes	[redacted]	[redacted]	£47,606	3.7%	£1,690
Axi-cel discount percentage: [redacted]%; rebate: [redacted]%	[redacted]	[redacted]	£49,159	7.1%	£3,243

Key: ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; SMR, standardized mortality ratio.

Reference:

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NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Guidance review following a period of managed access - Patient organisation submission

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for this treatment is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 20 pages.

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This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted]
2. Name of organisation	Anthony Nolan
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	**Anthony Nolan** saves the lives of people with blood cancer and other blood disorders. Founded in 1974 as the world's first stem cell register, we're motivated by a mother's determination to save her son, Anthony. Now saving three lives every day, our charity is a lifesaving legacy. By growing our register of potential stem cell donors, conducting ground-breaking research into improving transplant outcomes, and providing outstanding support and clinical care for patients and their families, Anthony Nolan cures people's blood cancer and blood disorders. A stem cell transplant is a potentially curative treatment for patients with blood cancers and blood disorders, and usually their last chance of survival. Anthony Nolan's main source of income is the provision of stem cells for transplant to NHS providers, collected from volunteer donors. Voluntary income (and fundraising events through Anthony Nolan Trading Ltd (ANTL) comes from a wide variety of generous supporters, including individual giving, legacies, community and events fundraising, corporate support, and charitable trusts. This helps to fund our ground-breaking scientific research, and growth and diversity of the stem cell donor register.

4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	Company Kite, Gilead – Anthony Nolan has received the following funding contributions from Kite, Gilead in the last 12 months: - Attendance of Anthony Nolan staff member to Kite CAR-T public affairs advisory board (£420) - Attendance of Anthony Nolan staff member to a speaker panel on cancer virtual series webinar 'Living with and Beyond Cancer (£230) Anthony Nolan has not received any funding from any of the comparator product companies in the last 12 months.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information for this appraisal was based on feedback received from people personally affected by diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMLBCL) and from people who have experience caring for axicabtagene ciloleucel (YESCARTA) recipients. This information was gathered through an online survey, with follow-up telephone interviews to understand more about their experiences. Our survey was shared on Anthony Nolan's Patients and Families Panel; via the Anthony Nolan Patients and Families Facebook page and social media channels. Clinical nurse specialists were also consulted to build our understanding of the experiences of patients and carers.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition?
Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life).
For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?
	Impact on daily life
	• Patients told us that both DLBCL and PMLBCL had a significant effect on their day-to-day life, including their ability to look after themselves, to be home with their family and plan for the future. Many said that DLBCL and PMLBCL '*took over their lives'* and that looking after themselves '*felt like a full-time job'*
	  ○ '*I was unable to socialise for years'* said one patient.
	  ○ Reflecting on the impact a PMLBCL diagnosis had on their son's ability to work, exercise, and live a typical lifestyle one carer commented *'it was devastating'.* The condition had a significant impact on family life, which was severely disrupted.
	  ○ Another patient, who was self-employed, said that DLBCL impacted every aspect of their life. They worried about their business, which was struggling as they couldn't work, their relationship, as they felt like a burden, and about catching an infection or becoming unwell again.
	• The financial impact of the condition and treatment is also very significant. Patients and carers are in many cases unable to work during both treatment and recovery. Some patients have been unable to return to work at all. Patients and carers often need to travel long distances to be near a treatment centre that delivers CAR-T, which further exacerbates the financial burden of the condition.
	• Many of the patients we spoke to told us about the lack of independence brought about by their condition, with the need to rely on networks of families and friends, and the generosity of others to help them get by.
	Mental health and wellbeing impact
	• The treatment journey for many patients takes several years, but the mental health impact can be even longer-term, outlasting their physical recovery. Patients told us that they frequently felt extremely depressed during points of their treatment, with one commenting that despite best efforts they '*often broke down'*.

	• One person said they were '*downhill, mentally for a prolonged period*' despite excellent support from friends and family members. Another commented that their support network was '*completely essential'* to their recovery.
7. What do carers experience when caring for someone with the condition?	**Experience of Carers** • Carers feel isolated, lonely, anxious and helpless when caring for someone with DLBCL or PMLBCL. • One carer we spoke to reflected on the huge amount of strain that caring for someone with DLBCL brought, saying that they were '*at breaking point*' trying to juggle work, home life and family time, while also traveling to visit their partner in hospital. • Another person we spoke to discussed the '*pressure'* that falls on carers, who often need to '*put on a brave face'* to keep the patient in a good frame of mind. They reflected that this can often cause a lot of stress and worry. • Many carers also experience a negative financial impact and may take a leave of absence from work or stop working all together to care for a loved one. One cared discussed the added stress of needing to rent a house near the treatment centre to facilitate almost daily hospital visits. They said, *'you are sleep deprived, stressed, anxious, scared – the lot, but you just keep going'*. • A patient who experienced relapsed DLBCL noted that their carer (and spouse) was in the most difficult position of anyone. They said, '*while I tried to focus my attention on treatment and recovery, my partner took a lot on, everything from childcare, to work, finances, family life, and my health'*.

8. What do patients and carers think of current treatments and care available on the NHS
Please state how they help and what the limitations are.
	Patient experience of current standard of care treatments and side effects
	• The patients that we spoke to had experience with a range of non-CAR-T treatments currently available on the NHS.
	• The need to take multiple drugs over a prolonged period often requires patients to remain in hospital for extended stays due to the need for ongoing clinical monitoring and supervision. This can have a disruptive impact on work and home life, impacting mental health and wellbeing.
	• The high-dose conditioning regimen required ahead of stem cell transplantation hit several people that we spoke to particularly hard, with one patient reflecting on vomiting '*all day long',* commenting '*I was so wiped out that I could hardly stand up*'.
	• Others described their experience of current routinely available treatment as '*totally debilitating'* causing them to experience '*every unpleasant side effect imaginable. Excruciating pain, severe sickness, constipation, peripheral neuropathy, hair loss, extreme fatigue and many more'.*
	• Others described the transplant and post-transplant recovery and being incredibly difficult, leaving one feeling at their '*absolute worst'* post HSCT.
	
	• R-CHOP (CHOP) chemotherapy (combination therapy of cyclophosphamide, doxorubicin (Adriamycin) vincristine, (Oncovin) and prednisolone, with the drug rituximab)
	  ○ One patient described feeling '*so weak after R-CHOP that I really didn't know how my body or my mind was going to cope with everything that was to come'.* They also described being '*on the floor'* due to the pain of the R-CHOP treatment, which they felt unprepared for.
	• DHAP (dexamethasone, cytarabine, cisplatin)
	  ○ Another patient reported that cisplatin was poorly tolerated, with tingling in their fingers and feet, and neuropathic pain in their feet from damaged nerve endings.
	• GDP (gemcitabine, dexamethasone, cisplatin)
	  ○ One patient who was given GDP as part of their treatment described it as making them feel extremely unwell and knocking them back significantly in their recovery process.

9. Considering all treatments available to patients are there any unmet needs for patients with this condition?	**The need for new treatments** • Patients can develop relapsed or refractory disease either during or following key treatment interventions, be that primary chemotherapy, transplantation or CAR-T infusion. These are key

If yes please state what these are	indicators for poor prognosis, with new treatments offering potential for improved survival and a sustained increased in quality of life. • Patients, particularly those with relapsed and refractory disease, described a '*narrow path to follow'* when talking about the number of treatment options they felt were available to them. They spoke about potential through clinical trials, rather than drugs that were routinely available. • A carer for someone with PMLBCL said they ran out of options after CAR-T treatment failed and they were forced to self-fund for experimental treatments as they '*reached the stage where there was nothing else available'*. • Some patients may not be eligible for HSCT due to their age and co-morbidities, highlighting the need for further treatment options.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	**Accessing the treatment** • Patients need to be monitored very closely when receiving axicabtagene ciloleucel and will commonly require regular assessment and prolonged inpatient stays for signs of cytokine release syndrome (CRS) and neurotoxicity. Some patients and carers commented that being in hospital and monitored closely for a new and complex treatment like CAR-T made them feel safer. • As previously mentioned, many patients and carers experience additional practical and financial strain due to the need to travel long distances to access this specialist treatment. One carer had to rent a property close to the hospital to facilitate the regular visits that had to be made as part of the treatment. This caused additional financial strain on the family. • Some patients noted that their referral to the CAR-T pathway had been delayed, which was highly concerning because treatment eligibility checks and condition monitoring prior to treatment is required and takes a significant period of time. Late referrals into treatment can mean that there is not enough time for these checks to be completed before the disease advances and patients become ineligible.

	• Patients also told us about their difficulties in accessing CAR-T through their clinical teams, with many patients and their carers having to self-advocate for access. One carer described the sheer volume of desk research they had to do in order to discover appropriate treatment options to discuss with the consultant. **Receiving the treatment** • Although patients predominantly receive CAR-T treatments like axicabtagene ciloleucel at present as in-patients, some hospitals can deliver follow-up treatment in ambulatory care settings (such as a hotel room or other off-site accommodation near the treating hospital) after the patient is discharged. Patients who have been offered accommodation to receive follow-up treatment in an ambulatory setting are very supportive of this option. • Patients can find the experience of being in hospital to receive axicabtagene cilolecuel uncomfortable and exhausting. For example, one patient we spoke to said they were not able to get as much rest as they would like, due to being disturbed by nursing staff needing to observe symptoms. • Patients can feel apprehensive and worried when they have had their CAR-T infusion as some of the potential side effects are '*scary to think about'*.
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	• Patients and carers spoke very passionately about the benefits of the treatment, providing a potentially effective treatment option where few others exist. • One carer said they were *'grateful'* their loved one could receive it, saying '*if it were possible, we would have asked for it again'*. They went on to say that the treatment was well tolerated, despite the long list of potential side effects. • The main benefit identified by patients and carers we spoke of was an increase in overall survival, and the importance of having this treatment option for when other treatments were no longer effective.

12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	• Patients are concerned about the lack of knowledge on the long-term outcomes and effects of the treatment. Patients and carers feel that long term follow-up and data collection is very important. • As the treatment can only be delivered in specialist centres, some patients may need to travel long distances for their care, causing significant practical and financial challenges. Receiving ambulatory care where applicable can help to make long stays away from home more comfortable and affordable for patients and their families. • For patients with aggressive disease, the treatment is only viable within a '*small window of opportunity'.* This is due to the length of time the delivery of the treatment can take, which can be a problem for rapidly deteriorating patients. • The therapy can have serious complications and side-effects; however, these risks can be mitigated with robust clinical protocols and monitoring. Patients and carers feel it is important to manage the balance of '*expectation vs reality'* with any new and exciting treatment. It is key to fully support patients and ensure they are aware of the potential side-effects and risks, as well as other aspects of the treatment like the need to travel, time in hospital etc.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	• Patients and carers were very positive about the current state and future of the treatment within the NHS, saying they were '*excited'* about the future benefit that could be brought to patients. • One patient we spoke to suggested they would like to see the technology delivered to patients sooner, if appropriate clinical evidence existed to support this. • Many of the patients and carers we spoke to were also optimistic about the potential for this treatment to treat other conditions, with new studies coming out to show its potential to benefit patients in a range of areas.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	• Anthony Nolan's involvement in the MAA for this treatment was not extensive, and our oversight of the tests and assessments was limited. • Commenting from a patient perspective, some patients derived a sense of comfort from the frequency of observations and tests that were undertaken during treatment, knowing that their condition was being regularly monitored for treatment effectiveness and side-effect tolerance. • A carer described differing results at the 30-day and 90-day scan as difficult, with early scans indicating there was '*no sign of cancer*' leaving the family feeling elated. Later scans showed the presence of lymphoma again.
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	Patients and carers did not comment on this
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	• One carer we spoke to commented that their experiences were captured well by the range of tests and assessments within the MMA, particularly highlighting the availability of psychological support services available to them during the treatment journey of the person they cared for.

17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	Patients and carers did not comment on this

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	• Patients who have begun a second-line therapy but who have struggled to tolerate the specific toxicity profile of comparator regimens or similar standard of care treatments. In pursuit of achieving a Complete Remission (CR) state, axicabtagene ciloleucel and similar CD19 therapies could be considered viable alternatives on account of its improved tolerance in some patients. • Patients with severe medical or psychiatric illness, active central nervous system involvement, or HIV seropositivity can be considered ineligible for autologous transplantation. • Patients with chemo refractory, relapsed disease, including acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and NHL could benefit more from accessing CD19 CAR-T therapies.

19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	We only received feedback from patients who had started their treatment of axicabtagene ciloleucel.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

- For ethnicity - there is little data presented but in many other diseases ethnic groups tend to fare worse with respect to patient outcomes.
- For age – ZUMA-1 demonstrates that advanced age is a risk factor for large B-cell lymphomas and is associated with an increased risk of relapse and death.
- For existing co-morbidities - axicabtagene ciloleucel can carry significant toxicity profiles for patients and clear information should be available to all patients in understanding the cost/benefit analysis to their quality of life, as well as additional support required in their recovery following treatment.

Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

None

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- DLBCL and PMLBCL can have a significant impact on the daily lives of patients and carers, particularly their mental health and wellbeing, and their ability to look after themselves and live independently.
- Many currently available treatment options can have a very significant impact on patients and are seen as harsh with significant side effects.
- Patients and carers were supportive of axicabtagene ciloleucel and spoke about the potential for better response rates longer term, with a key benefit being the hope of improved survival outcomes and progression free survival.
- Patients and carers felt it was appropriate to be so closely monitored during treatment, given the complexities of the treatment and its new and innovative nature.
- Patients and carers would strongly welcome the routine availability of axicabtagene ciloleucel within the NHS.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS Digital

Axicabtagene ciloleucel for treating diffuse large B–cell lymphoma and primary mediastinal B-cell lymphoma-data review

Commissioned by NHS England and NHS Improvement

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS Digital (NHSD). Its purpose is to collect and quality-assure high-quality, timely data on a wide range of diseases and provide robust surveillance to monitor and detect changes in health and disease in the population.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
NATIONAL DISEASE REGISTRATION SERVICE

National Disease Registration Service
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Improving lives with data and technology – NHS Digital support NHS staff at work, help people get the best care, and use the nation's health data to drive research and transform services.

NHS Digital

Contents

1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of axicabtagene ciloleucel for treating diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL). The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended the commissioning of axicabtagene ciloleucel through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned NHS Digital (NHSD) to evaluate the real-world treatment effectiveness of axicabtagene ciloleucel in the CDF population, during the managed access period. This report presents the results of the use of axicabtagene ciloleucel in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and NHSD partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 97% of patients and 92% of patient outcomes reported in the SACT dataset. NHSD and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma in the CDF. Patient NHS numbers were used to link Blueteq applications to NHSD's routinely collected SACT data to provide SACT treatment history.

Between 7 December 2018 and 31 October 2021, 358 applications for the axicabtagene ciloleucel infusion were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 318 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

318/329 (97%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

At data cut off, outcomes were expected for all 318 patients, having all been identified as receiving the single infusion. Of the 318 patients, 291 had an outcome as completed as prescribed in the SACT dataset.

The median OS was 28.5 months[a]. OS at 6 months was 77% [95% CI: 72%, 81%], 12 months OS was 64% [95% CI: 58%, 69%], OS at 18 months was 55% [95% CI: 49%, 61%], OS at 24 months was 52% [95% CI: 45%, 58%], OS at 30 months was 49% [95% CI: 41%, 56%] and OS at 36 months was 45% [95% CI: 34%, 55%].

An analysis on the use of Intravenous immunoglobulin (IVIG) use was carried out, results showed that 16% of patients who received axicabtagene ciloleucel also received IVIG treatment.

An OS sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with axicabtagene ciloleucel for DLBCL and PMBCL in the CDF. It evaluates OS and treatment outcomes for all patients treated with axicabtagene ciloleucel for this indication.

[a] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

2. Introduction

Diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) (ICD-10: C83.3 and C85.1) accounts for 2% of all cancer diagnoses in England. In 2018, 5,179 patients were diagnosed with either DLBCL or PMBCL (males 2,902, females 2,277)[2].

- axicabtagene ciloleucel therapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies, only if the conditions in the managed access agreement are followed[3].

3. Background to this report

The NHS Digital and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and NHS Digital's (NHSD's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the NHSD and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by NHSD. This includes NHS England and NHS Improvement commissioning NHSD to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHSD analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Disease Registration Service (NDRS), which is part of NHSD.

NICE Appraisal Committee review of axicabtagene ciloleucel for treating DLBCL and PMBCL [TA559]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of axicabtagene ciloleucel (Gilead/Kite Sciences LTD) in treating DLBCL and PMBCL [TA559] and published guidance for this indication in January 2019[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of axicabtagene ciloleucel for the treatment of DLBCL and PMBCL through the CDF for a period 38 months, from December 2018 to February 2022.

During the CDF funding period, results from an ongoing clinical trial (ZUMA-1[7]) evaluating axicabtagene ciloleucel in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the ZUMA-1 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for axicabtagene ciloleucel for the treatment of DLBCL and PMBCL in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the ZUMA-1 clinical trial[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- convergence of progression-free survival and overall survival curves
- the use of intravenous immunoglobulin
- overall survival from the infusion of axicabtagene ciloleucel

As part of the guidance review, Gilead/Kite Sciences LTD will provide supportive data from the ZUMA-1 clinical trial, the phase I/II single group assignment, open label, clinical trial[7], and NHSD will supplement this by providing information on overall survival and patient characteristics.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, NHSD and the company (Gilead/Kite Sciences LTD) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of axicabtagene ciloleucel. It also detailed the eligibility criteria for patient access to axicabtagene ciloleucel through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for axicabtagene ciloleucel, approved through Blueteq® and followed up in the SACT dataset collected by NHSD.

4. Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHSD has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS Digital (NHSD), through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England and NHS Improvement.

