NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic treatment [ID1684]

Contents:

The following documents are made available to consultees and commentators:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Kite, a Gilead company

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Anthony Nolan
   b. Blood Cancer UK
   c. Lymphoma Action
   d. Royal College of Pathologists
   e. NHSE CAR-T tariff summary
   f. Gilead response to NHSE CAR-T tariff documents

4. **Evidence Review Group report** prepared by Aberdeen HTA Group

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 Andrew McMillan – clinical expert, nominated by NHS England
   b. Dr Sridhar Chaganti – clinical expert, nominated by The Royal College of Pathologists
   c. Robert Cross – patient expert, nominated by Anthony Nolan
   d. Rebecca Hallam – patient expert, nominated by Anthony Nolan

8. **Evidence Review Group critique of company response to technical engagement** prepared by Aberdeen HTA Group
   a. ERG critique of company TE response
   b. ERG critique of CAR-T tariff

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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

Single technology appraisal

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

Document B

Company evidence submission

March 2022

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ID1684 Document B_v1.0_AICCIC	1.0	Yes	10/03/2022

Contents

Tables and figures

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

This submission focuses on part of the expected technology's marketing authorisation, aligning the proposed population to the pivotal evidence base.

The decision problem addressed is therefore the potential value of axicabtagene ciloleucel (axi-cel; Yescarta®) for the treatment of adults with primary refractory or early relapse (≤ 12 months) diffuse large B-cell lymphoma (DLBCL) who are intended for transplant. In this position, axi-cel would displace current second-line standard of care (SOC) of re-induction therapy followed by high-dose therapy (HDT) plus autologous stem-cell transplant (auto-SCT) consolidation in responders.

ZUMA-7 provides direct data of relevance to this decision problem and shows that in this poor prognosis patient group with high unmet need, axi-cel offers a three-fold increase in the number of patients receiving definitive therapy and a 2.5-fold increase in the number of patients living event-free for at least 2 years compared with current second-line SOC.[1]

Full details of the decision problem that the submission addresses are summarised in Table 1. Full details of the technology and health condition are provided in Sections B.1.2 and B.1.3; full details of the clinical effectiveness evidence are provided in Section B.2.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory DLBCL after one systemic therapy.	Adults with primary refractory or early relapse (≤ 12 months) DLBCL who are intended for transplant.	Population aligned to the ZUMA-7 trial population.
Intervention	Axicabtagene ciloleucel	Axicabtagene ciloleucel	Not applicable
Comparator(s)	Established clinical management without axicabtagene ciloleucel, including but not limited to: • Salvage chemotherapy with or without rituximab and with or without stem cell transplantation, such as: – DHAP (dexamethasone, cytarabine, cisplatin) – ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) – GDP (gemcitabine, dexamethasone, cisplatin) – GEMOX (gemcitabine and oxaliplatin) – ICE (ifosfamide, carboplatin, etoposide) – IVE (ifosfamide, etoposide, epirubicin) • Polatuzumab vedotin with rituximab and bendamustine	Re-induction therapy with HDT-auto-SCT consolidation in responders.	As detailed in the NICE pathway for treating DLBCL, patients who are fit enough to tolerate intensive therapy should be offered multi-agent immunochemotherapy at first relapse, primarily to obtain sufficient response to allow consolidation with auto-SCT. Of the salvage chemotherapy options listed, GEMOX is generally reserved for less fit patients who are not able to tolerate intensive HDT plus auto-SCT, and who would therefore not be included in the target population of patients intended for transplant. The term ‘salvage chemotherapy’ has potential negative connotations and is arguably inaccurate in a market where novel treatments are available at later lines. We have therefore replaced this terminology with ‘re-induction therapy’ from this point in the document, which is more aligned with the medical community. Polatuzumab vedotin with rituximab and bendamustine is only a treatment option for patients who have been determined as non-candidates for transplant, as per its marketing authorisation and NICE recommendation.[2]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	(only when stem cell transplantation is not suitable) • Tafasitamab with lenalidomide (only when stem cell transplantation is unsuitable and subject to ongoing NICE appraisal)		Tafasitamab with lenalidomide is also being assessed for use in patients who have been determined as non-candidates for transplant. It is not yet reimbursed for use in England. As we are submitting for reimbursement in patients intended for transplant, these are not relevant comparators to the decision problem that we will address.
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rates • Adverse effects of treatment • HRQL	The outcome measures to be considered include: • EFS • OS • PFS • Response rates • Adverse effects of treatment • HRQL	EFS as a primary endpoint is defined as the time from randomisation to the earliest date of disease progression, commencement of new anti-lymphoma therapy, death from any cause or a best 'response' of stable disease . This is the most clinically relevant endpoint for relapsed/refractory DLBCL given the curative intent of treatment. Additionally, patients who do not respond to re-induction therapy in the second-line setting (i.e. patients who have either progressive disease or stable disease) will not benefit from HDT plus auto-SCT, and so an immediate change in therapeutic intervention is often needed. Reflecting its relevance to this setting, EFS is an established endpoint in DLBCL trials and is the primary endpoint in the ZUMA-7 trial. EFS will therefore be used alongside OS and HRQL data to capture the most important health-related benefits of axicabtagene ciloleucel in the cost-effectiveness modelling.

Key: auto-SCT, autologous stem cell transplant; DHAP, dexamethasone, cytarabine and cisplatin; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; GDP, gemcitabine, dexamethasone and cisplatin; GEMOX, gemcitabine and oxaliplatin; HDT, high dose therapy; HRQL, health-related quality of life; ICE, ifosfamide, carboplatin and etoposide; IVE, ifosfamide, etoposide and epirubicin; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival.

B.1.2. Description of the technology being appraised

A description of axicabtagene ciloleucel (axi-cel; Yescarta®) is presented in Table 2.