NHSD collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Axicabtagene ciloleucel clinical treatment criteria

- applications are made for leucapheresis and the treatment of axicabtagene ciloleucel and will be initiated by a consultant haematologist or medical oncologist specifically trained and accredited in the use of systemic anti-cancer therapy and working in an accredited CAR-T cell treatment centre and who is
    - a member of the National CAR-T Clinical Panel for diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma and transformed follicular lymphoma; and
    - a member of the treating Trust's diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma and transformed follicular lymphoma and CAR-T cell multidisciplinary teams
- patient has a confirmed histological diagnosis of diffuse large B-cell lymphoma or primary mediastinal B-cell lymphoma or transformed follicular lymphoma and the diagnosis has been either made by or reviewed and confirmed by a designated lymphoma stem cell transplant centre.
- prior to consideration of CAR-T cell therapy the patient's disease has been re-biopsied, unless a biopsy was unsafe, in which case the patient must have progressive disease at previously known sites of active disease. In such situations the original diagnostic biopsy review is acceptable. All patients with transformed follicular lymphoma who fulfil criteria 5 below must have a re-biopsy and confirmation of transformed follicular lymphoma histology prior to consideration of CAR-T cell therapy
    - re-biopsy has confirmed diffuse large B-cell lymphoma or
    - re-biopsy has confirmed primary mediastinal B-cell lymphoma or
    - re-biopsy has confirmed transformed follicular lymphoma to diffuse large B-cell lymphoma or
    - re-biopsy is unsafe, there is progressive disease at previously documented sites of active disease and previous histology was diffuse large B-cell lymphoma or
    - re-biopsy is unsafe, there is progressive disease at previously documented sites of active disease and previous histology was primary mediastinal B-cell lymphoma
- patient fulfils one of the following clinical scenarios relating to the definition of relapsed or refractory lymphoma:

Note: Refractory disease is defined as progressive disease or stable disease (lasting <6 months) as best response to last line of therapy, or disease progression within 12 months of stem cell transplantation. Neither radiotherapy nor steroids can be counted as a line of therapy.

- patient has diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy and relapsed after the last line of systemic therapy OR
- patient has diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy and was refractory to the last line of systemic therapy OR
- patient has primary mediastinal B-cell lymphoma and received 2 or more lines of systemic therapy and relapsed after the last line of systemic therapy OR
- patient has primary mediastinal B-cell lymphoma and received 2 or more lines of systemic therapy and was refractory to the last line of systemic therapy OR
- patient has transformed follicular lymphoma to diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy since diagnosis of transformation and relapsed after the last line of systemic therapy OR

- patient has transformed follicular lymphoma to diffuse large B-cell lymphoma and received 2 or more lines of systemic therapy since diagnosis of transformation and was refractory to the last line of systemic therapy OR
- patient has transformed follicular lymphoma to diffuse large B-cell lymphoma, received an anthracycline-containing regimen before transformation and then received 1 or more lines of systemic therapy and was refractory to the last line of systemic therapy
- patient has been previously treated with a full dose of anthracycline-containing regimen for the lymphoma
- patient has been previously treated with at least one anti-CD20 monoclonal antibody unless there is clear documentation of the determination of CD20 negative disease
- confirm whether the patient has not had stem cell transplantation or has had stem cell transplantation
- patient has not previously been treated with an anti-CD19 antibody-drug conjugate or if previously treated with an anti-CD19 antibody-drug conjugate that a biopsy of the relapsed/refractory disease has been done and has been shown to be CD19 positive
- patient does not have primary CNS lymphoma
- patient does not have known active CNS involvement by the lymphoma
- patient is aged 18 years or older on the date of approval for axicabtagene ciloleucel by the National CAR-T Clinical Panel
- patient has an ECOG performance score of 0 or 1 at the time of leucapheresis and an ECOG performance score of 0-2 at the time of infusion
- patient has sufficient end organ function to tolerate treatment with axicabtagene ciloleucel
- patient has had no previous therapy with any genetically modified autologous T cell immunotherapy1[b]
- prior to infusion a minimum of 4 doses of tocilizumab are available for use in this patient in the event of the development of cytokine release syndrome
- axicabtagene ciloleucel-modified CAR-T cell therapy will otherwise be used as set out in its Summary of Product Characteristics
- approval for the use of axicabtagene ciloleucel has been formally given by the National DLBCL/PMBCL/TFL CAR-T cell Clinical Panel
- following national approval for use of axicabtagene ciloleucel there has been local CAR-T cell multidisciplinary team agreement, that this patient continues to have the necessary fitness for treatment and fulfils all of the treatment criteria listed here

[b] This criteria has been expanded by NHS England and NHS Improvement to include patients that have either had no previous therapy with any genetically modified autologous or allogeneic T cell immunotherapy or the patient has been treated with doses of genetically modified autologous or allogeneic T cell immunotherapy within an abandoned dosing cohort in a first in human dose-escalation phase I clinical trial. This change has been incorporated into NHS England and NHS Improvement's Blueteq criteria.

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply for axicabtagene ciloleucel for the treatment of DLBCL and PMBCL for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for axicabtagene ciloleucel for the treatment of DLBCL and PMBCL for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted axicabtagene ciloleucel for the treatment of DLBCL and PMBCL and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

5.Initial CDF cohorts

The analysis cohort is limited to the date axicabtagene ciloleucel entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 7 December 2018 to 31 October 2021. A snapshot of SACT data was taken on 5 February 2022 and made available for analysis on 11 February 2022 and includes SACT activity up to the 31 October 2021. Tracing the patients' vital status was carried out on 3 March 2022 using the Personal Demographics Service (PDS)[1].

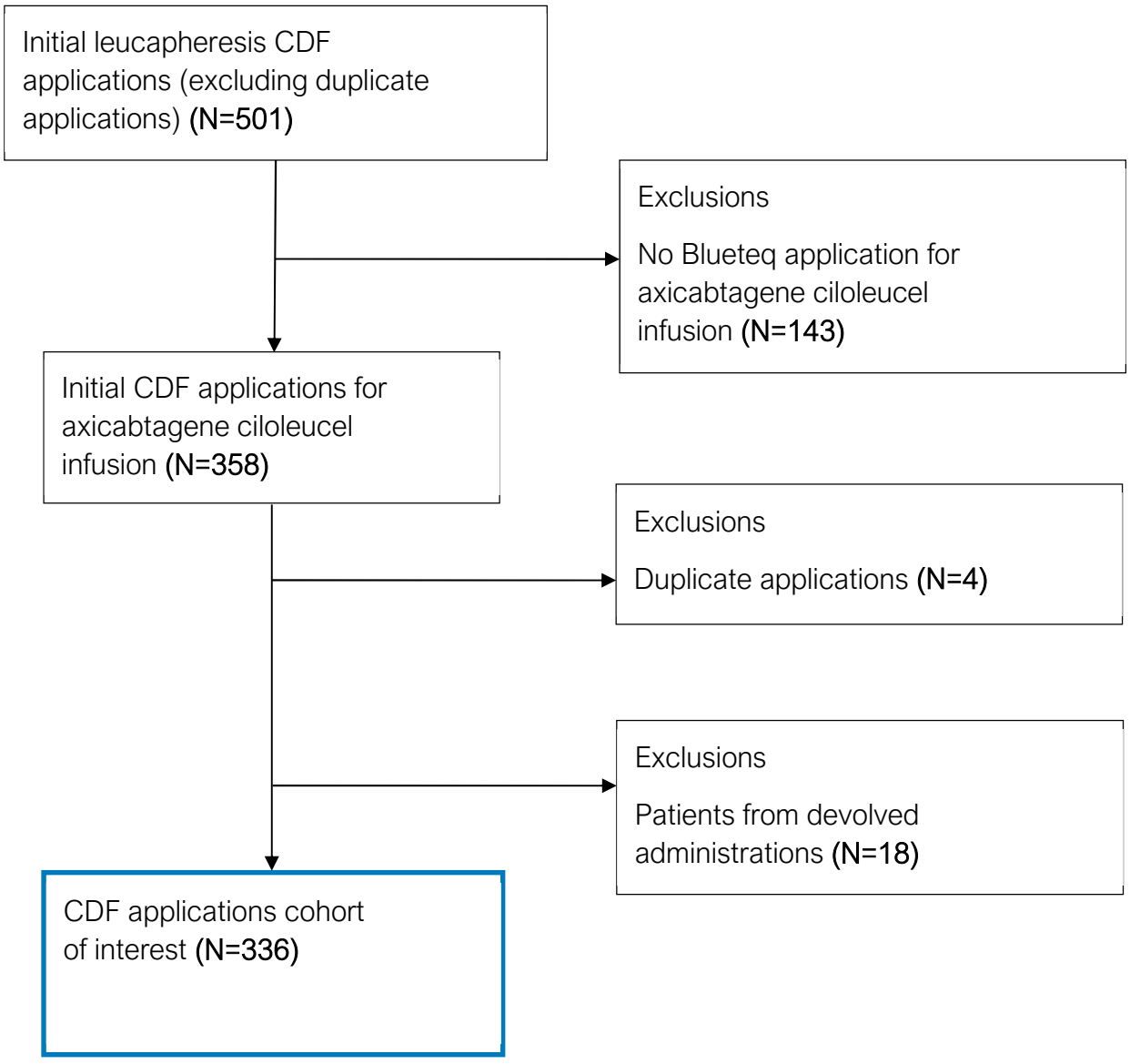
Two CDF applications are required for axicabtagene ciloleucel. The initial application is made at the point of leucapheresis and manufacture of the CAR-T cells, and a subsequent application is required at the point of infusion of the CAR-T cells. It was not possible to collect reasons why any subsequent infusion application was not made following a leucapheresis application.

There were 507 CDF funding applications for leucapheresis between 7 December 2018 and 31 October 2021, relating to 501 unique patients.

There were 358 applications for CDF funding for axicabtagene ciloleucel infusion for the treatment of DLBCL and PMBCL between 7 December 2018 and 31 October 2021 in the NHS England and

NHS Improvement Blueteq database. This relates to 336 unique patients after the exclusion of four duplicate application and 18 patients who were registered at GP practices in either Scotland, Wales or Northern Ireland. No patients received axicabtagene ciloleucel infusion before the CDF start date.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for axicabtagene ciloleucel for the treatment of DLBCL and PMBCL between 7 December 2018 and 31 October 2021



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for the axicabtagene ciloleucel infusion in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date[8] in the SACT dataset for the treatment of interest. Data items[9] used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27
- administration date – SACT data item #34

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

Dead (event):

At the date of death recorded on the PDS.

Alive (censored):

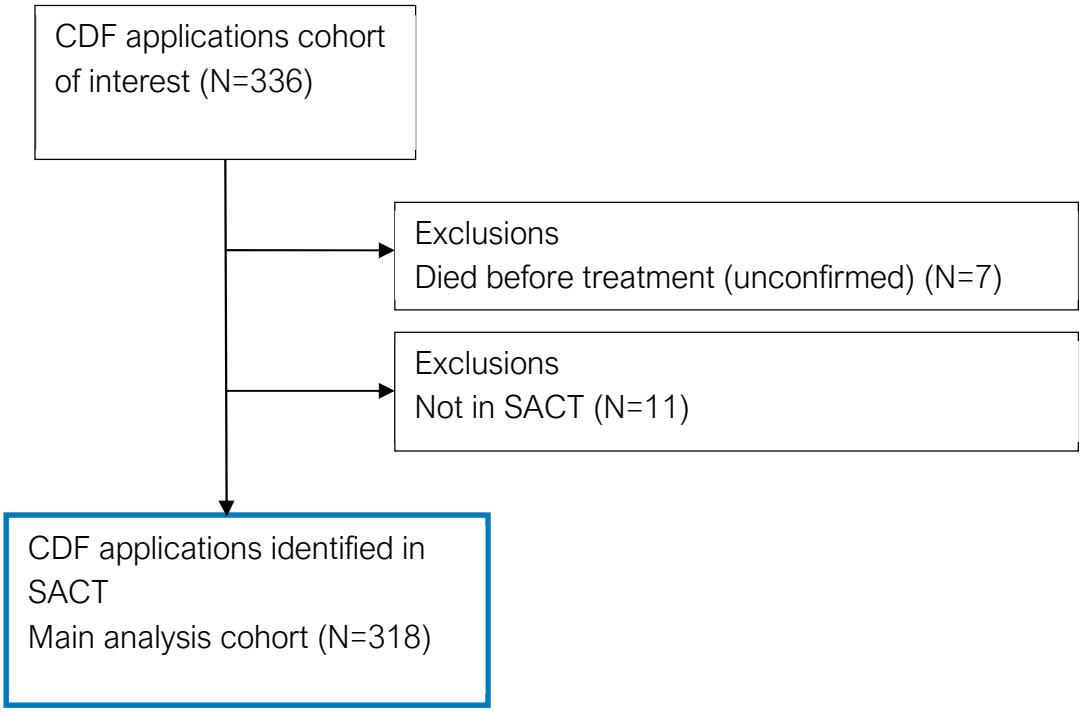
At the date patients were traced for their vital status as patients are confirmed as alive on this date.

6. Results

Cohort of interest

Of the 336 applications for CDF funding axicabtagene ciloleucel for the treatment of DLBCL and PMBCL, seven patients died before treatment and 11 patients were missing from SACT[c] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for axicabtagene ciloleucel for the treatment of DLBCL and PMBCL between 7 December 2018 and 31 October 2021



A maximum of 329 axicabtagene ciloleucel records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 97% (318/329) of these applicants for CDF funding have a treatment record in SACT.

[c] Of the seven patients who died before treatment, none were confirmed by the relevant trust as deaths before treatment by the SACT data liaison team.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender, start date of regimen and start date of cycle. Administration date is 99% and performance status at the start of regimen is 63% complete.

Table 1: Completeness of key SACT data items for the axicabtagene ciloleucel cohort (N=318)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Gender	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	99%
Performance status at start of regimen	63%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment for this indication all 318 patients have received a single infusion of axicabtagene ciloleucel, and as such, a treatment completed as prescribed outcome is expected. Of the 318 patients that have received the single infusion, 291 have an outcome summary recorded in the SACT dataset 92% (291/318).

Table 2: Completeness of outcome summary for patients that have ended treatment (N=318)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	92%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq.

Table 3: Completeness of Blueteq key variables for the axicabtagene ciloleucel infusion cohort (N=318)

Variable	Completeness (%)
Stem cell transplant suitability	100%
Confirmed histological diagnosis	100%
Re-biopsied options	100%
Relapsed or refractory and line of therapy	100%
Previous immunotherapy	99.7%
Bridging therapy	100%

Patient characteristics

The median age of the 318 patients receiving the axicabtagene ciloleucel infusion for DLBCL and PMBCL was 59.5 years. The median age in males and females was 60 and 59 years respectively.

Table 4: Patient characteristics (N=318)

Patient characteristics[d]			
		N	%
Gender	Male	191	60%
	Female	127	40%
Age	<40	34	11%
	40 to 49	43	14%
	50 to 59	82	26%
	60 to 69	124	39%
	70 to 79	35	11%
	80+	0	0%
Performance status	0	75	24%
	1	111	35%
	2	13	4%
	3	0	0%
	4	0	0%
	Missing	119	37%

[d] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items.

Table 5: Distribution of key Blueteq data items (N=318)

Blueteq data items[e]		N	%
Stem cell transplant suitability	Has not had a SCT	247	78%
	Has had an autologous SCT	66	21%
	Has had an allogeneic SCT	5	2%
Confirmed histological diagnosis	Diffuse large B-cell lymphoma	222	70%
	Transformed follicular lymphoma	73	23%
	Primary mediastinal B-cell lymphoma	23	7%
Re-biopsied options	Re-Biopsy has confirmed DLBCL	203	64%
	Re-biopsy is unsafe, DLBCL	47	15%
	Re-Biopsy has confirmed transformed TFL to DLBCL	46	14%
	Re-Biopsy has confirmed PMBCL	18	6%
	Re-biopsy is unsafe, PMBCL	4	1%
Relapsed or refractory and line of therapy	Has DLBCL and received 2 or more lines of systemic therapy and was refractory	159	50%
	Has DLBCL and received 2 or more lines of systemic therapy and relapsed	72	23%
	Has TFL to DLBCL and received 2 or more lines of systemic therapy and relapsed	23	7%
	has TFL to DLBCL, received an anthracycline-containing regimen before transformation and then received 1 or more lines of systemic therapy and was refractory to the last line of systemic therapy	23	7%
	Has PMBCL and received 2 or more lines of systemic therapy and was refractory	22	7%
	Has TFL to DLBCL and received 2 or more lines of systemic therapy and was refractory	19	6%

[e] Figures may not add to 100% due to rounding.

Blueteq data items[f]		N	%
Previous immunotherapy	No previous therapy with any genetically modified T cell immunotherapy	316	99%
	Previously treated with doses of genetically modified T cell immunotherapy	1	Less than 1%
	Not captured	1	Less than 1%
Bridging therapy	Chemo(immuno)therapy only	141	44%
	Corticosteroids and chemo(immuno)therapy	45	14%
	Radiotherapy only	39	12%
	No bridging therapy at all	30	9%
	Corticosteroids only	25	8%
	Chemo(immuno)therapy and radiotherapy ± corticosteroids	20	6%
	Corticosteroids and radiotherapy	18	6%

Treatment outcomes

Of the 318 patients with CDF applications, all have completed treatment after receiving a single infusion of axicabtagene ciloleucel. 132 patients have since died (see Table 6).

Table 6: Treatment outcomes for patients that received axicabtagene ciloleucel infusion for treating DLBCL and PMBCL (N=318)[g,h]

Treatment outcome	Frequency	Percentage
Completed treatment – received single infusion and are still alive	186	58%
Completed treatment – died after single infusion	132	42%
Total	**318**	**100%**

[f] Figures may not add to 100% due to rounding.
[g] Figures may not sum to 100% due to rounding.
[h] Table 10 presents the outcome summary data for patients that have received axicabtagene ciloleucel infusion for the treatment of DLBCL and PMBCL.