The draft summary of product characteristics (SmPC) for the licence extension to the second-line setting is presented in Appendix C. The European Public Assessment Report (EPAR) can be provided on receipt.

Axi-cel was the first in a breakthrough class of chimeric antigen receptor (CAR) T-cell therapies that are manufactured from patients' own T-cells and is engineered ex vivo to express antigen-specific CARs, enabling them to target and kill antigen-expressing tumour cells on return to the patient. The CAR construct used in axi-cel is a single-chain antibody fragment directed against CD19 and linked to CD3ζ and CD28 T-cell activating domains; CD19 is a B-cell-specific cell surface antigen ubiquitously expressed in B-cell malignancies.[3]

Axi-cel is given as a single infusion treatment. The median target timescale from collection of the patient's T-cells by leukapheresis, through transportation to the manufacturing facility, product manufacture, and qualified person (QP) release in Europe is [redacted].[4]

The axi-cel construct and mode of action is depicted in Figure 1. The manufacturing and administration process for axi-cel is depicted in Figure 2.

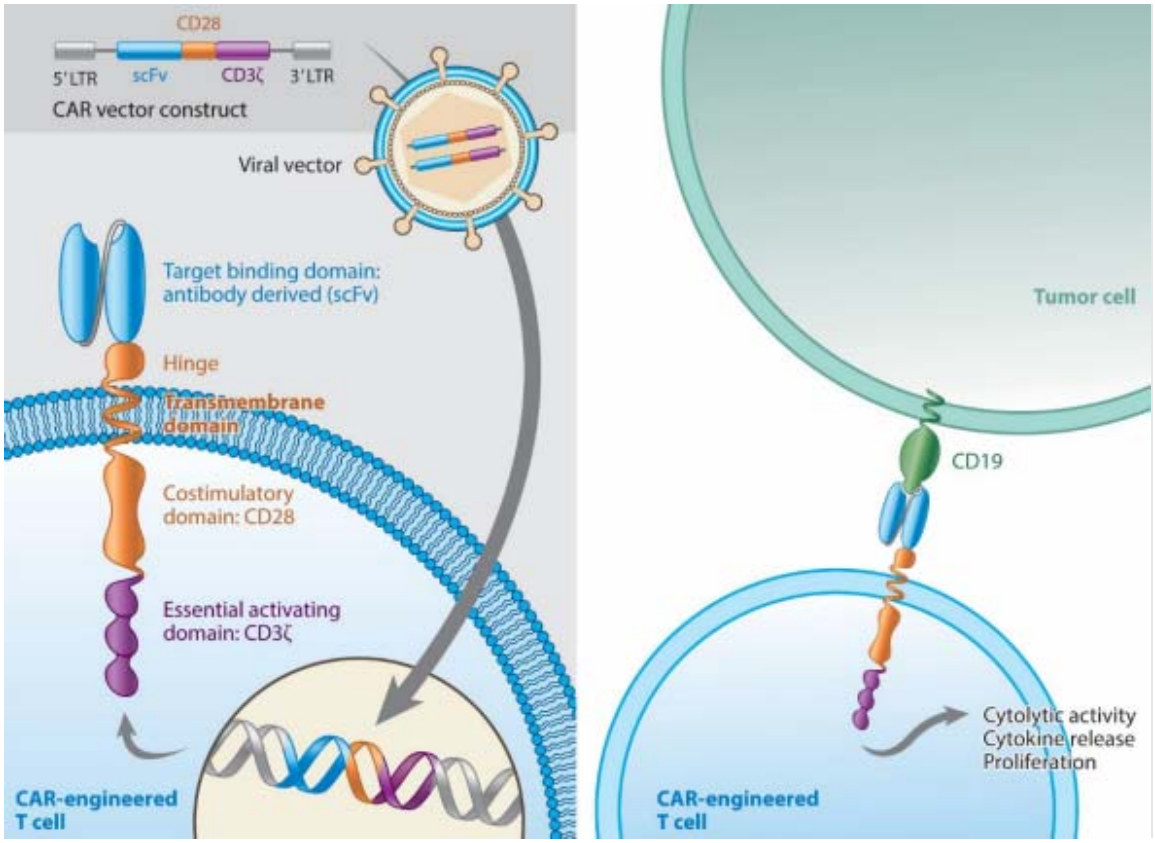
Table 2: Technology being appraised

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 mAb, then transduced with the anti-CD19 CAR transgene-containing γ-retroviral vector. The structure of the anti-CD19 CAR construct comprises the following domains: an anti-human CD19 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.[5] 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. The mechanism of action of axi-cel is shown in Figure 1. Following infusion of axi-cel into the patient, the anti-CD19 region of axi-cel binds to CD19 and the 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 together with the primary CD3ζ signal to augment T-cell function, including IL-2 production.[6] These signals act together, which results 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 antitumour immune cells.[7]
Marketing authorisation	The application for EMA filing was submitted in [redacted] for a marketing authorisation extension. The anticipated indication of Yescarta of relevance to this submission is for '[redacted]. The target date for GB filing is [redacted] and the anticipated date of marketing authorisation for this licence extension is [redacted]. Yescarta is already indicated for the treatment of adult patients with r/r DLBCL and PMBCL, after two or more lines of systemic therapy
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	At least one dose of tocilizumab in the event of CRS and emergency equipment must be available prior to axi-cel infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. [redacted]
Method of administration and dosage	Each patient-specific single infusion bag of axi-cel contains a target dose of 2 x 10^6 CAR-positive viable T-cells per kg of body weight (range: 1 x 10^6 to 2 x 10^6, or a maximum of 2 x 10^8 CAR-positive viable T-cells for patients who are 100 kg and above) in approximately 68 mL dispersion. Axi-cel is intended