Overall survival (OS)

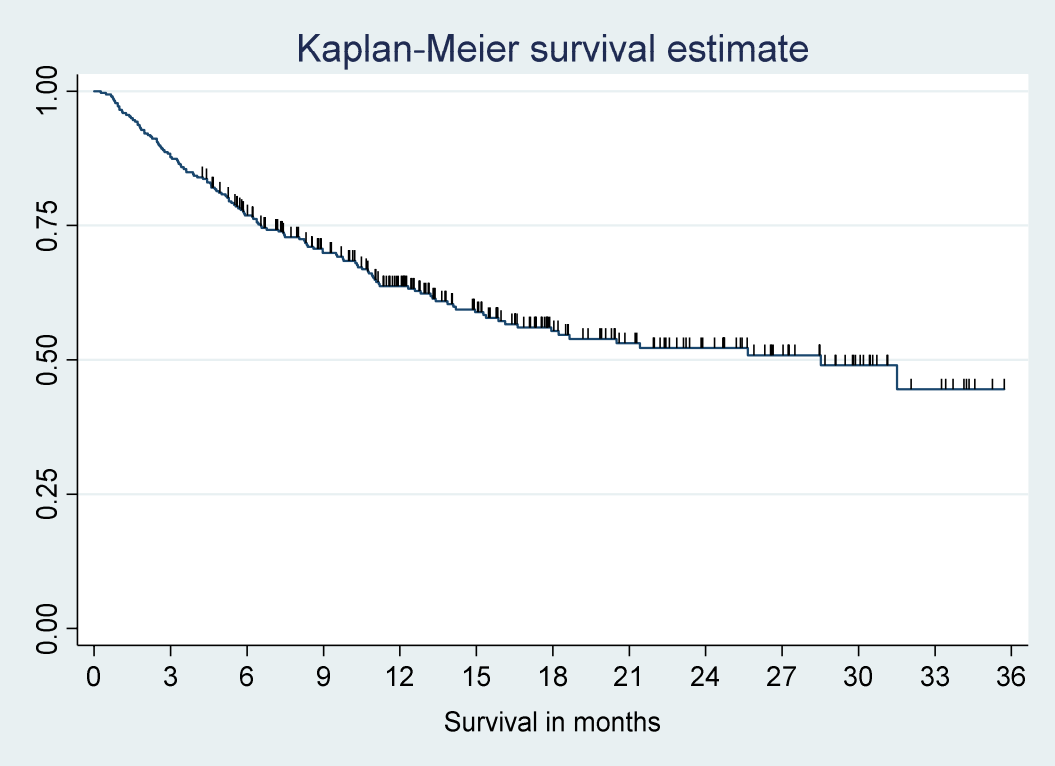
Of the 318 patients with a treatment record in SACT, the minimum follow-up was four months (121 days) from the last CDF application. Patients were traced for their vital status on 3 March 2022. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 11.2 months (340 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 7: OS at 6, 12, 18, 24, 30 and 36-month intervals

Time period	OS (%)
6 months	77% [95% CI: 72%, 81%]
12 months	64% [95% CI: 58%, 69%]
18 months	55% [95% CI: 49%, 61%]
24 months	52% [95% CI: 45%, 58%]
30 months	49% [95% CI: 41%, 56%]
36 months	45% [95% CI: 34%, 55%]

Figure 3 provides the Kaplan-Meier curve for OS, censored at 3 March 2022. The median OS was 28.5 months[i] .

Figure 3: Kaplan-Meier survival plot (N=318)



[i] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Table 8 and Table 9 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 38.8 months (1,180 days), all patients were traced on 3 March 2022.

Table 8: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Number at risk	318	279	232	188	148	110	79	62	47	32	18	9

Table 9 shows that for all patients who received treatment, 186 were still alive (censored) at the date of follow-up and 132 had died (events).

Table 9: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Censored	186	186	173	149	125	97	72	58	44	30	17	9
Events	132	93	59	39	23	13	7	4	3	2	1	0

Intravenous immunoglobulin (IVIG) use

Of the 318 patients who received axicabtagene ciloleucel between 7 December 2018 and 31 October 2021, 262 (82%) patients were included in this analysis as CDF applications from Kings College Hospital NHS Foundation Trust were excluded due to no IVIG data being available at the point of this report being produced, and as such, Kings was removed from the denominator.

All patients who received axicabtagene ciloleucel were followed up in the immunoglobulin database (MDSAS) on 24 May 2022.

Of the 262 patients, 41 (16%) patients received IVIG, of which, 39 patients received IVIG after receiving a single infusion of axicabtagene ciloleucel[j]. The average duration of therapy was 8.5 months (258 days) with the range being <1 month up to 33 months.

Of the 41 patients who received IVIG, 25 (61%) were identified as having completed treatment by 24 May 2022 (see Table 10). Patients are assumed to have completed IVIG treatment if they have died, or they have not received treatment with IVIG in at least three months.

Table 10: Breakdown by patients' IVIG treatment status

Patient status	Frequency (N)	Percentage (%)
Patient died	9	22%
Treatment stopped	16	39%
Treatment ongoing	16	39%
Total	41	100%

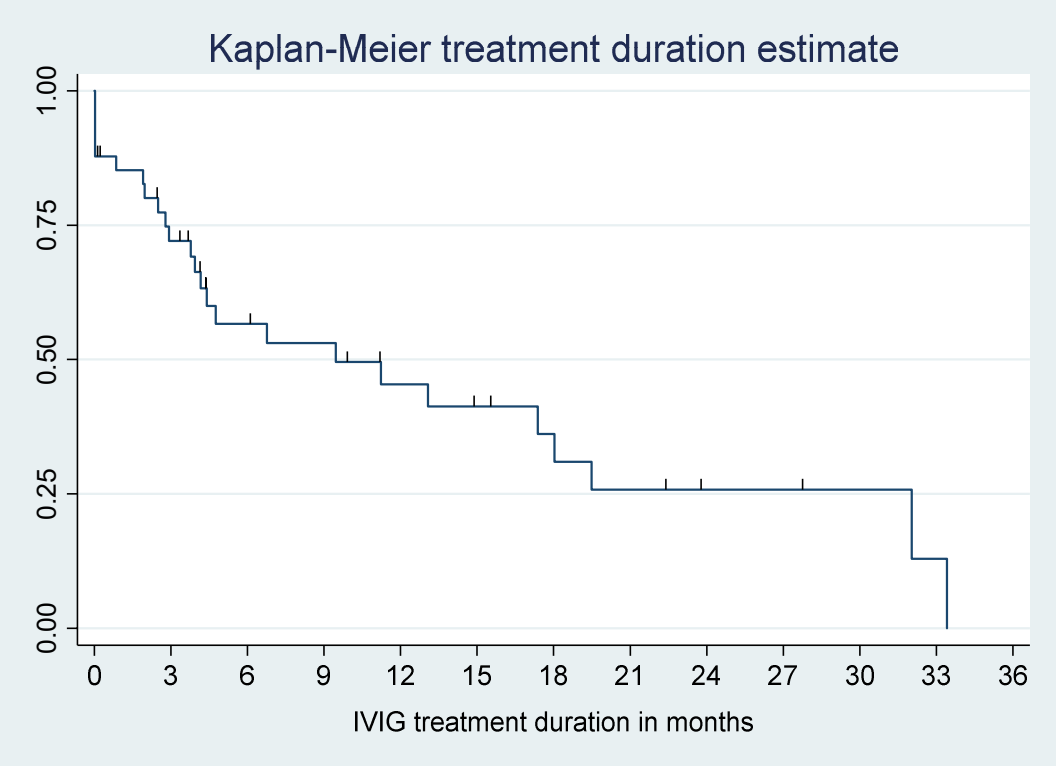
Table 11: Number and percentage of patients who received IVIG.

Total number of patients	Patients who received IVIG	
	N	%
262	41	16%

[j] One patient started IVIG before receiving the single axicabtagene ciloleucel infusion and continued to receive IVIG after the infusion.

The Kaplan-Meier curve shown in Figure 4 shows the median treatment duration for all patients was 9.5 months [95% CI: 3.9, 18.0] (289 days).

Figure 4: Kaplan-Meier treatment duration (N=41)[k]



[k] A prescription length of one day was added to the end of each patient's treatment duration.

Table 12 and Table 13 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started IVIG treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 41.5 months (1,263 days), all patients were linked to the immunoglobulin database (MDSAS) on 24 May 2022.

Table 12 show the number of patients at risk, from the time patients started treatment to the time patient ended IVIG treatment.

Table 12: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Number at risk	41	27	17	15	11	9	7	5	3	3	2	1

Table 13 shows that for all patients who received IVIG treatment, 16 were still on treatment (censored) at the date of follow-up (24 May 2022) and 25 had ended treatment (events).

Table 13: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Censored	16	13	8	7	5	4	3	3	1	1	0	0
Events	25	14	9	8	6	5	4	2	2	2	2	1

7. Sensitivity analysis

6-month SACT follow up

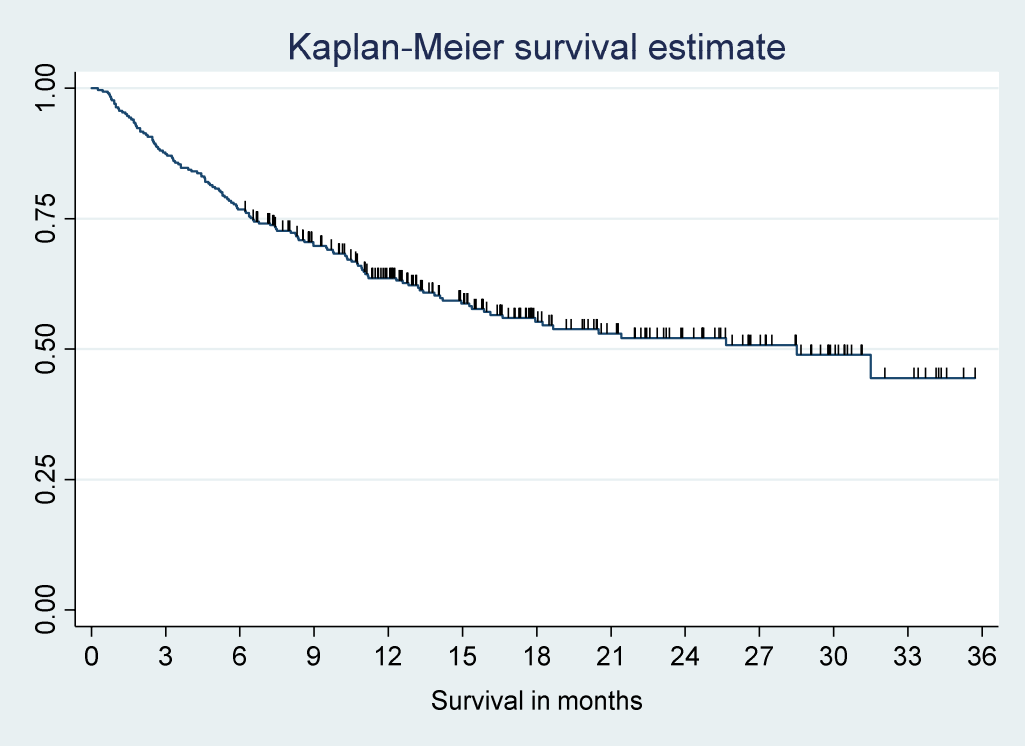
Overall survival (OS)

Sensitivity analyses were also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 7 December 2018 to 3 September 2021.

Following the exclusions above, 301 patients (95%) were included in these analyses. The median follow-up time in SACT was 11.8 months (359 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 5 provides the Kaplan-Meier curve for OS, censored at 3 March 2022. The median OS was 28.5 months[I] .

Figure 5: Kaplan-Meier survival plot (N=301)



[I] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

Table 14 and Table 15 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 38.8 months (1,180 days), all patients were traced on 3 March 2022.

Table 14: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Number at risk	301	263	231	188	148	110	79	62	47	32	18	9

Table 15 shows that for all patients who received treatment,172 were still alive (censored) at the date of follow-up and 129 had died (events).

Table 15: Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Censored	172	172	172	149	125	97	72	58	44	30	17	9
Events	129	91	59	39	23	13	7	4	3	2	1	0

Table 16: Median OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort:
N	318	301
OS[m]	28.5 months	28.5 months

[m] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

8. Conclusions

329 patients received axicabtagene ciloleucel infusion for the treatment of DLBCL and PMBCL [TA559] through the CDF in the reporting period (7 December 2018 to 31 October 2021). 318 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 97%. An additional seven patients with a CDF application died before treatment. None of the seven patients identified as death before treatment were confirmed by the trust responsible for the CDF application.

Patient characteristics from the SACT dataset show that 60% (N=191) of patients that received axicabtagene ciloleucel infusion for the treatment of DLBCL and PMBCL were male, 40% (N=127) of patients were female. 65% of the cohort were aged between 50 and 69, (N=206) and 63% (N=199) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, outcomes were expected for all 318 patients, having all been identified as receiving the single infusion. Of the 318 patients, 291 had an outcome of treatment completed as prescribed in the SACT dataset.

The median OS was 28.5 months[n]. OS at 6 months was 77% [95% CI: 72%, 81%], 12 months OS was 64% [95% CI: 58%, 69%], OS at 18 months was 55% [95% CI: 49%, 61%], OS at 24 months was 52% [95% CI: 45%, 58%], OS at 30 months was 49% [95% CI: 41%, 56%] and OS at 36 months was 45% [95% CI: 34%, 55%].

IVIG treatment use showed the median treatment duration for all 41 patients who received IVIG after receiving the single infusion of axicabtagene ciloleucel was 9.5 months [95% CI: 3.9, 18.0] (289 days).

Sensitivity analysis was carried out on OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results showed no difference in the median OS (full cohort = 28.5 months; sensitivity analysis cohort = 28.5 months).

[n] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

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10. Addendum

Intravenous immunoglobulin (IVIG) use

All 318 patients who received axicabtagene ciloleucel between 7 December 2018 and 31 October 2021 were followed up in the immunoglobulin database (MDSAS). 262 patients were followed up in MDSAS on 24 May 2022 and the remaining 56 patients of Kings College Hospital NHS Foundation Trust were followed up in MDSAS on 4 July 2022[o], due to a delay in IVIG data availability. As a result, two follow-up dates have been applied.

Of the 318 patients, 61 (19%) patients received IVIG, of which, 57 patients received IVIG after receiving a single infusion of axicabtagene ciloleucel[p]. The average duration of therapy was 9.6 months (292 days) with the range being <1 month up to 33 months.

Of the 61 patients who received IVIG, 38 (62%) were identified as having completed treatment by 24 May 2022 or 4 July 2022 if treated at Kings (see Table 1). Patients are assumed to have completed IVIG treatment if they have died, or they have not received treatment with IVIG in at least three months.

Table 1: Breakdown by patients' IVIG treatment status

Patient status	Frequency (N)	Percentage (%)
Patient died	16	26%
Treatment stopped	22	36%
Treatment ongoing	23	38%
Total	61	100%

[o] Addendum includes Kings IVIG data which was not included in the final report

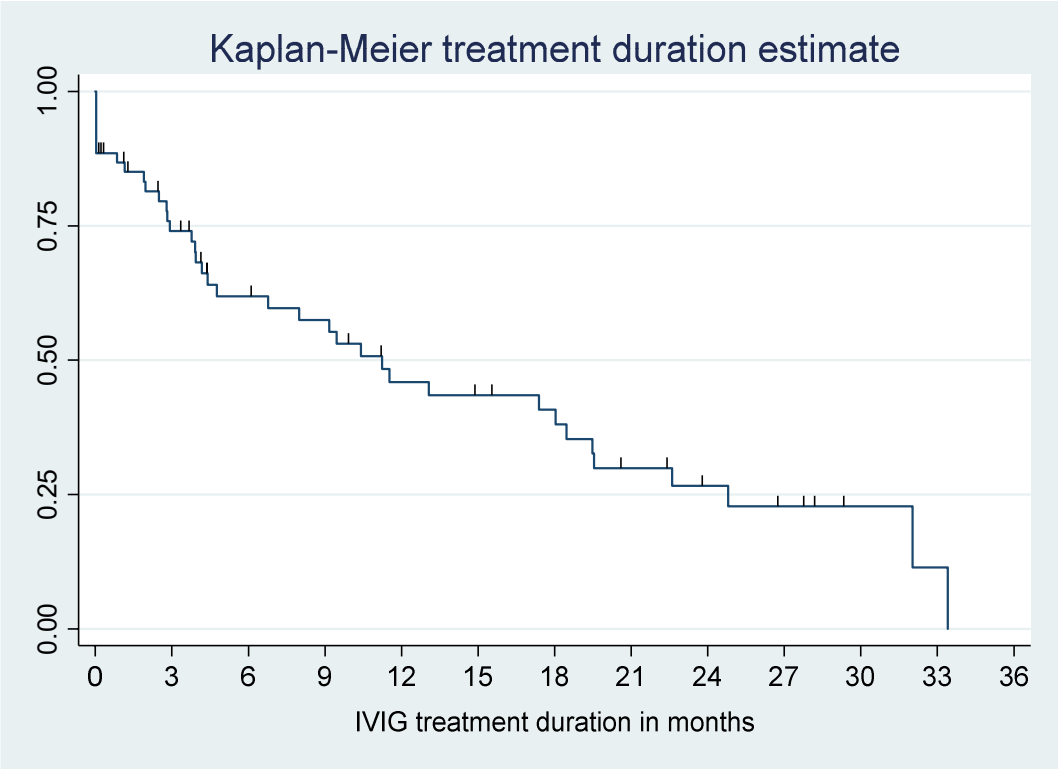
[p] One patient started IVIG before receiving the single axicabtagene ciloleucel infusion and continued to receive IVIG after the infusion.

Table 2: Number and percentage of patients who received IVIG.

Total number of patients	Patients who received IVIG	
	N	%
318	61	19%

The Kaplan-Meier curve shown in Figure 4 shows the median treatment duration for all patients was 11.2 months [95% CI: 4.4, 18.5] (340 days).

Figure 1: Kaplan-Meier treatment duration (N=61)[q]



[q] A prescription length of one day was added to the end of each patient's treatment duration.

Table 3 and 4 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started IVIG treatment to the end of the follow-up period. The maximum follow-up period for all patients (excluding Kings) for treatment duration was 41.5 months (1,263 days), patients were linked to the immunoglobulin database (MDSAS) on 24 May 2022 or 4 July 2022 if Kings where the maximum follow-up period was 42.9 months (1,305 days).

Table 3 shows the number of patients at risk, from the time patients started treatment to the time patient ended IVIG treatment.

Table 3: Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Number at risk	61	40	29	26	19	17	15	10	7	5	2	1

Table 4 shows that for all patients who received IVIG treatment, 23 were still on treatment (censored) at the date of follow-up (24 May 2022, or 4 July 2022 if Kings) and 38 had ended treatment (events).

Table 4: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-36	3-36	6-36	9-36	12-36	15-36	18-36	21-36	24-36	27-36	30-36	33-36
Censored	23	17	12	11	9	8	7	6	4	3	0	0
Events	38	23	17	15	10	9	8	4	3	2	2	1

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

Produced by

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

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

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

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

Abbreviations

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

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

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1. EXECUTIVE SUMMARY

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

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

Table 1.1: Preferred assumptions from Terms of Engagement

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

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

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

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

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

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

1.2 Summary of key issues in the clinical effectiveness evidence

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

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

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

1.3 Summary of the key issues in the cost effectiveness evidence

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2. INTRODUCTION AND BACKGROUND

2.1 Background

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

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

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

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

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

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

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

Table 2.1: Preferred assumptions from Terms of Engagement

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

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

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

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

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

2.2.1 Assumption 1: Population

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

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

2.2.2 Assumption 2: Comparator

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

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

2.2.3 Assumption 3: Indirect treatment comparison

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

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

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

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

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

Table 2.2:Summary of SCHOLAR-1 adjustments

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

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

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

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

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

2.2.4 Assumption 4: Sources of comparator data

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

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

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

2.2.5 Assumption 5: Subsequent treatments

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

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

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

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

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

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

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

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

2.2.7 Assumption 7: Cure assumption

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

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

2.2.8 Assumption 8: Most plausible ICER

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

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

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

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

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

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

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

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

3. CLINICAL EFFECTIVENESS

3.1 Overview of the new clinical evidence

3.1.1 Sources of evidence

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

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

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

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

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

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

1. MD Anderson Cancer Centre (MDACC) database,

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

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

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

Table 3.1 summarises the methodology of the included studies.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.2 Results of the new clinical evidence

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

3.2.1 Overall survival

3.2.1.1 ZUMA-1

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

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

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

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

Time point	Survival rate by Kaplan–Meier estimation	
	Phase I (N=7)	Phase II (N=101)
12 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
36 months	[redacted]	[redacted]
48 months	[redacted]	[redacted]
60 months	[redacted]	[redacted]

Based on Table 4, CES[2]

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

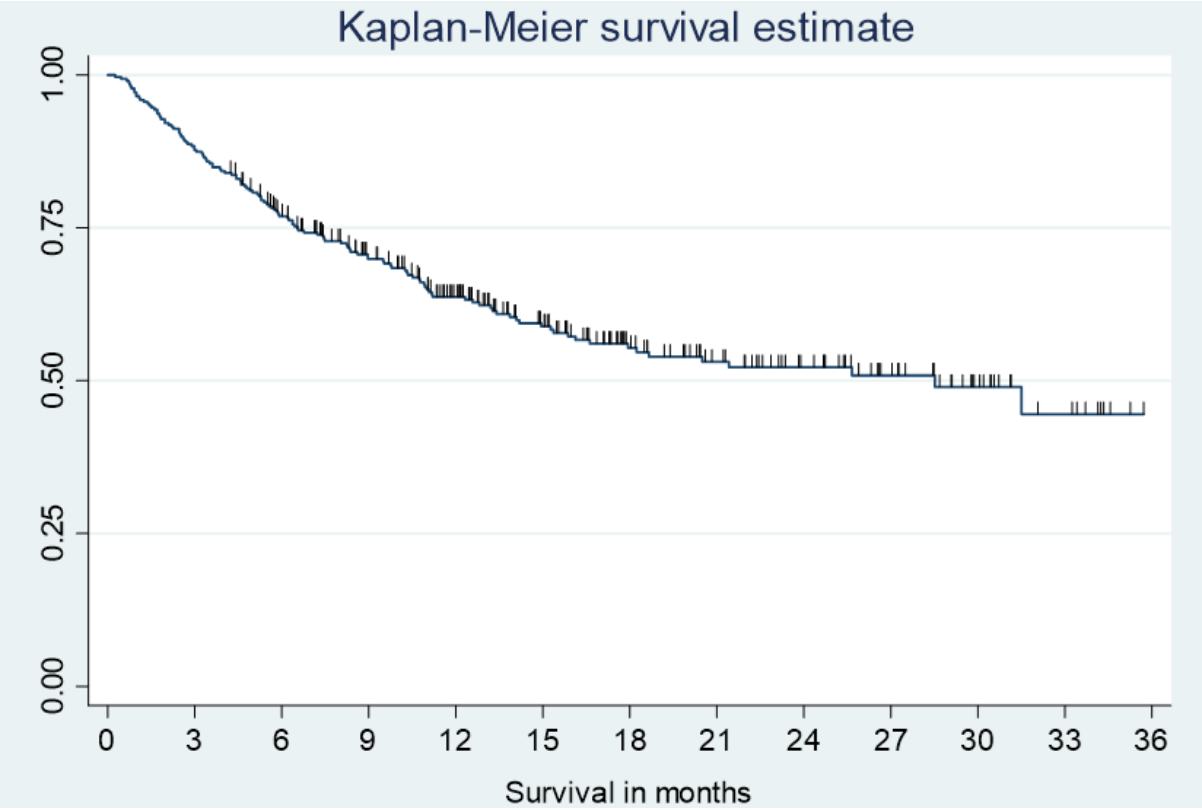
Among patients who achieved a complete response (CR) (N= [redacted]), the estimated 60-month survival rate was [redacted]% in Phase I and [redacted]% in Phase II.

3.2.1.2 SACT data

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

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

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



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

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

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

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

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

3.2.1.3 SCHOLAR-1 cohort (comparator data)

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

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

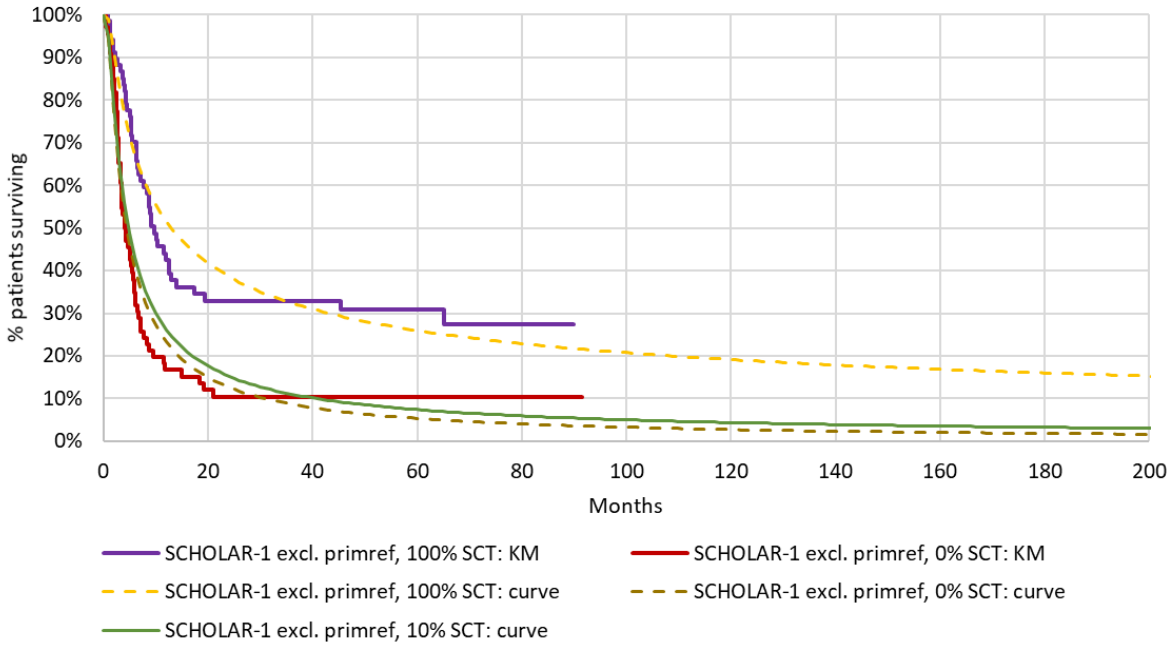
Regarding the adjustment for SCT, the 10% estimate was based on clinical opinion (CDF discussions and tisagenlecleucel appraisal meeting) that approximately 10% of patients would receive SCT in clinical practice after undergoing two or more lines of systemic treatment.[14]

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

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

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

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



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

3.2.1.4 Additional comparator data from three additional sources

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

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

3.2.1.5 Indirect treatment comparison

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

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

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

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

3.2.2 Overall survival by best objective response

3.2.2.1 ZUMA-1

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

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

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

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

3.2.2.2 SACT data

No data provided in the CES.

3.2.2.3 SCHOLAR-1 cohort

No data provided in the CES.

3.2.2.4 Additional comparator data from three additional sources

No data provided in the CES.

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

3.2.3 Progression-free survival

3.2.3.1 ZUMA-1

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

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

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

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

3.2.3.2 SACT data

No data provided in the CES.

3.2.3.3 SCHOLAR-1 cohort

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

3.2.3.4 Additional comparator data from three additional sources

No data provided in the CES.

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

3.2.1.4 Indirect treatment comparison

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

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

3.2.4 Intravenous immunoglobulins use

3.2.4.1 ZUMA-1 data

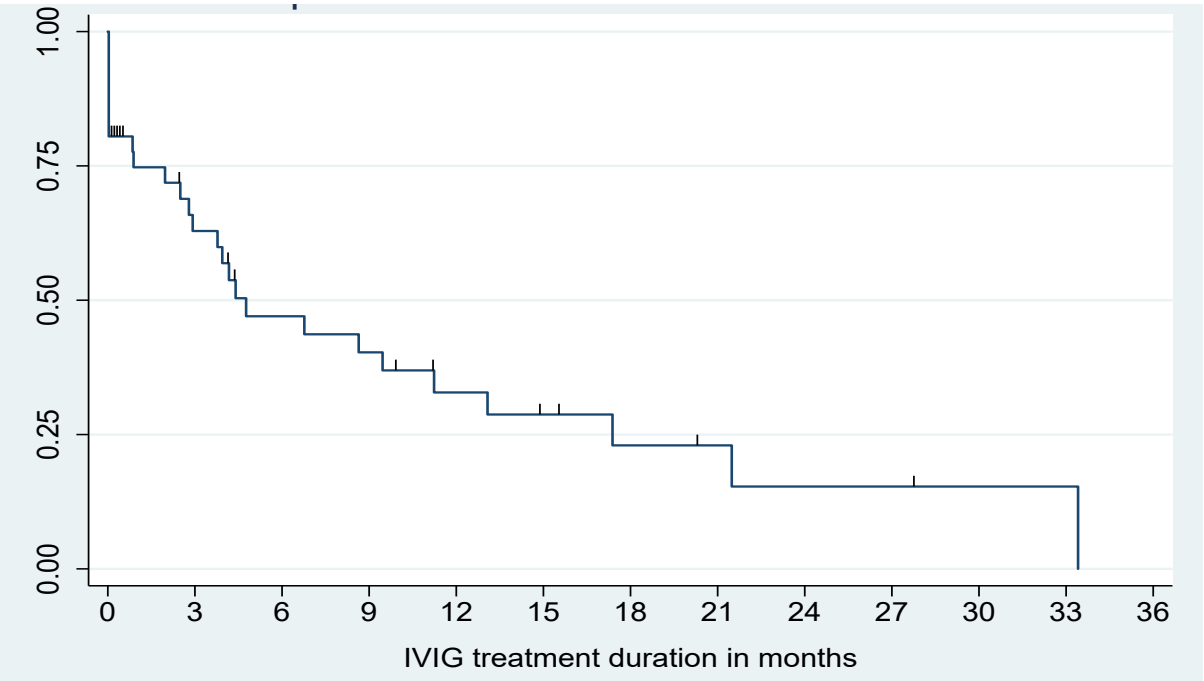
The proportion of patients receiving IVIG that was used in the original submitted economic model for TA559 was [redacted].[17] This is reported by the CES to be consistent with the expected low rates in today's clinical practice, as confirmed by expert clinical opinion.[2]

3.2.4.2 SACT data

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

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

Figure 3.7: KM treatment duration (N=41)



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

3.2.4.3 SCHOLAR-1 cohort

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

3.2.4.4 Additional comparator data from three additional sources

No data provided in the CES.

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

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

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

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

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

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

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

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

4. COST EFFECTIVENESS

4.1 Population

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

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

4.2 Comparator

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

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

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

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

4.3 Indirect treatment comparison

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

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

4.4 Sources of comparator data

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

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

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

4.5 Subsequent treatments

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

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

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

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

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

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

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

4.6 Extrapolation of OS and PFS

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

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

4.6.1 Overall survival

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

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

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

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

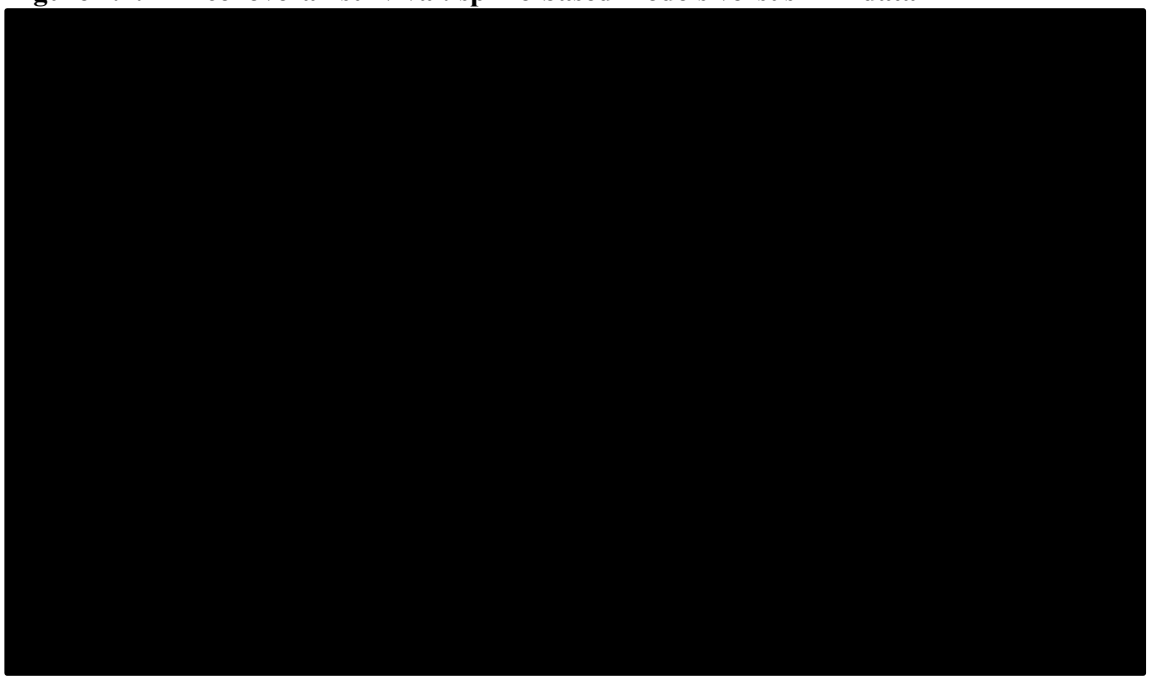
Based on Table 6 of the CES.[2]
Axi-cel = axicabtagene ciloleucel; CES = company evidence submission

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.6.2 Progression-free survival

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.6.3 Validation with SACT data

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

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

4.7 Assumption of cure

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

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

The company's original model used a MCM for OS, with around [redacted]% long-term survivors at 2 years, whereas MCM for PFS produced cure fractions of [redacted]% to [redacted]%. The EAG's preferred approach in the original submission suggested that the differences in the PFS and OS cure fractions estimated for axi-cel may result from the survival follow-up not being sufficient to capture the mortality of patients experiencing a late progression and that with longer follow-up, the cure fraction for OS for axi-cel would converge towards the cure fraction for PFS.[2] The cure fraction for OS in the CES using the 60-month data cut from the ZUMA-1 study is lower than in the original model varying from [redacted]% for the log-lognormal model to [redacted]% for the exponential model, with the base-case model using the log-lognormal prediction at [redacted]%, as shown in Table 4.1. The cure fraction estimates for PFS using the 24-month data cut from the ZUMA-1 trial vary from [redacted]% for the log-logistic to [redacted]% for the Weibull, while the log-normal provides the best model fit with a cure fraction of [redacted]%.[2]

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

4.8 Most plausible ICER

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

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

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

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

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

5. COST EFFECTIVENESS RESULTS

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

5.1 Company's deterministic cost effectiveness results

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

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

Table 5.1: Company's deterministic cost effectiveness results

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

Based on Table 11 of the CES.[2]

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

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

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

Based on Table 21 of the CES.[2]