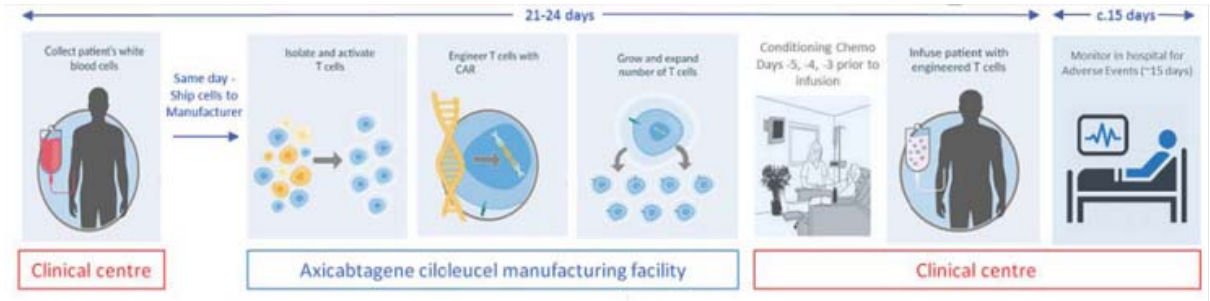
	for autologous use only and must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and who is trained in the administration and management of patients treated with axi-cel. All patients will receive lymphodepleting chemotherapy consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous on the 5th, 4th and 3rd day before axi-cel infusion. Premedication with oral paracetamol 500–1,000 mg and oral or intravenous diphenhydramine 12.5–25 mg approximately 1 hour prior to axi-cel infusion is also recommended.
Additional tests or investigations	Patients will be considered for CAR T-cell therapy eligibility by a panel of expert clinicians following referral from a specialist doctor. Treatment will be provided in one of the 12 CAR T-cell therapy centres currently set up to deliver CAR T-cell therapy across NHS England (the number of CAR T-cell therapy centres is expected to increase throughout 2022). The treating clinician in the respective CAR T-cell therapy delivery centre will determine the appropriate CAR T-cell therapy for each patient. Patients should be monitored for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first 10 days, the patient should be monitored at the physician's discretion, but patients should remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.
List price and average cost of a course of treatment	Axi-cel list price (including shipping, engineering and generation of the CAR T-cells): £280,451.
Patient access scheme (if applicable)	A simple patient access scheme discount of [redacted] on the list price of axi-cel, resulting in a net cost for a single infusion of [redacted]
Key: CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; HGBL, high-grade B-cell lymphoma; mAb, monoclonal antibody; MHRA, Medicines & Healthcare products Regulatory Agency; NHS, National Health Service; PMBCL, primary mediastinal large B-cell lymphoma; r/r, relapsed or refractory; scFv, single-chain variable region fragment; SmPC, Summary of Product Characteristics.	

Figure 1: Axi-cel anti-CD19 CAR construct and mode of action



Key: CAR, chimeric antigen receptor; LTR, long terminal repeat; scFv, single-chain variable region fragment.

Figure 2: Process of manufacturing and administering axi-cel



Key: CAR, chimeric antigen receptor.

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

Non-Hodgkin's lymphoma (NHL) comprises a diverse group of cancers of the lymphatic system.[8] DLBCL is the most common type of NHL, accounting for approximately 40% of all NHL cases.[8] DLBCL is an aggressive, high-grade form of NHL, characterised by abnormal and enlarged B-cells that quickly grow and spread if left untreated.[8] An estimated 5,180 people are diagnosed with DLBCL each year in the UK.[9]

There are several different subtypes of DLBCL, which demonstrates the heterogeneity of the clinical and pathological features of this disease beyond B-cell abnormality. DLBCL, not otherwise specified (NOS) is defined by excluding unique features and is the most common subtype, estimated to account for over 80% of large B-cell lymphomas.[10] Rarer subtypes recognised by the World Health Organization (WHO) include: T-cell/histiocyte-rich large B-cell lymphoma; primary DLBCL of the central nervous system (CNS); primary cutaneous DLBCL; and Epstein-Barr virus (EBV)-positive DLBCL.[11] Double-hit or triple-hit lymphoma (i.e. lymphoma with *MYC*, *BCL2* and/or *BCL6* genetic aberrations) was also traditionally considered a DLBCL subtype, but it is now included in the new category of high-grade B-cell lymphoma (HGBL) in the most recent WHO classification of lymphomas.[11] There are no therapies specifically indicated for HGBL and there is no consensus on whether a different management approach is needed for these lymphoma types, although patients with double-hit or triple-hit lymphoma typically have a poor prognosis.[12-14] From this point in the document, DLBCL is used to describe patients with any DLBCL/HGBL subtype that aligns to the eligibility criteria of the pivotal trial supporting the use of axi-cel (see Section B.2).

DLBCL has a complex and multifactorial aetiology with several risk factors identified. These include: demographic characteristics such as body mass index; clinical characteristics such as weakened immune function; environmental factors such as carcinogen exposure; and genetic susceptibility.[15, 16] Most patients are at least 60 years old at diagnosis (median age at diagnosis estimates range from 61 to 70 years

across datasets) and almost all patients (~90%) present with advanced-stage disease (Ann Arbor III/IV). [9, 17-19] There is a slight male dominance in cases.[9, 17]

Following diagnosis of DLBCL, patients will undergo prognostic assessment via the International Prognostic Index (IPI) which considers: age (> 60 years = 1 risk factor); lactate dehydrogenase (LDH) levels (> upper limit of normal [ULN] = 1 risk factor); Ann Arbor disease staging (III/IV = 1 risk factor); performance status (> 1 = 1 risk factor); and spread of disease (extranodal sites of disease > 1 = 1 risk factor) to estimate a prognostic risk (low = 0–1 risk factors; high = 4–5 risk factors).[20] Additional poor prognostic factors include genetic factors (see previous note on double-hit or triple-hit lymphoma) and bulky disease (tumour diameter > 7.5 cm).[21] Further factors predicting prognosis at relapse are captured in the secondary age-adjusted IPI (sAAIPI), which considers three of the IPI risk factors (LDH, disease staging and performance status) to estimate a prognostic risk (low = 0 risk factors; high = 3 risk factors).[22]