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

5.2 Company's sensitivity and scenario analyses

5.2.1 Probabilistic sensitivity analysis

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

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

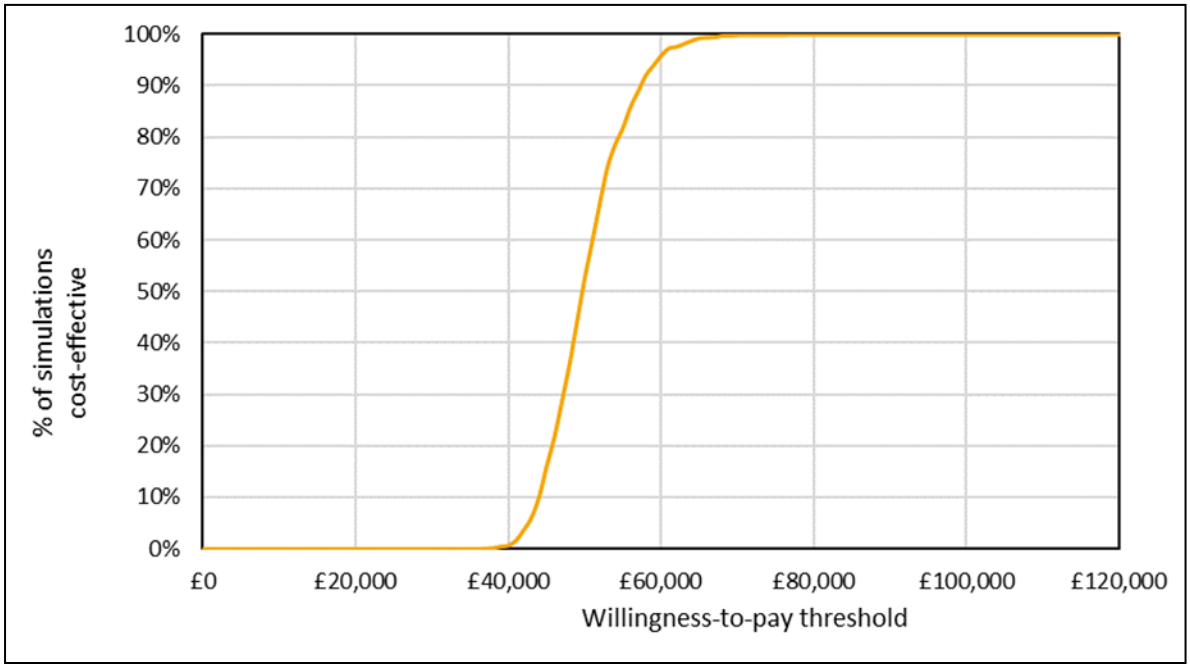
The company also plotted the PSA outcomes on a CE-plane, as can be seen in Figure 5.1. [redacted]. From the PSA results, a cost effectiveness acceptability curve (CEAC) was also calculated and plot in Figure 5.2. At the threshold of £50,000 per QALY gained, the estimated probability that axi-cel is a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

Figure 5.1: Probabilistic sensitivity analysis cost effectiveness plane

[redacted]

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

Figure 5.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve

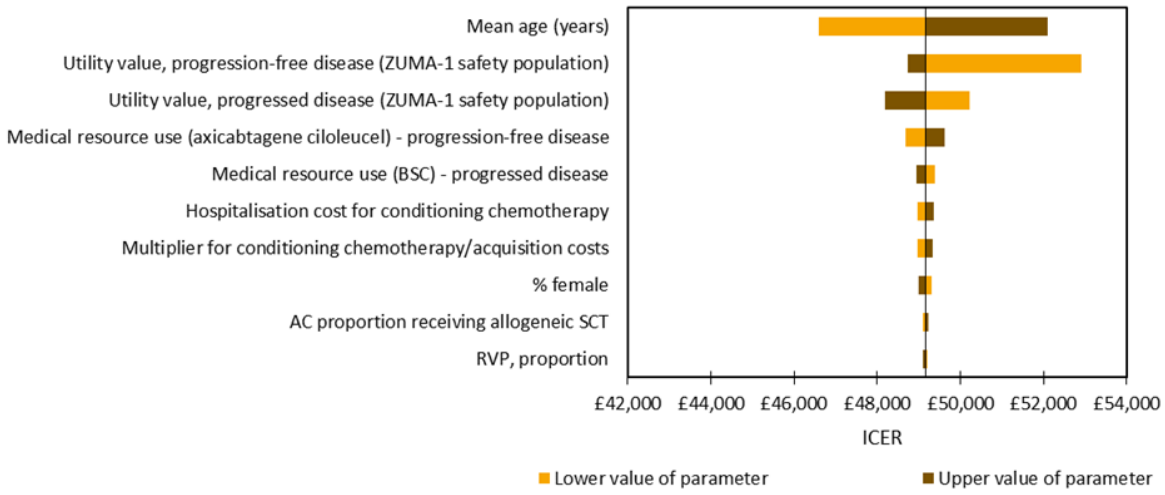


Based Figure 2 of the response to the request for clarification[3]

5.2.2 Deterministic sensitivity analysis

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

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



Based on Figure 16 of the CES.[2]

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

5.2.3 Scenario analysis

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

Table 5.3: Summary of company scenario analyses

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

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

5.3 Model validation and face validity check

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

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

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

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

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

5.4 Exploratory and sensitivity analyses undertaken by the EAG

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

Table 5.4: Company and EAG base-case preferred assumptions

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

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

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

Table 5.5: EAG additional scenarios

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

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

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

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

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

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

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

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

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

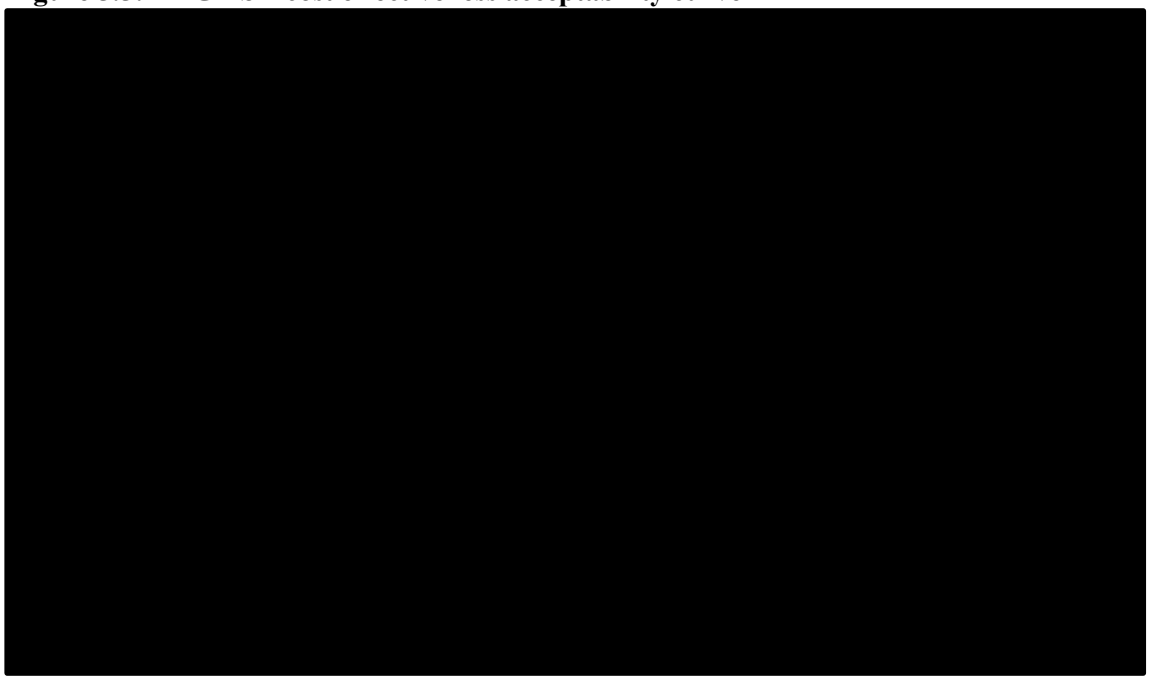
The average PSA results of the EAG preferred base-case were broadly in line with the deterministic ones shown in Table 5.6. Compared to salvage chemotherapy, axi-cel accrued [redacted] incremental QALYs at £[redacted] additional costs. Therefore, the probabilistic ICER was £49,921. The PSA outcomes on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

Figure 5.4: EAG PSA cost effectiveness plane

[redacted]

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

Figure 5.5: EAG PSA cost effectiveness acceptability curve



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

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

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

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

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

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

Table 5.7: EAG scenario analyses results

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

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

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

5.6 Conclusions of the cost effectiveness section

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

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

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

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

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

6. REFERENCES

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 23 June 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 10 – Table 1.1, Page 17 – Table 2.1: comment that the SACT database does not effectively validate ZUMA-1 OS	For Assumption 6, the EAG comments that ZUMA-1 outcomes are "not effectively validated, as follow up in the SACT database only continued to 36 months." We would like to note that in the terms of engagement (ToE), the following was stated: "The company should use the latest data cut from ZUMA-1 to inform the survival outcomes and SACT dataset to validate the trial outputs." The SACT dataset was used to validate the ZUMA-1 outcomes, therefore, we consider this to be effectively validated, per the ToE. Please remove the quoted sentence on page 10.	Edit will provide clarity on how the company has addressed the ToE	Not a factual inaccuracy The EAG comment reflect the interpretation of the EAG.
Page 10 – Table 1.1, Page 17 – Table 2.1: out of place discussion of comparator data source	For Assumption 6, the EAG comments that "analysis and presentation of the SCHOLAR-1 data in relation to the ZUMA-1 data was unclear, and so it is uncertain how much of the survival benefit is related to axi-cel." We would like to request that this sentence is removed as it is not relevant to this specific assumption detailed in the ToE (Assumption 6 is regarding the extrapolation of OS and PFS from ZUMA-1).	Edit will provide clarity on how the company has addressed the ToE	Not a factual inaccuracy As detailed in Section 2.2.6, this issue should be seen in a wider context.
Page 11 – Table 1.1, Page 18 – Table 2.1: end of life criteria	For Assumption 9, the EAG comments that "the company did not fulfil the remit of verifying the	Clarification	Not a factual inaccuracy As detailed in Section 2.2.9,

discussion	assumptions underlying assumption 9." In TA559, the committee concluded that axi-cel meets the end-of-life criteria, and this was not highlighted as an uncertainty in the ToE; hence, this was not discussed further in the company submission. This is also consistent with the submission template guidance, which requests that the section is completed only if highlighted as a key committee uncertainty. If this explanation provides the EAG with clarity, please reconsider page 11 text.		the "committee accepted that, although there was significant uncertainty in the cost effectiveness estimates, many of the assumptions in the company's base-case appear plausible and might be verified through further data collection". The EAG comment relates to that statement.
Page 12 – Section 1.2: commentary around provision of a combined ZUMA-1/SACT analysis	As noted in our response to clarification questions, a combined ZUMA-1/SACT analysis was not possible due to lack of SACT patient level data. Please consider rewording the below sentence to make this clear: "The company has been asked to present combined ZUMA 1/SACT and SCHOLAR 1 results in a clear way, with appropriate statistical adjustments, to facilitate a more meaningful interpretation of clinical effectiveness, but unfortunately the company was unable to provide this."	Clarification to avoid misinterpretation of the company's response	Not a factual inaccuracy Of note, a detailed discussion of this issue is provided in Section 2.2.3.
Page 19 – Section 2.2.2: exclusion of pixantrone from the comparator list	Given the decision problem considered in the resubmission was identical to that considered in the original submission (TA559), pixantrone was not considered an appropriate comparator. Hence, in the ToE, it states that axi-cel should be compared with salvage therapy, excluding pixantrone. Therefore, pixantrone was not considered or discussed any further in the resubmission, as it was deemed to be not	Clarification	Section 2.2.2 was revised accordingly.

	relevant. Please reconsider stance that the comparator used in the resubmission does not adhere to the ToE.		
Page 19 – Section 2.2.3: indirect treatment comparison using SCHOLAR-1 discussion	The EAG comments that the comparator analysis "cannot be described as an indirect treatment comparison, because no quantitative comparison is made." In the post-CDF model, adjusted SCHOLAR-1 data were used to model salvage chemotherapy OS, consistent with the committee-preferred approach in TA559. This was modelled as a naïve comparison, given only single-arm data were available from ZUMA-1. The resulting OS curve is provided graphically alongside the modelled axi-cel OS curve in Figure 13 of the submission. Given the adjusted SCHOLAR-1 OS data is used in the model to inform relative effectiveness estimates of axi-cel versus salvage chemotherapy, we disagree with the EAG's comment that no quantitative comparison is made. Please could the EAG clarify what is meant be "no quantitative comparison is made" and revise the page 19 text to be clear.	Clarification	Thank you for highlighting the information presented in Figure 13. Figure 13 has been added to the EAG report, as Figure 3.4, with an appropriate amendment in words. However, the EAG is concerned about the lack of any measures of uncertainty in the Figure, which makes the graph potentially misleading.
Page 21-22 – out of place discussion of comparator data source	The EAG discusses the use of SCHOLAR-1 to inform comparator estimates, however, this section (Assumption 6) is specifically regarding the extrapolation of ZUMA-1 OS and PFS. We therefore do not believe this is relevant	Edit will provide clarity on how the company has addressed the ToE	Not a factual inaccuracy As stated before, this issue should be seen in a wider context.

	context for this section and request it is deleted to avoid confusion.		
Page 26 – Section 3.1.2: presentation of axi-cel versus salvage chemotherapy outcomes	The EAG comments: "Therefore, in addition to failing to provide a clear presentation of how axi-cel performs compared to the SCHOLAR-1 comparator data…" This is presented in Figure 13 of the submission. Please revise the text.	Clarification	Thank you for highlighting the information presented in Figure 13. Figure 13 has been added to the EAG report, as Figure 3.4, with an appropriate amendment in words. However, the EAG is concerned about the lack of any measures of uncertainty in the Figure, which makes the graph potentially misleading. Therefore, the EAG does not think that a clear presentation was made of how axi-cel performs compared to the SCHOLAR-1 comparator data.
Page 40 – Section 3.2.1.4, Page 44 – Section 3.3: misinterpretation of SCT usage in SCHOLAR-1 and ZUMA-1	There appears to be a misunderstanding regarding the SCT usage values. The EAG comments that "in the ZUMA-1 trial, rates of previous SCT usage were observed at around 25%, and so the SCHOLAR-1 subgroup with the most similar SCT usage is the 10% subgroup." However, the 10% SCT usage is referring to *subsequent* SCT (i.e. after salvage chemotherapy). The SCHOLAR-1 dataset was adjusted (using a weighted average approach, detailed in the TA559 FAD) to reflect outcomes	Edit to correct for misinterpretation	Changed accordingly

	where 10% of patients would receive subsequent SCT in line with expected clinical practice. In ZUMA-1, 3% of patients received subsequent SCT. If this explanation provides the EAG with clarity, please reconsider pages 40 and 44 text.		
Page 50-51: reporting of axi-cel OS single parametric models	The EAG noted that "the model included the option to fit single parametric models to the 60-month ZUMA-1 data for OS, despite that no further details on those options were provided in the CES" and "in the absence of further details on these model fits". Detail around the standard parametric models explored for axi-cel OS, including AIC/BIC statistics and smoothed hazard plots, was provided in the company submission, appendix A.16.3. Please revise this text.	Clarification	The company is right that model fits for single parametric models of OS for axi-cel were provided in appendix A.16.3 of the CES. In line with this, the EAG noted that Figure 17 in Appendix A.16.3 of the CES does not match the OS extrapolations included in the model. Therefore, the text on pages 50 to 51 was revised as follows: *"The EAG noted that the model included the option to fit single parametric models to the 60-month ZUMA-1 data for OS, with details on AIC/BIC statistics and smoothed hazard plots provided in appendix A.16.3 of the CES.[2] Nonetheless, the EAG also noted that Figure 17 in the appendix A.16.3 of the CES does not match with the OS extrapolations included in the*

			model for axi-cel from single parametric models. Therefore, the EAG reproduced Figure 17 of the appendix A.16.3 in the CES based on the model inputs with results shown below in Figure 4.3. Figure 4.3 below shows the estimated OS for each of the parametric models compared with the ZUMA-1 OS KM data. From the model it could also be seen that none of the adjusted extrapolations based on the single parametric curves crosses the OS curve of salvage chemotherapy. Based on the visual assessment of the extrapolations of the single parametric models and the AIC/BIC statistics shown in Table 16 of appendix A.16.3 in the CES, the EAG considered that the Gompertz and generalised gamma distributions provided a good fit to the data and explored their impact in the scenario analyses presented in Section 5.4."

Issue 2 Minor edits

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 24 – Section 3.1.1: superscript required	Update to the text: All survival analyses for axi-cel were conducted using the modified intention-to-treat (mITT) population from combined phases I and II of ZUMA-1 (N=108), i.e. those patients who received at least 1 x **10^6** anti-CD19 CAR T-cells/kg body weight.	Edit to present CAR T-cell dosing correctly	Changed accordingly
Page 52 – The text refers to the wrong figure and OS KM data, when describing the PFS.	Update to the text: **Figure 4.4** presents the PFS estimated for each of the parametric models compared with the ZUMA-1 **PFS** KM data.	Edit refers to the correct figure and KM data for PFS	Changed accordingly

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Technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 18 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Kite, a Gilead company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Key issues for engagement

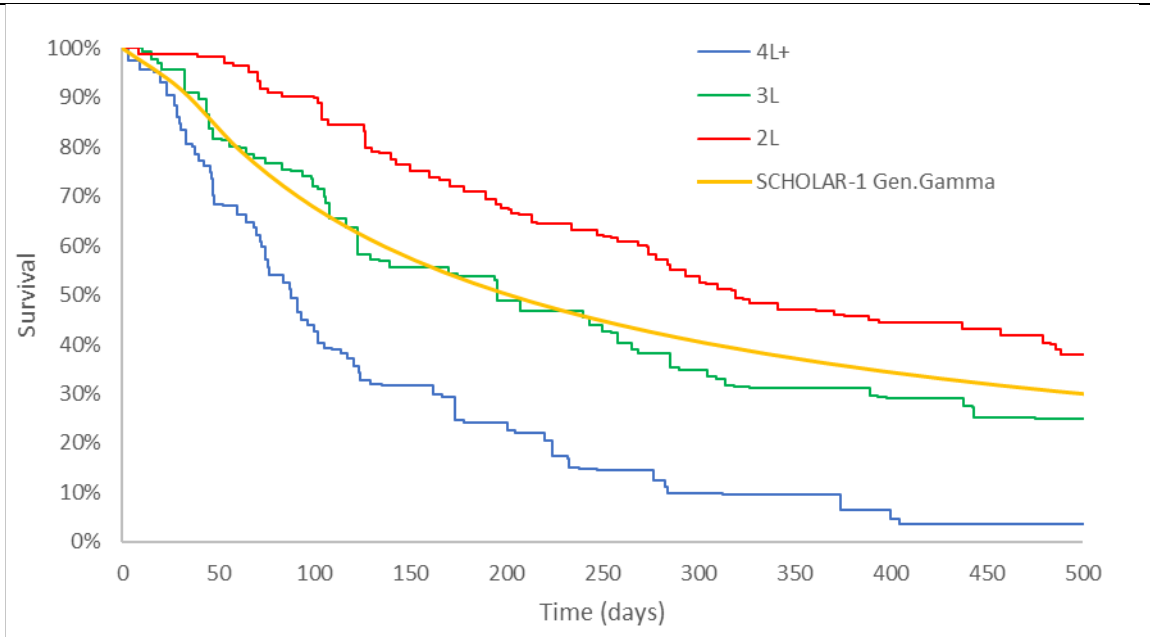
All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Table 1

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 2: Additional data that has become available during the period of managed access to inform the comparator arm	No	SCHOLAR-1 is still the most appropriate source for modelling long-term OS outcomes for the comparator. In the original submission (TA559), because ZUMA-1 was a single-arm study with no direct comparator data, results from SCHOLAR-1 were used to model long-term OS for the salvage chemotherapy arm. As outlined in the original submission's Final Appraisal Document (FAD), to address the baseline imbalances between the 2 studies, patients with an ECOG performance status of 2 to 4, patients with an unknown ECOG status, and patients with primary refractory disease were excluded from SCHOLAR-1. To address the committee's concern around the high rate of stem cell transplant, separate survival curves to generate a weighted survival estimate conditioned on if patients had or had not had a stem cell transplant. This approach was accepted by both the NICE committee and ERG in the original submission, noting *"the committee concluded that using 2 single-arm studies was suitable and that it would consider the results of these studies in its decision-making."*

		The terms of engagement (ToE) states that in addition to using SCHOLAR-1 data, the submission should use *"any additional data that has become available during the period of managed access to inform the comparator arm"*. As such, we conducted a targeted literature search to identify any additional data pertaining the use of conventional chemotherapy within the 3L DLBCL; commented on in Section A.7 of the company evidence submission (CES). Of the additional data identified, only one study (Radford et al. 2019) was based in the UK. Figure 1 below overlays the SCHOLAR-1 base case curve (unadjusted excluding ECOG 2-4, Generalized Gamma) with the 2L, 3L, and 4L+ KM curves for the full patient population in Radford et al. 2019.[1] The figure demonstrates that the SCHOLAR-1 KM data is broadly consistent with the 3L data from Radford et al. 2019. **Figure 1: SCHOLAR-1 and Radford et al. 2019**

		 As detailed in our response to Section A.A1 of the clarification questions, the limited number of studies identified is to be expected. The establishment of CAR T-cell therapy for DLBCL after two or more prior therapies in the last few years has meant that a counterfactual 'world' without CAR T is expected to have significantly limited the use of chemotherapy for patients treated with curative intent in this setting. Therefore SCHOLAR-1, remains the most rigorous study available for informing the comparator arm in this appraisal. This conclusion was deemed very reasonable by UK clinical expert validation when reviewing the economic modelling and clinical assumptions part of this resubmission.[2]

		1. Radford J, White E, Castro FA, et al. Treatment patterns and outcomes in patients with relapsed or refractory diffuse large B-cell lymphoma: Experience from a single UK centre. Blood. 2019; 134:2917. 2. Professor John Gribben. Clinical expert validation. Data on file. Personal Communication. 2022.
Issue 3: Long-term salvage therapy overall survival	No	As outlined in the response to Key Issue 2, the approach used to model long-term outcomes for salvage chemotherapy in the resubmission was consistent with the Committee's and EAG's preferred approach as outlined in the original submission. In addition, since the original submission, to the best of our knowledge, no new evidence has been published for salvage chemotherapy in 3L+ DLBCL. This has been checked via a review of the literature as outlined previously. We believe the approach agreed to in the original submission remains the best approach to model long-term salvage chemotherapy overall survival.
Issue 4: Long-term plateau in progression-free survival	No	As outlined in our response to the clarification questions, the trial protocol for ZUMA-1 did not mandate the collection of PFS data beyond 24 months. Any PFS data collected beyond 24 months was done per institutional standard of care and may not be consistent with the ZUMA-1 criteria which requires progression to be recorded after positron emission tomography–computed tomography (PET-CT) every 3 months and confirmed by blinded central review committee. The EAG note the model is sensitive to the approach adopted to extrapolating PFS outcomes. However, this only remains the case if clinically implausible options are considered alongside the more plausible alternatives. Specifically, the plausible candidates for consideration are the Gompertz curve used in the original submission (which plateaus) and the mixture cure modelling approaches. In contrast the generalized gamma lacks clinical plausibility (Figure 2). This is because the Generalized Gamma curve fails to capture the plateauing of the PFS curve, which is at odds with a visual assessment of the KM curve, UK clinical expert opinion, and UK real-world evidence (detailed in Section B1.c. of the ERG clarification letter response, and Section B.B1.c. of the technical engagement document).[3] Furthermore, the long-term ZUMA-1 data demonstrates a plateauing in the OS data over 5 years; unfeasible if the cohort of patients progressed rapidly following the 24-month follow-up.

		Figure 2: Axi-cel PFS for Gompertz vs. Generalized Gamma  The ERG report states, *"the EAG considers that MCMs could have also been appropriate to extrapolate axi-cel PFS (as stipulated in the ToE) allowing for consistent modelling between OS and PFS."* (Section 4.6.2). We acknowledge this statement, however decided to use the Gompertz single parametric curve for the purpose of maintaining consistency with the original approach and parsimony of methods (a simple parametric model rather than a MCM). However, as an alternative, we explore a scenario using the best fitting MCM (log-logistic) curve to model long-term PFS as we believe this approach results in a curve that has greater clinical validity compared to the ERGs scenario analysis of using

		the standard parametric Generalized Gamma curve. Figure 3 shows all modelling MCM curves for axi-cel PFS 24-month data, demonstrating all curves are consistent. When applied to the submitted base case, as highlighted in our response the clarification questions, selecting the log-logistic MCM distribution increases the ICER from £49,159 to £49,802, demonstrating a consistent ICER independent of the choice of clinically plausible curves and methods. **Figure 3: Axi-cel mixture cure modelling, 24-month data** 

		In the Technical Engagements call on the 14th of June 2022, NICE noted that based on the axi-cel OS Kaplan-Meier data, there may be PFS events beyond 24-months that are not captured in the current model. This is because, as would be expected and as modelled in Gilead's OS extrapolations, patients continue to die over time. Drawing on NICE's feedback in the Technical Engagement meeting, we have subsequently updated the cost-effectiveness model to allow for scenarios where an SMR can be applied to the PFS curve to capture the increased risk of death events in this 3L+ population (in comparison to the general population). This scenario applied the SMR of 1.09 to the general population probability of death at the end of the PFS KM data (24 months). Noting PFS is capped by OS in this scenario, and the relative survival framework is still applied to the 24-month PFS ZUMA-1 data cut. In this scenario, the ICER increased from £49,159 to £49,543, demonstrating that accounting for the progression events beyond 24 months has a marginal effect on the ICER, and the likelihood that the events observed in the OS KM data beyond 24 months are primarily due to progressed patients. 3. A Kuhnl AK, M O'Reilly, R Sanderson, E Tholouli, A Patel, C Besley, S Iyengar, C Jones, A Latif, J Norman, W Osborne, GP Collins, A McMillan, K Ardeshna, S Chaganti, T Menne,. Outcome of large B-cell lymphoma patients failing CD19 targeted CAR T therapy. *ICML virtual meeting*. 2021.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Summary of EAG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)	Section 1.4	No	The EAG made two changes to the company's base-case. • Update the model using 2019/2020 National Health Service (NHS) Reference costs and align all the other cost inputs to the same cost year (done by the company response to request for clarification question B7). • Proportion of patients using intravenous immunoglobulins (IVIG) treatment equal to 16% and a treatment duration at 6.5 months, as observed in the systemic anti-cancer therapy (SACT) cohort. We agree with both changes. However, we have explored alternative scenarios varying the frequency of IVIG dosing. After conversations with NHS England and clinical experts, the 4-week IVIG frequency utilised in the base-case analysis is considered to be the worst-case scenario for patients, with a frequency of 12 weeks being considered a best case. Given this, we present a 8-week IVIG frequency scenario (50% of patients receiving IVIG evert 4 weeks, 50% of patients receiving IVIG every 12 weeks). Changing the IVIG frequency from 4 weeks to 8 weeks decreases the ICER from £50,480 to £50,299. The scenario was implemented in the cost-effectiveness model by changing the formula in D235 of the 'New Cost Data' and 'Cost Data' sheet to =((365.25/12)/7)/D226*D234.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Original company base case			**£49,159**
1.4: Summary of EAG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)	Model uses cost prices from the year 2015/2016.	Update the model using 2019/2020 National Health Service (NHS) Reference costs and align all the other cost inputs to the same cost year (done by the company response to request for clarification question B7).	£50,254 (+£1,095)
1.4: Summary of EAG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)	In the absence of SACT data, an IVIG rate of [redacted] was used based on real-world evidence.	Proportion of patients using intravenous immunoglobulins (IVIG) treatment equal to [redacted] and a treatment duration at 6.5 months, as observed in the systemic anti-cancer therapy (SACT) cohort.	£49,373 (+£214)
Revised base case (incorporating all of the above changes)	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	**£50,480 (+£1,321)**

Sensitivity analyses around revised base case

The below table is an updated version of the scenario analysis presented in Table 13 of the CDF re-submission document, using the ICER incorporating the changes made in response to the technical engagement.

Table 5: Updated Scenario analysis

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER
Revised company base case			£50,480
Axi-cel overall survival – alternative extrapolation	Best fitting spline model used for axi-cel overall survival (two knots, normal)	A splines model is explored based on new NICE guidance outlined in TSD 21, as discussed previously	£50,709 [+£229]
Axi-cel progression-free survival – alternative extrapolation	MCM (log-logistic) used for axi-cel PFS	PFS MCM used to match the preferred model used for overall survival	£51,197 [+£717]
No standard mortality ratio	The standard mortality ratio (1.09 after 60 months) is not applied	This is consistent with the original submitted model	£47,706 [-£2,774]

Key: ERG, Evidence Review Group, FAD, final appraisal determination; IVIG, intravenous immunoglobulin; MCM, mixture cure model; PFS, progression-free survival; TSD, technical support document.
Notes: simple PAS applied.

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Clinical expert statement and technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) ID3980

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday 12 August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

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

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

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Part 1: Treating DLBCL or PMBCL and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Graham Collins
2. Name of organisation	Oxford University Hospital NHS Foundation Trust
3. Job title or position	Consultant Haematology, Associate Professor of Haematology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with DLBCL or PMBCL? ☐ A specialist in the clinical evidence base for DLBCL or PMBCL or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for DLBCL or PMBCL?	To cure the disease (in the short term it is to obtain a complete metabolic remission on PET scan)

Clinical expert statement

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A complete metabolic response is the short-term goal as the majority of patients achieving this have long term benefit (and likely cure) whereas most patients not achieving this sadly relapse.
10. In your view, is there an unmet need for patients and healthcare professionals in DLBCL or PMBCL?	Absolutely. Whilst 60-70% of patients are cured with R-CHOP chemotherapy frontline, for those who are refractory or relapse, the current 'standard of care' (2nd line chemotherapy aiming for an autologous transplant) only cures around 20%. Furthermore, a considerable number of patients are not fit for this approach and 2nd line treatment is purely with palliative intent.
11. How is DLBCL or PMBCL currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are BSH and ESMO guidelines for treatment DLBCL. First line treatment: R-CHOP for the majority. Alternatives for certain populations include: R-GCVP or R-CEOP (for those with cardiac problems making an anthracycline unsafe) R-miniCHOP (reduced dose R-CHOP for elderly or frail patients) R-CODox-M / R-IVAC or DA-EPOCH-R (more intense regimens, which some centres use for so called 'double hit' or other especially high-risk patients The Marietta approach (MATRix then RICE then autologous stem cell transplant) for patients with DLBCL affecting the central nervous system as well as the body. The majority (60-70%) are cured with this approach although less in older and frail patients. For those who relapse there are 2 main groups: – Younger / fitter patients. They receive 2nd line chemotherapy (e.g. R-GDP or R-ICE), 2-3 cycles, with stem cell collection. For responding patients

	who have collected stem cells successful they then proceed to an autologous stem cell transplant. The cure rate with this approach is approx. 20%. – Older / frail patients. They receive 2nd line chemo such as R-GemOx or RB-polatuzumab with the aim of controlling symptoms, maintaining quality of life and prolonging life. It is not curative though. For patients who relapse after 2nd line therapy, there is no standard of care for 3rd line therapy. For young, fit patients, 3rd line chemotherapy with an aim to proceed to allogeneic stem cell transplant is an option but is high risk (mortality rate from the transplant of 20%) with a low chance of cure (approx. 30%) and a risk of potentially debilitating graft-vs-host disease. For older / frailer patients, 3rd line chemotherapy may be an option but pure palliative care also becomes appropriate for many. CAR-T cells are currently accessed by the CDF for 3rd line treatment in both young / fit patients and older / frailer patient who are deemed fit (there is good evidence now that a significant number of patients deemed not suitable for an autologous transplant can benefit from CAR-T cell therapy safely). The availability through the CDF has had a huge impact on the 3rd line space.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	CAR-T cell therapy is only administered in centres who are JACIE accredited for immune effector cell therapy, who have been 'on boarded' by the pharma companies involved and who are specifically commissioned by NHSE. This has happened already for CAR-T available via the CDF. A number of additional centres are undergoing that process now in an effort to improve access for patients.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It is now established practise to refer suitable patients for CAR-T therapy in 3rd (or subsequent) line DLBCL. Approval by NICE for this current indication would not increase the resources needed for CAR-T delivery.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. For younger patients relapsing after autologous stem cell transplant, or not being able to get to stem cell transplant due to refractory disease; and for older patients not suitable for stem cell transplantation there is no curative therapy available. CAR-T therapy produces durable remissions (and probable cures) in a significant minority of patients. For patients receiving cells, approximately 40% have such a favourable response. Sadly some patients will not make it to infusion due to rapidly progressive disease or other factors, so this rate is less when all 3rd line patients are considered however. Therefore yes I would expect it to increase length of life and HR-QoL over other technologies.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	A number of publications have reported on factors which predict for a worse outcome. These include: - Patients with high tumour volume at infusion - Patients with raised LDH at infusion (reflecting tumour burden) - Patients with rapidly progressive lymphoma - Patients with a poor performance status Whilst poor PS (PS 2+ at apheresis or 3+ at infusion) are currently excluded for eligibility through the CDF, the other factors are not. And although patients may do worse, CAR-T still seem to offer the best chance of durable remission in these groups.

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	CAR-T delivery requires delivery in an accredited centre, in a unit dedicated to delivery of cellular therapy and other intensive therapies. It requires patients to be either admitted to the ward, or to be very close to the infusion centre for 30 days after infusion. Preparation of the cells involves an apheresis procedure for the patient at an apheresis centre with arrangement to ship and receive cells. It is therefore a complex process. Whilst more complex than current standard of care, an autologous stem cell transplant does require a similar set up (apheresis unit, accredited transplant delivery unit, expert specialist healthcare professionals).
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is accepted that patients with performance status 2 or higher are not eligible to proceed to apheresis and those with performance status 3 or higher are not eligible to receive CAR-T infusion. This requires assessment by the CAR-T infusion centre. Other pre-requisites are adequate organ function (assessed by bloods, echocardiography, lung function testing and creatinine clearance). Active uncontrolled infection, active hepatitis B / C and uncontrolled HIV are also considered exclusions.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No I don't think so.

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes – CAR-T cell therapy is highly innovative and representatives the culmination of decades of work developing cellular therapies. It meets the unmet need of providing a potentially curative option for patients with no other curative options.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are: • Short term side effects (usually within 30 days) of cytokine release syndrome and neurotoxicity. These occur at the infusion centre and are managed at site. There are generally no long term physical sequalae of these toxicities. • Long term side effects. These are mainly infectious in nature. Patients can be neutropenic for some time after infusion requiring GCSF injections. This usually improves with time. Patients may be rendered hypogammaglobulinaemic (low antibody levels) and a minority may require prophylactic antibiotics and / or immunoglobulin replacement.