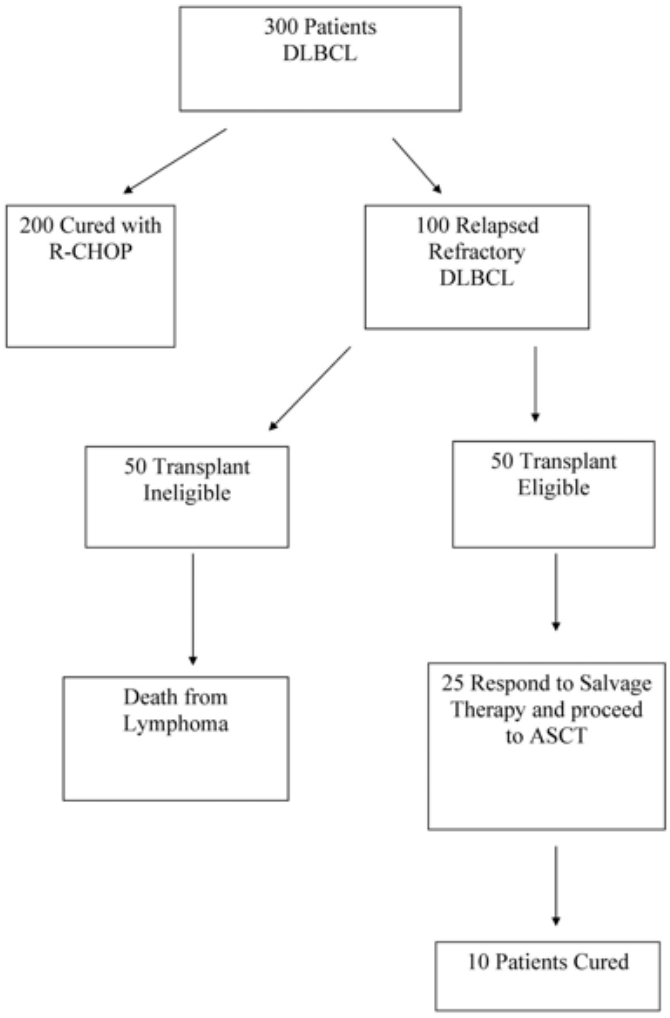
B.1.3.2. Clinical outcomes

DLBCL is a curable disease with 80% of patients receiving frontline therapy of rituximab with cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone (R-CHOP) with curative intent.[23] Despite this, frontline R-CHOP does not cure all patients; approximately 10–15% of patients develop primary refractory disease (i.e. an inadequate response to frontline treatment) and a further 20–25% patients relapse following treatment.[10] Outcomes remain poor for these patients in whom frontline treatment fails, particularly for those with primary refractory or early relapse disease.[24-27]

The only potentially curative treatment option available at first relapse is currently HDT-auto-SCT, which can only follow a response to re-induction therapy (Figure 4). Due to advanced age and coexisting medical conditions, only half of relapsed or refractory (r/r) DLBCL patients are fit enough to be considered for such high-intensity treatment, and only half again go on to receive auto-SCT.[10, 26, 28] Reasons why r/r DLBCL patients intended for transplant may not receive auto-SCT include: insufficient response or intolerance to re-induction therapy; intolerance to HDT; progressive disease during re-induction therapy or HDT; and stem cell mobilisation failure. In the primary refractory or early relapse patient group intended for

transplant, there is a higher risk of one or more of these factors preventing auto-SCT receipt, and closer to two-thirds of patients in this group will not receive auto-SCT despite intent.[1, 27, 29] Primarily, patients refractory to or relapsing quickly after frontline R-CHOP have a lower chance of sufficient response to chemotherapy-based re-induction therapy to accommodate HDT-auto-SCT and a higher chance of platinum-salvage toxicity.[30] Even for patients who do receive auto-SCT there is no guarantee of cure, with approximately half of r/r DLBCL patients treated with auto-SCT experiencing further relapse.[26, 28] It has previously been estimated that out of 100 r/r DLBCL patients, only 10 will be cured with current second-line care, as depicted in Figure 3.

Figure 3: Estimated cure rates with current treatment for DLBCL



Key: ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab with cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone.
Source: Friedberg 2011.[31]

Historical trial data that are specific to the primary refractory or early relapse DLBCL group intended for transplant and reflective of current pathways of care are limited. However, some studies provide insight into the poor prognosis of this population, as summarised in Table 3. Further data from historical randomised controlled trials (RCT) are provided in Appendix N. Event-free survival (EFS) rates were approximately 16% at 2 years and 13% at 3 years in the subgroup of patients with primary refractory or early relapse DLBCL who had received frontline rituximab-based therapy in the CORAL trial. Similarly, this was 17% at 2 years in all patients enrolled in the ORCHARRD trial (r/r DLBCL despite frontline rituximab-based therapy) which included a majority (71%) of patients with either primary refractory or early-relapse disease.[25, 27] Median overall survival (OS) in this primary refractory or early relapse DLBCL group of the ORCHARRD trial (all of whom received frontline rituximab-based therapy) was less than 1 year (estimated at approximately 9 months from the Kaplan–Meier curve) and the 2-year OS rate was 31%.[27] Median OS in the primary refractory DLBCL group of the SCHOLAR-1 study was 7.1 months and the 2-year OS rate was 24%; in the overall population (refractory to frontline or later-line therapy or relapsed ≤ 12 months from auto-SCT), median OS was 6.3 months, and the 2-year OS rate was 20%.[24]