	Some patients are left with low CD4+ T-cells, requiring prolonged prophylactic antibiotics.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The pivotal trial is a single arm phase II studies in 3rd line patients. Eligible patients had failed R-CHOP or R-CHOP like regimens in addition to at least one further line of treatment. This reflects the UK setting. The most important outcomes are overall survival, progression free survival and complete response rate in that order. These were assessed. Quality of life is clearly also important and was not assessed to my knowledge. Some uncommon side effects have come to light since this publication – such a CAR-T related colitis, but this is very uncommon.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA559]?	There was no comparator in the pivotal trials. Very little new data has emerged on comparators used in TA559. This is because most of the developed world has embraced CAR-T so most data is on this technology.
23. How do data on real-world experience compare with the trial data?	There is extensive real world published data from the US, Germany, France Spain and, crucially, the UK. Encouragingly the data from all countries largely mirrors that seen in the pivotal studies both in terms of efficacy and toxicity.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering DLBCL or PMBCL and this treatment? Please explain if you think any groups of	I am not aware of any inequality issues.

people with DLBCL or PMBCL are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement (ERG report, Section 1.2 and 1.3)

Issue 2: Additional data that has become available during the period of managed access to inform the comparator arm	There is very little available for comparator arms. This is because there is no standard treatment at 3rd line. Furthermore, most developed countries have adopted CAR-T so most of the literature concerning the third line data is reporting on the real world effectiveness of CAR-T. The most relevant data still is SCHOLAR-1.
Issue 3: Long-term salvage therapy overall survival	4 year OS data has been presented at the American Society of Hematology congress 2021. In my view there is a convincing OS plateau using the 4-year data. I am rather surprised by the uncertainty expressed here.

Clinical expert statement

Issue 4: Long-term plateau in progression-free survival	Similar comments to above. My interpretation of the 4 year follow up data is that there is a very convincing plateau.
Are there any important issues that have been missed in ERG report?	This reiterates mainly what I stated above. Since the widespread adoption of CAR-T therapy by most developed countries, there has been very little relevant comparator data presented during the managed access period. Instead we have seen a lot of real world data of CAR-T therapy in this setting along with longer follow up of the pivotal trials.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

CAR-T is the only relatively safe curative therapy in the 3rd line setting

CAR-T represents a step change in innovation of cancer immune therapies

Little further comparative data has been generated in the last 2-3 years

The real world CAR-T evidence (including UK data) has largely mirrored clinical trial data

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) ID3980

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with diffuse large B-cell lymphoma (DLBCL) or primary mediastinal large B-cell lymphoma (PMBCL) or caring for a patient with DLBCL or PMBCL. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday 12 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

Part 1: Living with this condition or caring for a patient with DLBCL or PMBCL

Table 1 About you, DLBCL or PMBCL, current treatments and equality

1. Your name	Cerys Thompson
2. Are you (please tick all that apply)	☒ A patient with DLBCL or PMBCL? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with DLBCL or PMBCL? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Blood Cancer UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with DLBCL or PMBCL? **If you are a carer (for someone with DLBCL or PMBCL) please share your experience of caring for them**	I was diagnosed with DLBCL in October 2020 at the age of 29. I had no symptoms other than a lump near my collar bone that was causing discomfort. I was otherwise fit and healthy with no health problems or concerns! Just a normal 29 year old, recently married, with big plans for her life including thoughts to start a family. I was initially diagnosed as stage 1E but this was later updated as stage 2E as although the disease was small, it started on my thyroid and moved into the lymph node so was classed as two locations I went on to have 6 cycles of R-CHOP. After 4 cycles, 70% of the disease had gone. However, after the final 2 cycles, the disease had regrown to the amount I had started with. This had a massive impact to me mentally as I just about managed to gear myself up for 6 months of difficult treatment, knowing there was an end in sight – but to find it hadn't achieved anything and that I would have to find more energy for something harder, was incredibly demoralising and scary. I had also already been off work for 6 months and now didn't know when I would return. My husband was also off work to be able to help look after me as well as shield from covid. And we had shut ourselves away from friends and family to keep protected. It was incredibly isolating with no end in sight. At this point, I was put on the pathway for a stem cell transplant. I had 2 cycles of salvage chemo (R-ICE) yet found this had had no impact at all either and my disease had even started to form in my armpit and there were questions about activity in my ovaries. I had another cycle of R-ICE whilst I was put forward for CAR-T.

	I was approved for CAR-T and had radiotherapy as bridging treatment. My scan before CAR-T showed I had responded very well to radiotherapy in my throat but the activity had grown in my ovaries and surrounding pelvis area significantly – the disease was spreading. I went through CAR-T and experienced side effects of fever (CRS), nausea, headaches, swelling and mild neurotoxicity. However, this was all over relatively quickly (4 days) so the remaining time in hospital was simple monitoring and ongoing medicine. At day 28 following CAR-T, I had responded fully to treatment (including the activity in my ovaries) and at day 90 I was classed as in remission. It has now been a year since CAR-T and I am fully well and back to my old life before cancer – I am working, socialising, going on holiday and having the best time. Something that would never have been possible without CAR-T.
7a. What do you think of the current treatments and care available for DLBCL or PMBCL on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The chemo (both R-CHOP and R-ICE) was incredibly harsh on my body. I managed much better than other patients I witnessed but it had a significant impact on my life including nausea, fatigue, headaches, hair loss and a general feeling of being unwell over a long period of time. This, on top of the mental exhaustion of anxiety and worry, during the pandemic too, was a difficult journey. The R-ICE in particular had to be administered every day for 4 days and then I had to go back for multiple blood and urine tests in between cycles – I felt like I lived in the hospital. To go through those treatments and find out they did not work was very difficult for my mind and body. Each treatment knocked my confidence as well as impacted my immunity, skin (I started reacting to dressings the more time went by) and my veins were more difficult for cannulas, making each trip more and more traumatic. When I read up on the stem cell transplant, this sounded even worse and I was worried about the impact it would have on my body.

	CAR-T sounded difficult but more manageable with more positive longer-term prospects – which is what others had confirmed on social media who had been unfortunate to have both. I believe now that treatments like CAR-T are available, it feels “old fashioned” to still be using treatments like chemo that are so harsh and unsuccessful. My mother-in-law passed away in 2011 to DLBCL yet I still had the exact treatment plan that she did 10 years on… Unfortunately stem cell transplants were fairly new but her disease was not shrinking so, after a clinical trial failed, she was placed in palliative care. She would’ve been an ideal candidate for CAR-T treatment had it existed at the time – and she may still be here today. CAR-T was quicker, less harsh on my body and achieved a full response – ultimately it saved my life. If CAR-T wasn’t an option, I would’ve been placed on clinical trials to manage the disease. CAR-T was my last chance at a curative treatment.
8. If there are disadvantages for patients of current NHS treatments for DLBCL or PMBCL (for example, how axicabtagene ciloleucel is given or taken, side effects of treatment, and any others) please describe these	The major disadvantages of treatments such as chemo is how harsh it is on your body. As a young, healthy person I was still impacted by tough side effects which only got worse with every cycle. R-CHOP was difficult enough but R-ICE was even worse – and involved even more treatment which could also impact my kidney. The biggest downside to CAR-T is the time away from home at a hospital far away. I live in Essex and had to travel to UCLH for meetings, cell collection and treatment. Once treatment started, I was away from home for 5 weeks and because of the pandemic I was only allowed 1 visitor twice a week for the first 2 weeks and then my husband could stay with me in the hospital hotel for 2 weeks. Mentally this was quite difficult to be away from home for so long, however I did find comfort being monitored and so close to medical professionals for questions and concerns. However, I only felt ill for a couple of days. And then it was more a nuisance of being disturbed in a hospital environment when I just wanted to rest. But this was something I was more than happy to endure for a curative treatment! And to not

	repeat as a cyclical treatment like with chemo – i.e. once the fever was over, it was over. I didn't have to think about repeating it in a month's time. The other downside is the way and the time it takes to collect the cells – this is very intrusive and a long day. However this is a small price for a cure!
9a. If there are advantages of axicabtagene ciloleucel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does axicabtagene ciloleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	There are many advantages to CAR-T over other treatments. For starters, knowing it's your own body / immune system fighting the disease helps psychologically for many reasons. It feels like you're "capable" and strong enough to fight the cancer AND keep it at bay. After almost a year of relying on chemicals and drugs that didn't work yet damaged my body, I was fully on board with "training up my cells" to do the fighting themselves. Whilst it was 5 weeks in hospital, the number of days I actually felt unwell for was about 4 days in total. And once it was done, it was done and nothing had to be repeated. Compared to the monotonous nature of cyclical chemo, where each one made me feel worse and the symptoms and nausea would extend over 14 days, CAR-T was quicker and psychologically more manageable. Therefore CAR-T as a treatment is very quick compared to the months of chemo. This meant my body could recover quicker and enable it to get stronger, my skin rest, my veins repair. I could start to see friends and family again and think about returning to work. Knowing it was my own cells that were used also gave me more confidence coming out of treatment – after over a year of being told I'm vulnerable and my immune system is low etc, to be told I'm in remission from my own T Cells is something incredibly special. The most important advantage above all is the success of the treatment. Chemo failed for me and I was told other types would likely have a similar response. However CAR-T worked and continues to work. I am alive because of CAR-T – and at 31 years old, I am very grateful to be able to continue to live my life as I did before cancer.

10. If there are disadvantages of axicabtagene ciloleucel over current treatments on the NHS please describe these. For example, are there any risks with axicabtagene ciloleucel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As mentioned above, a big disadvantage is the time away from home. However the other disadvantage is the risk of intensive care for things such as CRS or neurotoxicity. I was lucky in that I had a small amount of both but those who are more vulnerable may be at a higher risk.
11. Are there any groups of patients who might benefit more from axicabtagene ciloleucel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I think any person with DLBCL who is otherwise fit and healthy, should be offered car-t as I believe they would have a positive outcome such as myself I think those more vulnerable would have to weigh up the risks of intensive care – however as a curative treatment, I would personally still have chosen this route even if I was considered a higher risk as there would have been no other options for me.
12. Are there any potential equality issues that should be taken into account when considering DLBCL or PMBCL and axicabtagene ciloleucel? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	No

Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	Ultimately, CAR-T saved my life. I cannot thank everyone who is involved in CAR-T enough. Neither can my husband (who lost his Mum to DLBCL) or my family and friends. I am 31 years old with my whole life ahead of me, because of science and technology. And I am even considering the possibility of starting a family in the future. Please make this treatment routinely available on the NHS so that other people can also have an opportunity to be cured from this awful disease. If anyone is interested, I wrote a blog throughout my entire cancer journey which will give further insight to the impacts for all the treatment I faced: https://mylittlebitofcancer.wordpress.com/

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report (ERG report Section 1.2 and 1.3)

Issue 2: Additional data that has become available during the period of managed access to inform the comparator arm	
Issue 3: Long-term salvage therapy overall survival	
Issue 4: Long-term plateau in progression-free survival	
Are there any important issues that have been missed in ERG report?	

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- I am **alive** today because of CAR-T
- A year on from CAR-T, I am living my life as a normal 31 year old with big plans for the future
- Whilst CAR-T involves an extended period away from home, the treatment and side effects are much more manageable than the cyclical and damaging effects of chemo treatments
- Even with the risks of ICU, I would've chosen CAR-T as my final chance of a cure
- Please make this treatment routinely available on the NHS so that other people, like myself, have the opportunity to be cured of this horrible disease

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) ID3980

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with diffuse large B-cell lymphoma (DLBCL) or primary mediastinal large B-cell lymphoma (PMBCL) or caring for a patient with DLBCL or PMBCL. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday 12 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with DLBCL or PMBCL

Table 1 About you, DLBCL or PMBCL, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with DLBCL or PMBCL? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with DLBCL or PMBCL? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Anthony Nolan
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. If you are a carer (for someone with DLBCL or PMBCL) please share your experience of caring for them	**PMBCL diagnosis** • When my son was diagnosed with PMBCL, it was an enormous shock to us all. He was young and very fit and healthy. He exercised regularly, ate well and generally looked after himself. He was the last person you would have expected to receive a diagnosis like this; it was an enormous blow to the whole family unit. • After the diagnosis we were stressed, worried and nervous, upset – you just experience all emotions when you receive news like this. • Despite the diagnosis, my son remained very positive and was determined to get better, an attitude that continued through the majority of his treatment. **Treatment and Care** • He received a lot of treatment for his condition, including several rounds of chemotherapy, such as RCHOP, CAR-T cell therapy (YESCARTA), a haematopoietic stem cell transplant, and other treatments that we had to self-fund when we had run out of other options. • During this time, his condition varied dramatically. During the chemotherapy he could still live fairly independently, despite being unwell. My husband and I would travel across the country 300 miles from my home every weekend to look after him and help to take him to appointments while his wife cared for their young son who was only 10 weeks old when he was diagnosed. The expense of the traveling added up quickly.

	• As his disease relapsed and his treatment progressed we lost all quality of life, as did my son. We never went anywhere other than the hospital and his home. His condition was very changeable, we would gain hope when new treatments started, only for that hope to be taken away when it didn't work, it was like living on a rollercoaster. • As a carer you often need to put on a brave face, even when you don't want to. This can be mentally challenging. Even though he often remained positive and kept us going, it was emotionally very hard. This weighed on me heavily and I often broke down. • We researched treatments that might be available constantly, with all members of the family pitching in. It was a lot of work and stress, we called all over the world to understand what treatments were available. • At the time, CAR-T was not available on the NHS and we talked about selling our house to pay for it. This caused significant stress on the whole family and it threw our whole lives into turmoil. Having to sell your house to pay for treatment is not a decision that we wanted to take, but we would have done it had CAR-T not become available a few weeks later. • Caring for a loved one full time takes over every aspect of your life. It significantly impacted our quality of life, and that of my son who wasn't able to spend time with his family and young child.
7a. What do you think of the current treatments and care available for DLBCL or PMBCL on the NHS?	• Going into the treatment at the start we were very hopeful it would work. I had known someone from when I was younger who had NHL and they recovered and went on to start a family. This was certainly at the back of my mind when my son was diagnosed.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	• The treatment options were harsh, some very harsh. As my son was young, fit and healthy, I think that he tolerated many of them well. RCHOP was tough but he was still able to care for himself somewhat during treatment, with the support of his wife, myself and my husband. • The CAR-T treatment was generally well tolerated by my son. He said himself that it was less harsh than the HSCT. The treatment, delivery and recovery were tough and not without its challenges, discussed below, but it gave us a lot of hope. • Mentally, he remained very positive during his CAR-T treatment, often he was the one keeping us going. • We were all very invested in the -T treatment. We really thought that it was going to work and had met others where it had. This contributed to the disappointment when it did not and this was mentally very difficult. We asked if we could try again, but this was not possible. • After his CAR-T failed, we ran out of options, so we were self-funded for pembrolizumab, which was not available on the NHS at the time. This was a very scary and uncertain time as well as being a financial strain. Although it did cause his cancer to go into remission, which allowed him to receive a stem cell transplant, it had a number of unpleasant side effects. It caused significant issues with his bowels and he also had issues moving his legs, causing problems with walking. • The stem cell transplant that he received was probably the most debilitating of all of them and I am not sure how prepared we were for this. Post-HSCT was the first time that his mood really began to take a turn. I think he became quite depressed, isolated and lonely. His transplant also coincided with the Covid-19 pandemic which only made things harder. • Impacts of the transplant were very significant, he had acute (skin) GvHD which was debilitating and he was eventually hospitalised with gut problems. We followed lots of blogs and online posts from others, with many

	commenting that they did not realise or fully understand some of the impacts of GvHD, which can be life changing. He went through some very dark moments and needed some counselling from the stem cell team physiacrist. I do think he was really going through all these treatments due to having a young family and because we were trying so hard to cure him he didnt want to give up but the SCT was very hard on him for sure. He said he felt guilty as he could see the effects of what the amount of care was having on us. Ultimately the SCT caused him to develop viral encephalitis 5 months later and he was then hospitalized for the following 4 months with myself in hospital with him caring for him 13 hours each day until he sadly passed away. I will be forever grateful that I was able to be by his side for those 4 months during covid. The hospital allowed me in each day and i was able to stay in a hospital flat each night.
8. If there are disadvantages for patients of current NHS treatments for DLBCL or PMBCL (for example, how axicabtagene ciloleucel is given or taken, side effects of treatment, and any others) please describe these	Chemotherapy Stem cell transplant • My son was extremely unwell after his stem cell transplant, as well as having a very low mood. The isolation after the treatment was particularly difficult, exacerbated by the Covid-19 pandemic. • The GvHD he experienced was also lifechanging and I think can be overlooked or not well understood. Axicabtagene ciloleucel • At the time when my son received his CAR-T therapy it was a very new treatment. It had only been made available a few weeks, or even days before

	he received it. As mentioned, we were already aware of the treatment and considered selling our house to finance it ourselves. • Given the new nature of the therapy, there were lots of unknowns, which were scary, alongside concerning sounding side effects like neurotoxicity and the possibility of being taken to intensive care (both of which occurred after his treatment). This was a scary time for us all and many may see these significant sounding side effects as a negative of the treatment. • As an early CAR-T recipient, the treatment was only available in a few centres in the UK. It was a stipulation that to receive the treatment, we had to move to be within 30 minutes of the hospital. As a result, we had to rent a property in close to the hospital, which was a significant financial strain. This was funded via a go-fund-me page. • It was also an emotional strain, living in a small house with my son, his wife, our young grandson, myself, my husband and often my son's parents-in-law, who also helped. • My husband and I were also both forced to leave our work at this time and assume full time caring responsibilities of our son. • At the time, knowledge of the availability of this treatment was poor, probably as it was not widespread. We were aware that it had been approved, but my son's consultant was not, it was only our own research that allowed us to get access to it so quickly. • The whole family were very invested in my son's treatment and we put a lot of time and effort into researching treatment options. Many people would not have the time, knowledge, money, or ability to navigate the healthcare systems that we do. • Axicabtagene ciloleucel delivery involves a lot of time in the hospital with lots of visits. As mentioned, to facilitate this, my husband and I had to give up work and we had to fundraise to allow us to stay close to the hospital. Although delivery in a hospital is difficult and time consuming, it also made us feel

	reassured that he was being cared for. This treatment was (and still is) very new and we were aware of many of the scary side-effects so it does provide some ease and comfort that he was being very closely monitored, despite the challenges that comes with all of the testing and evaluations. • Another challenge when receiving the CAR-T was the delay in receiving the cells. My son's treatment coincided with Brexit and Covid-19 and the cells were being manufactured in the USA. The CAR-T cells were held up at a border somewhere for a few additional days at a very critical time of his treatment when he was acutely unwell.
9a. If there are advantages of axicabtagene ciloleucel over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does axicabtagene ciloleucel help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	• My son reacted well to receiving axicabtagene ciloleucel. He was mentally very positive and remained relatively well during this treatment. • He did suffer from some of the more worrying side effects of the treatment, but he often told me that he didn't feel too bad, despite the scariness of being admitted to intensive care. • The treatment involved being in hospital a lot, which could be an issue for some. After spending so much time in hospital, may like to get treated at home where possible. However, we also got some comfort by the care and attention given. We both felt that, if there were any issues, he was in the best place. • We received a lot of excellent information throughout the treatment, which really helped to address some of our issues and concerns. Although it was complex and there was a lot to know, we were very well informed throughout.