Table 3: Studies providing insight into the prognosis of primary refractory or early relapse DLBCL patients intended for transplant

Study	Design (n)	Population	Auto-SCT	EFS / PFS	OS
ORCHARRD[27]	Phase III RCT designed to compare the efficacy and safety of ofatumumab-based vs rituximab-based re-induction therapy for r/r DLBCL followed by auto-SCT in responders. (n = 447)	CD20+ DLBCL patients relapsing, or with persistent disease after frontline treatment with rituximab-based therapy, and who are intended for transplant (71% of whom had primary refractory or early relapse disease).	Total population: Receipt rate: 35% 2-year PFS: 51% 2-year OS: 72%	Total population: Median PFS: ~3M[a] 2-year EFS: 17% 2-year PFS: 25% Primary refractory / early relapse patients (n = 316): Median PFS: ~3M[a] 2-year PFS: ~15%[a]	Total population: Median OS: 13.6M 2-year OS: 40% Primary refractory / early relapse patients (n = 316): Median OS: ~9M[a] 2-year OS: ~30%[a]
CORAL[25, 26]	Phase III RCT designed to compare the efficacy and safety of R-ICE vs R-DHAP re-induction therapy for r/r B-cell NHL followed by auto-SCT ± rituximab maintenance in responders. (n = 396; treated n = 388)	CD20+ B-cell NHL including DLBCL patients relapsing, or not achieving CR with anthracycline-based frontline treatment. 62% of patients had prior rituximab and 54% had primary refractory or early relapse disease. Only 13 patients did not have DLBCL.	Total population: Receipt rate: 53% 3-year PFS: 53% Primary refractory / early relapse patients who received prior rituximab (n = 187): Receipt rate: 36% 3-year PFS: 39%	Total population: 3-year EFS: 31% 4-year EFS: 30% Median PFS: ~12M[a] 3-year PFS: 37% Primary refractory / early relapse patients who received prior rituximab (n = 187): 2-year EFS: ~16%[a] 3-year EFS: ~13%[a] 3-year PFS: 23%	Total population: Median OS: ~34M[a] 2-year OS: ~57%[a] 3-year OS: 49% 4-year OS: 47%

Study	Design (n)	Population	Auto-SCT	EFS / PFS	OS
LY-12[32]	Phase III RCT designed to compare the efficacy of GDP vs DHAP re-induction therapy for r/r aggressive lymphoma followed by auto-SCT in responders. All DLBCL patients also received rituximab. (n = 619)	Aggressive lymphoma including DLBCL patients relapsing or having refractory disease to frontline treatment with anthracycline-based frontline treatment. 68% of patients had r/r DLBCL, 66% had prior rituximab and 72% had primary refractory or early relapse disease.	Total population: Receipt rate: 50% 2-year EFS: ~54%[a] 4-year EFS: 46% 2-year OS: ~69%[a] 4-year OS: 63%	Total population: Median EFS: ~6M[a] 2-year EFS: ~30%[a] 4-year EFS: 26%	Total population: Median OS: ~13M[a] 2-year OS: ~46%[a] 4-year OS: 39%
SCHOLAR-1[24]	Retrospective cohort study designed to evaluate outcomes in patients with refractory DLBCL. Data were pooled from CORAL and LY-12 and two observational cohorts. (n = 636)	Refractory DLBCL patients defined as best 'response' of stable or progressive disease, or relapsed ≤ 12 months from auto-SCT. 28% of patients had primary refractory disease (i.e. were refractory to frontline therapy).	-	-	Total population: Median OS: 6.3M 2-year OS: 20% Primary refractory population: Median OS: 7.1M 2-year OS: 24%

Key: auto-SCT, autologous stem cell transplant; CR, complete response; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; GDP, gemcitabine, dexamethasone and cisplatin; R-ICE, rituximab + ifosfamide, carboplatin and etoposide; M, month; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival, RCT randomised controlled trial.
Notes: [a], estimated from Kaplan–Meier curve.

B.1.3.3. Burden of disease

The most common symptoms of DLBCL include enlarged lymph nodes and general 'B symptoms' that include night sweats, fever, involuntary weight loss and unexplained itching.[33] Other physical symptoms may depend on where DLBCL appears and spreads. For example, patients may experience breathlessness if lymphoma is affecting nodes in their chest.[33]

There is also an emotional burden associated with a diagnosis of DLBCL, and this is exacerbated for patients who experience treatment inefficacy[34], such as primary refractory or early relapse disease. Ineligibility to receive effective treatment can also impact patients' emotional status. For example, patients who go through the process of assessment and preparation for auto-SCT, but who then do not receive auto-SCT treatment, may experience a range of negative emotions. The emotional burden extends to carers of patients with r/r DLBCL who are often trying to support the patient with their feelings while coping with their own, which can lead to high levels of anxiety and stress.[35]

Patients undergoing treatment can experience additional physical and emotional symptoms relating to treatment side effects, and these are shown to negatively impact health-related quality of life (HRQL).[36] Patients undergoing stem cell transplant are at particular risk of treatment side effects that can adversely affect HRQL over the long term. A study investigating the HRQL of long-term survivors after auto-SCT using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 questionnaire showed that global health status did not return to general population levels until 4 years post-transplant.[37] Emotional, physical, role, social and cognitive functions were also all shown to be negatively impacted over the long term.

In addition to the long-term impact on HRQL, auto-SCT survivors are also at risk of late effects, such as secondary malignancies and cardiac or pulmonary toxicity that can be fatal, with late effects reported in around 10% of patients.[38, 39] In a retrospective long-term follow-up of r/r DLBCL patients undergoing auto-SCT in a US haematology clinic (n = 309), while relapse was initially the more likely cause of death, non-relapse mortality became the major cause of death after 8 years.[40]

B.1.3.4. Clinical pathway of care

The clinical pathway of care for DLBCL is depicted in Figure 4.

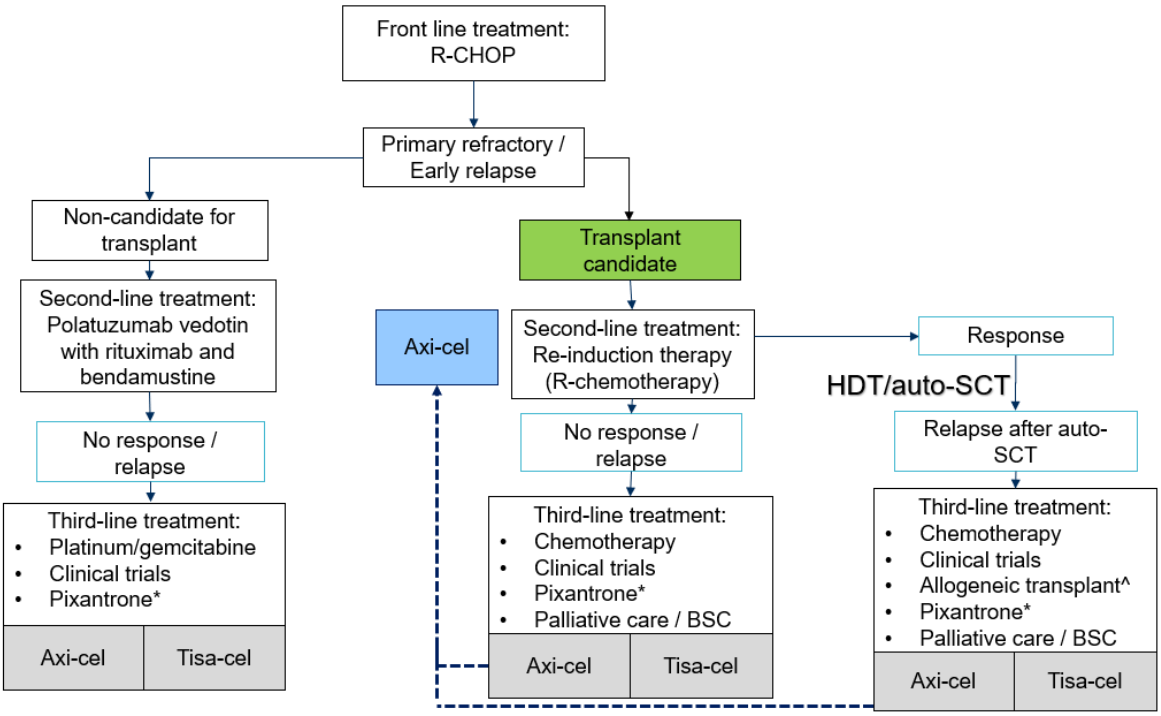
Frontline treatment consists of R-CHOP for nearly all newly diagnosed patients treated with curative intent, with the number of cycles determined according to baseline prognosis.[10, 21] Consolidation radiotherapy and CNS prophylaxis may also be considered alongside R-CHOP for patients with bulky disease or who are at risk of CNS lymphoma, respectively.[10, 21, 41]

At first relapse, patients who are who are fit enough to tolerate intensive therapy are offered further multi-agent immunochemotherapy (re-induction therapy) to try to obtain sufficient response for HDT-auto-SCT consolidation.[10, 21, 41] The most common re-induction therapy regimens used at first relapse are: rituximab with dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP); rituximab with ifosfamide, carboplatin, and etoposide (R-ICE); rituximab with etoposide, methylprednisolone, cytarabine and cisplatin (R-ESHAP); and rituximab with gemcitabine, dexamethasone, and cisplatin (R-GDP).[10, 17, 29, 41]

Allogeneic stem cell transplant (allo-SCT) can be considered instead of auto-SCT where stem cell harvesting is not possible, or for people with chemo-sensitive DLBCL that relapses after auto-SCT. Additional treatment options at second relapse (i.e. for people who have received two prior lines of therapy) include the CAR T-cell therapies axi-cel or tisagenlecleucel (tisa-cel), which are currently available through the Cancer Drugs Fund (CDF).[41] Patients who are not considered eligible for CAR T-cell therapy may be treated with further chemotherapy, enrolled to a clinical trial (if available) or managed with palliative or best supportive care.[17]

Axi-cel offers an alternative second-line treatment option to re-induction therapy plus HDT-auto-SCT in responders for patients with primary refractory or early relapse DLBCL who are intended for transplant (aligning with the ZUMA-7 trial population), as depicted in Figure 4.

Figure 4: Clinical pathway of care for DLBCL and proposed axi-cel positioning



Key: auto-SCT, autologous stem cell transplant; BSC, best supportive care; DLBCL, diffuse large B-cell lymphoma; HDT, high dose therapy; R-CHOP, rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone.
Notes: * Pixantrone is rarely used in clinical practice but is included here for completeness.
^ An allogeneic transplant can also be considered instead of auto-SCT where stem cell harvesting is not possible.
Green refers to the target population for axi-cel.
Blue refers to the proposed positioning of axi-cel at second-line.
Grey refers to treatments currently recommended within the Cancer Drugs Fund.
Source: Adapted from the NICE pathway for treating DLBCL[41] and the British Society for Haematology guidelines for the management of DLBCL.[21]