10. If there are disadvantages of axicabtagene ciloleucel over current treatments on the NHS please describe these. For example, are there any risks with axicabtagene ciloleucel? If you are concerned about any potential side effects you have heard about, please describe them and explain why	• In general, the treatment was quite well tolerated by my son, but he did have some very scary and unpleasant side effects. He had short term memory problems after the treatment and was also admitted to intensive care, which was also a very anxious time for us all. Despite this, he did often say that, even when in intensive care, it was not 'the most ill he felt' and it was by no means the most difficult treatment that he went through. • The delays with receiving the CAR-T cells from America was also a unique challenge of the treatment, with delays caused at customs due to Brexit and Covid-19 causing worry and stress. • Having to move and relocate to receive the treatment was also very challenging, as was having to leave work, however we would do anything to try and help him get better. • Long terms, the outcomes from CAR-T are unknown, which can also be a concern.
11. Are there any groups of patients who might benefit more from axicabtagene ciloleucel or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	• My husband and I helped a lot during my son's treatment, for those who do not have a person who can care for them full time, it would probably have been a significant challenge.
12. Are there any potential equality issues that should be taken into account when considering DLBCL or PMBCL and axicabtagene ciloleucel? Please explain if you think any groups of people with this condition are particularly disadvantaged	• As briefly discussed above, we did a lot of work to find out about the treatment, whether he was eligible, and when it became available. We also moved across the country, had to rent a house and leave our jobs to care for our son. Lots of people aren't able to do these things, which could impact their ability to receive the treatment.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	• It is also critically important to really understand the information that you are given by the doctors, particularly for some of the possible side effects that may occur after treatment. Those who are less familiar with how to navigate the healthcare system that myself and my family may struggle with this.
13. Are there any other issues that you would like the committee to consider?	That Car T Cells could be modified closer to home I.e. in the UK. My sons T cells had to go to California to be modified which was very costly and time consuming for everyone.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report (ERG report Section 1.2 and 1.3)

Issue 2: Additional data that has become available during the period of managed access to inform the comparator arm	
Issue 3: Long-term salvage therapy overall survival	
Issue 4: Long-term plateau in progression-free survival	
Are there any important issues that have been missed in ERG report?	

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

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Technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF review of TA559) [ID3980]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Monday 18 July**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Kite, a Gilead company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

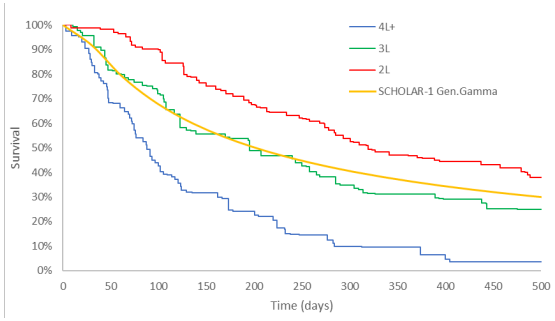
Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
Issue 2: Additional data that has become available during the period of managed access to inform the comparator arm	No	SCHOLAR-1 is still the most appropriate source for modelling long-term OS outcomes for the comparator. In the original submission (TA559), because ZUMA-1 was a single-arm study with no direct comparator data, results from SCHOLAR-1 were used to model long-term OS for the salvage chemotherapy arm. As outlined in the original submission's Final Appraisal Document (FAD), to address the baseline imbalances between the 2 studies, patients with an ECOG performance status of 2 to 4, patients with an unknown ECOG status, and patients with primary refractory disease were excluded from SCHOLAR-1. To address the committee's concern around the high rate of stem cell	Thank you for the new figure that incorporates the data from Radford with Scholar-1 data. It would have been useful for this to have been integrated into the overall analysis. The main EAG concerns in relation to this point have not been fully addressed by the company response. These were, and are: 1) There are no measures of uncertainty in the data comparing the ZUMA-1 and comparator data (figure 13 in the CS), making it difficult to interpret 2) The search for the additional trials was based on a single Pubmed search, which is insufficient to ensure that all potentially relevant studies were found.

		transplant, separate survival curves to generate a weighted survival estimate conditioned on if patients had or had not had a stem cell transplant. This approach was accepted by both the NICE committee and ERG in the original submission, noting *"the committee concluded that using 2 single-arm studies was suitable and that it would consider the results of these studies in its decision-making."* The terms of engagement (ToE) states that in addition to using SCHOLAR-1 data, the submission should use *"any additional data that has become available during the period of managed access to inform the comparator arm"*. As such, we conducted a targeted literature search to identify any additional data pertaining the use of conventional chemotherapy within the 3L DLBCL; commented on in Section A.7 of the company evidence submission (CES). Of the additional data identified, only one study (Radford et al. 2019) was based in the UK. Figure 1 below overlays the SCHOLAR-1 base case curve (unadjusted excluding ECOG 2-4, Generalized Gamma) with the 2L, 3L, and 4L+ KM curves for the full patient population in Radford et al. 2019.[1] The figure demonstrates that the SCHOLAR-1 KM data is broadly	3) Two studies were excluded from the above search because they were not based on participants from the UK. It should be noted that the ZUMA-1 and SCHOLR-1 trials were also not based on participants from the UK, i.e. the two aforementioned studies should have been included. 4) The alternative cost effectiveness scenarios explored by the EAG indicated that the model results are still sensitive to changes in OS extrapolations for salvage chemotherapy. The unresolved uncertainty around long-term OS for BSC is also evident on the impact of using alternative extrapolations. Assuming a Gompertz, a log-logistic and a lognormal extrapolation for salvage chemotherapy (selected based on goodness of fit statistics) resulted in an ICER of £55,787, £46,048 and £46,977 per QALY gained, respectively.

		consistent with the 3L data from Radford et al. 2019. **Figure 1: SCHOLAR-1 and Radford et al. 2019**  As detailed in our response to Section A.A1 of the clarification questions, the limited number of studies identified is to be expected. The establishment of CAR T-cell therapy for DLBCL after two or more prior therapies in the last few years has meant that a counterfactual 'world' without CAR T is expected to have significantly limited the use of chemotherapy for patients treated with curative intent in this setting. Therefore SCHOLAR-1, remains the most rigorous study available for informing the comparator arm in this appraisal. This conclusion was deemed very reasonable by UK clinical expert validation when reviewing the economic modelling and	

		clinical assumptions part of this resubmission.[2] 1. Radford J, White E, Castro FA, et al. Treatment patterns and outcomes in patients with relapsed or refractory diffuse large B-cell lymphoma: Experience from a single UK centre. Blood. 2019; 134:2917. 2. Professor John Gribben. Clinical expert validation. Data on file. Personal Communication. 2022.	
Issue 3: Long-term salvage therapy overall survival	No	As outlined in the response to Key Issue 2, the approach used to model long-term outcomes for salvage chemotherapy in the resubmission was consistent with the Committee's and EAG's preferred approach as outlined in the original submission. In addition, since the original submission, to the best of our knowledge, no new evidence has been published for salvage chemotherapy in 3L+ DLBCL. This has been checked via a review of the literature as outlined previously. We believe the approach agreed to in the original submission remains the best approach to model long-term salvage chemotherapy overall survival.	The EAG would reiterate the latter three points made in the previous section, that also apply here: 1) The search for the additional trials was based on a single Pubmed search, which is insufficient to ensure that all potentially relevant studies were found. 2) Two studies were excluded from the above search because they were not based on participants from the UK. It should be noted that the ZUMA-1 and SCHOLR-1 trials were also not based on participants from the UK, i.e. the two aforementioned studies should have been included. 3) The alternative cost effectiveness scenarios explored by the EAG indicated that the model results are still sensitive to changes in OS extrapolations for salvage chemotherapy. The unresolved uncertainty around long-term OS for BSC is also evident on the impact of using alternative extrapolations. Assuming a Gompertz, a log-logistic and a lognormal

			extrapolation for salvage chemotherapy (selected based on goodness of fit statistics) resulted in an ICER of £55,787, £46,048 and £46,977 per QALY gained, respectively. Furthermore, we would add another point. As stated in the TE document, the committee in the original appraisal noticed important differences in study populations between ZUMA-1 and SCHOLAR-1. The company adjusted the SCHOLAR-1 dataset to be more reflective of ZUMA-1 and UK practice, substantially reducing the sample size from 562 to 133, increasing uncertainty around OS extrapolations.
Issue 4: Long-term plateau in progression-free survival	No	As outlined in our response to the clarification questions, the trial protocol for ZUMA-1 did not mandate the collection of PFS data beyond 24 months. Any PFS data collected beyond 24 months was done per institutional standard of care and may not be consistent with the ZUMA-1 criteria which requires progression to be recorded after positron emission tomography–computed tomography (PET-CT) every 3 months and confirmed by blinded central review committee. The EAG note the model is sensitive to the approach adopted to extrapolating PFS outcomes. However, this only remains the case if clinically implausible options are considered alongside the more plausible alternatives. Specifically, the plausible	While the EAG recognises that the lack of sufficient long term PFS data was not necessarily the fault of the company, it is still a problem in terms of increasing the uncertainty of plateau estimation for PFS. Whichever model is used, if the raw data are insufficiently long-term any extrapolations may be inaccurate. Furthermore, the alternative cost effectiveness scenarios explored by the EAG also indicated that the model results are still sensitive to changes in PFS extrapolations for axi-cel. Assuming a generalised gamma (the second-best single parametric fit) PFS extrapolation for axi-cel resulted in an ICER of £67,765 per QALY gained. Assuming a two-knots normal spline model (best fit) resulted in an ICER of £55,257 per QALY gained.

		candidates for consideration are the Gompertz curve used in the original submission (which plateaus) and the mixture cure modelling approaches. In contrast the generalized gamma lacks clinical plausibility (Figure 2). This is because the Generalized Gamma curve fails to capture the plateauing of the PFS curve, which is at odds with a visual assessment of the KM curve, UK clinical expert opinion, and UK real-world evidence (detailed in Section B1.c. of the ERG clarification letter response, and Section B.B1.c. of the technical engagement document).[3] Furthermore, the long-term ZUMA-1 data demonstrates a plateauing in the OS data over 5 years; unfeasible if the cohort of patients progressed rapidly following the 24-month follow-up. **Figure 2: Axi-cel PFS for Gompertz vs. Generalized Gamma**	

		 The ERG report states, *"the EAG considers that MCMs could have also been appropriate to extrapolate axi-cel PFS (as stipulated in the ToE) allowing for consistent modelling between OS and PFS."* (Section 4.6.2). We acknowledge this statement, however decided to use the Gompertz single parametric curve for the purpose of maintaining consistency with the original approach and parsimony of methods (a simple parametric model rather than a MCM). However, as an alternative, we explore a scenario using the best fitting MCM (log-logistic) curve to model long-term PFS as we believe this approach results in a curve that has greater clinical validity compared to the ERGs scenario analysis of using the standard parametric Generalized Gamma curve. Figure 3 shows all modelling MCM curves for axi-cel PFS 24-month data, demonstrating all curves are consistent.	

		When applied to the submitted base case, as highlighted in our response the clarification questions, selecting the log-logistic MCM distribution increases the ICER from £49,159 to £49,802, demonstrating a consistent ICER independent of the choice of clinically plausible curves and methods. **Figure 3: Axi-cel mixture cure modelling, 24-month data**  In the Technical Engagements call on the 14th of June 2022, NICE noted that based on the axi-cel OS Kaplan-Meier data, there may be PFS events beyond 24-months that are not captured in the current model. This is because, as would be expected and as modelled in Gilead's OS extrapolations, patients continue to die over time. Drawing on NICE's feedback in the Technical Engagement meeting, we have	

		subsequently updated the cost-effectiveness model to allow for scenarios where an SMR can be applied to the PFS curve to capture the increased risk of death events in this 3L+ population (in comparison to the general population). This scenario applied the SMR of 1.09 to the general population probability of death at the end of the PFS KM data (24 months). Noting PFS is capped by OS in this scenario, and the relative survival framework is still applied to the 24-month PFS ZUMA-1 data cut. In this scenario, the ICER increased from £49,159 to £49,543, demonstrating that accounting for the progression events beyond 24 months has a marginal effect on the ICER, and the likelihood that the events observed in the OS KM data beyond 24 months are primarily due to progressed patients. 3. A Kuhnl AK, M O'Reilly, R Sanderson, E Tholouli, A Patel, C Besley, S Iyengar, C Jones, A Latif, J Norman, W Osborne, GP Collins, A McMillan, K Ardeshna, S Chaganti, T Menne,. Outcome of large B-cell lymphoma patients failing CD19 targeted CAR T therapy. *ICML virtual meeting*. 2021.	

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	EAG response
Additional issue 1: Summary of EAG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)	Section 1.4	No	The EAG made two changes to the company's base-case. • Update the model using 2019/2020 National Health Service (NHS) Reference costs and align all the other cost inputs to the same cost year (done by the company response to request for clarification question B7). • Proportion of patients using intravenous immunoglobulins (IVIG) treatment equal to 16% and a treatment duration at 6.5 months, as observed in the systemic anti-cancer therapy (SACT) cohort. We agree with both changes. However, we have explored alternative scenarios	There was an updated SACT report of July 12th, in which the 56 patients of Kings College Hospital NHS Foundation Trust were followed up in MDSAS and on 4 July 2022 were added in the analysis of IVIG usage of the 262 patients who were followed up in MDSAS on 24 May 2022 (262 patients). Adding the 56 patients from the Kings College Hospital NHS Foundation Trust (318 in total), increased the proportion of IVIG usage to 19% instead of 16%, and the treatment duration to 9.5 months instead of 6.5 months. As the EAG already mentioned in the EAG report, the impact of the assumptions on IVIG usage is relatively minor on the ICER. Nonetheless,

			varying the frequency of IVIG dosing. After conversations with NHS England and clinical experts, the 4-week IVIG frequency utilised in the base-case analysis is considered to be the worst-case scenario for patients, with a frequency of 12 weeks being considered a best case. Given this, we present a 8-week IVIG frequency scenario (50% of patients receiving IVIG evert 4 weeks, 50% of patients receiving IVIG every 12 weeks). Changing the IVIG frequency from 4 weeks to 8 weeks decreases the ICER from £50,480 to £50,299. The scenario was implemented in the cost-effectiveness model by changing the formula in D235 of the 'New Cost Data' and 'Cost Data' sheet to =((365.25/12)/7)/D226*D234.	accounting for these updated parameters slightly increases the ICER from £50,480 to £50,815, compensating for the potential reduction in IVIG frequency.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG response
Original company base case			**£49,159**	The ERG agrees with these changes.
1.4: Summary of EAG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)	Model uses cost prices from the year 2015/2016.	Update the model using 2019/2020 National Health Service (NHS) Reference costs and align all the other cost inputs to the same cost year (done by the company response to request for clarification question B7).	£50,254 (+£1,095)	
1.4: Summary of EAG's preferred assumptions and resulting incremental cost effectiveness ratio (ICER)	In the absence of SACT data, an IVIG rate of [redacted] was used base on real-world evidence.	Proportion of patients using intravenous immunoglobulins (IVIG) treatment equal to [redacted] and a treatment duration at 6.5 months, as observed in the systemic anti-cancer therapy (SACT) cohort.	£49,373 (+£214)	
Revised base case (incorporating all of the above changes)	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	**£50,480 (+£1,321)**	

Sensitivity analyses around revised base case

The below table is an updated version of the scenario analysis presented in Table 13 of the CDF re-submission document, using the ICER incorporating the changes made in response to the technical engagement.

Table 5: Updated Scenario analysis

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER	EAG response
Revised company base case			£50,480	The EAG would like to thank the company for providing these new scenarios. Please refer to the responses of issues 2 and 4 above for scenario analyses which are more sensitive to the ICER. Details on these scenarios can be found in the EAG report.
Axi-cel overall survival – alternative extrapolation	Best fitting spline model used for axi-cel overall survival (two knots, normal)	A splines model is explored based on new NICE guidance outlined in TSD 21, as discussed previously	£50,709 [+£229]	
Axi-cel progression-free survival – alternative extrapolation	MCM (log-logistic) used for axi-cel PFS	PFS MCM used to match the preferred model used for overall survival	£51,197 [+£717]	
No standard mortality ratio	The standard mortality ratio (1.09 after 60 months) is not applied	This is consistent with the original submitted model	£47,706 [-£2,774]	

Key: ERG, Evidence Review Group, FAD, final appraisal determination; IVIG, intravenous immunoglobulin; MCM, mixture cure model; PFS, progression-free survival; TSD, technical support document.
Notes: simple PAS applied.