B.1.3.5. Unmet need

DLBCL is a curable disease, but not all patients achieve cure within the current management pathway. Outcomes remain poor for patients for whom frontline treatment fails, particularly patients with primary refractory or early relapse disease. In this difficult-to-treat group, only a third of patients intended for transplant receive auto-SCT at first relapse, and the overall cure rate is expected to fall between 13–17% based on EFS rates reported in historical trials of current second-line care (re-induction therapy plus HDT-auto-SCT in responders) (Table 3). Those who do receive auto-SCT are also at risk of persistent and late side effects that can negatively impact long-term quality of life.[37-40]

During scoping consultation, the urgency of this appraisal in consideration of the significant unmet need in second-line therapy for r/r DLBCL was highlighted by commentators, where the specific target population (primary refractory or early relapse patients) was described as having a 'dismal outcome'.[42] In Kite-sponsored consultation settings, one clinical expert in the UK described the current treatment option of auto-SCT as 'unpleasant' and with 'modest expectation of success' in all second-line patients, but particularly in those with primary refractory or early relapse disease; another described auto-SCT as 'cruel punishment', adding that current second-line care 'fails the majority' of primary refractory or early relapse patients.[29, 43]

CAR T-cell therapy is an alternative, potentially curative, treatment option to HDT-auto-SCT for r/r DLBCL, but it is currently only available at the third- or later-line setting. By the time patients reach this setting, they have already received two intensive lines of treatment with suboptimal response and may not be fit enough (or willing) to receive another.[29] Generally we would expect decreased tumour burden and comorbidities in second-line versus third-line patients, and higher general and T-cell fitness.[30] This was also acknowledged by commentators during the scoping consultation, who noted that 'although patients can potentially access CAR T-cell therapy, third-line disease progression may result in poor performance score (i.e. not 0–1) and hence be ineligible for this treatment modality' and that 'second-line rather than third-line could result in improved access, with improvement in the outcomes measured'.[42]

ZUMA-7 directly investigates the potential benefit of treating primary refractory or early relapse DLBCL patients with axi-cel versus HDT-auto-SCT in the second-line setting and shows that patients intended for axi-cel treatment are three times more likely to receive definitive therapy than patients intended for transplant, and are 2-3 times more likely to live event-free for at least 2 years (see Section B.2).[1] The availability of axi-cel for primary refractory or early relapse DLBCL patients intended for transplant would not only increase the definitive therapy receipt and associated cure rates, but could also reduce the negative long-term physiological and psychological impacts of current second-line care.

B.1.4. Equality considerations

There is an age inequality issue with current second-line SOC in that auto-SCT is not considered a treatment option for older patients, with a typical 'cut-off' age between 65 and 70 years.[29, 43] Such an age restriction would not be applied to axi-cel and therefore its introduction could help to reduce this current age inequality.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. List of relevant clinical effectiveness evidence

Table 4 summarises the evidence that supports axi-cel for the treatment of adults with primary refractory or early relapse DLBCL who are intended for transplant.

Table 4: Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">ZUMA-7</td></tr>
<tr><td>Study design</td><td colspan="5">ZUMA-7 is an ongoing Phase III, randomised, open-label study evaluating the efficacy of axi-cel compared with SOC treatment.</td></tr>
<tr><td>Population</td><td colspan="5">Adults with primary refractory (no CR to frontline therapy) or early relapse (CR followed by relapse within 12 months of frontline therapy) DLBCL after one systemic therapy who are intended for transplant.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Axi-cel</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Re-induction therapy with HDT plus auto-SCT consolidation in responders</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">ZUMA-7 presents the pivotal, regulatory, clinical evidence in support of axi-cel in r/r DLBCL</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• EFS
• OS
• PFS
• Response rate
• Adverse effects of treatment
• HRQL</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Duration of response
• Time to next treatment
• Clinically significant changes in safety laboratory test values, including antibodies to axi-cel</td></tr>
<tr><td colspan="6">Key: auto-SCT, autologous stem cell transplant; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HDT, high dose therapy; HRQL, health-related quality of life; OS, overall survival; PFS, progression-free survival; r/r, relapsed or refractory; SOC, standard of care.
Notes: Bolded outcomes are those used in the economic modelling.</td></tr>
</table>

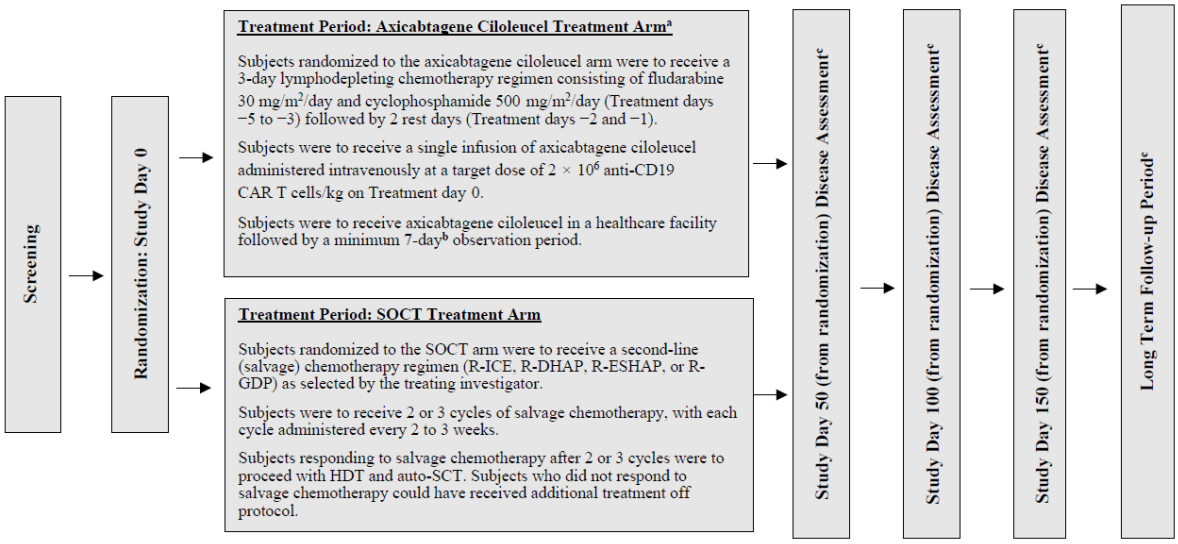
B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Table 5 provides a summary of the trial methodology for ZUMA-7.

ZUMA-7 is a Phase III, randomised, open-label, parallel assignment trial that evaluates the efficacy of axi-cel versus SOC therapy in adults with relapsed/refractory DLBCL. Eligible patients were at least 18 years of age. They had histologically confirmed DLBCL that was refractory to frontline treatment (no complete response [CR]), or that had relapsed from CR ≤ 12 months after the completion of frontline chemoimmunotherapy. This included an anti-CD20 monoclonal antibody and anthracycline-containing regimen. The patients also intended to proceed to HDT and auto-SCT.[1]

Patients were randomised in a 1:1 ratio to receive axi-cel or SOC.[1]. Randomisation was stratified according to response to frontline therapy (refractory versus relapsed disease) and the sAAIPI (0 or 1 risk factor versus 2 or 3 risk factors). Although crossover between the treatment groups was not permitted within the trial, patients who had no response to SOC could receive subsequent cellular immunotherapy outside of the trial protocol (reflecting 'treatment switching').OS outcomes in the SOC arm are therefore augmented and reflect a treatment sequence that includes CAR T-cell therapy at third- or later-line settings Each patient was to proceed through the study periods depicted in Figure 5.

Figure 5: Study scheme for ZUMA-7



Key: auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; HDT, high-dose therapy; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SCT, stem cell transplant; SOCT, standard of care therapy.
Notes: [a] At the discretion of the investigator, corticosteroid bridging therapy could have been considered for patients with high disease burden at screening. [b] Minimum observation period of 7 days unless otherwise required by country regulatory agencies (e.g. 10 days for patients treated in Germany, Switzerland, and France). [c] Disease assessments were to be calculated from the date of randomisation and not the date of dosing with axi-cel or SOCT. Independent of the treatment arm, study procedures and disease assessments were to occur at the same protocol-defined timepoints.
Source: ZUMA-7 CSR.[44]

The primary endpoint of the ZUMA-7 trial was EFS, defined as the time from randomisation to the earliest date of disease progression per the Lugano Classification [45] as determined by blinded central assessment, commencement of new lymphoma therapy, death from any cause, or a best response of stable disease (SD) up to and including the response on the Day 150 assessment after randomisation.[1] Secondary endpoints included: objective response rate (ORR); OS; progression-free survival (PFS); duration of response (DOR); modified EFS (mEFS); safety; and patient-reported outcome (PRO) endpoints (Table 5).

Table 5: Summary of trial methodology for ZUMA-7

Trial number (acronym)	NCT03391466 (ZUMA-7)
Location	A total of 77 investigative sites in 14 countries (US, Canada, Israel, Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, United Kingdom, and Australia)
Trial design	ZUMA-7 is a Phase III randomised, open-label, multicentre study evaluating the efficacy of axi-cel versus SOC in adult patients with primary refractory or early relapse DLBCL who are intended for transplant. Adult patients with r/r DLBCL after frontline rituximab and anthracycline-based chemotherapy will be randomised in a 1:1 ratio to receive axi-cel or SOC. For patients in the axi-cel arm, treatment consisted of lymphodepleting chemotherapy followed by a single intravenous infusion of axi-cel. Bridging therapy of corticosteroids only was permitted before lymphodepleting chemotherapy for patients with high disease burden, at the discretion of the investigator. For patients randomised to the control arm of the study, SOC will consist of a protocol-defined, platinum-based combination chemotherapy regimen. Patients who respond to second-line chemotherapy should proceed to HDT and auto-SCT
Eligibility criteria for participants	**Key inclusion criteria:** • Histologically proven DLBCL, including the following types defined by the WHO in 2016[11]: – DLBCL, NOS (including ABC or GCB) – HGBL with or without MYC and BCL2 and/or BCL6 rearrangement – DLBCL arising from FL – T-cell/histiocyte-rich LBCL – DLBCL associated with chronic inflammation – Primary cutaneous DLBCL, leg type – EBV+ DLBCL • Relapsed or refractory disease after frontline chemoimmunotherapy: – Refractory disease defined as no complete remission to frontline therapy (patients who were intolerant to frontline therapy were to be excluded) – Relapsed disease defined as complete remission to frontline therapy followed by biopsy-proven disease relapse ≤ 12 months of frontline therapy • Patients must have received adequate frontline therapy including, at a minimum: – An anti-CD20 monoclonal antibody, unless the investigator determined that the tumour was CD20-negative – An anthracycline-containing chemotherapy regimen • Intent to proceed to HDT and auto-SCT if there was a response to second-line chemotherapy

	• No known history or suspicion of CNS involvement by lymphoma • ECOG performance status of 0 or 1 • Adequate bone marrow, renal, hepatic, pulmonary and cardiac function defined as: – Absolute neutrophil count ≥ 1000/μL – Platelet count ≥ 75,000/μL – Absolute lymphocyte count ≥ 100/μL – Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min – Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 ULN – Total bilirubin ≤ 1.5 mg/dL, except in patients with Gilbert's syndrome – Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings – No clinically significant pleural effusion – Baseline oxygen saturation > 92% on room air **Key exclusion criteria:** • History of malignancy other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) unless disease-free for at least 3 years • Received more than one line of therapy for DLBCL • History of auto-SCT or allo-SCT • Presence of fungal, bacterial, viral, or other infection that was uncontrolled or requiring IV antimicrobials for management • Known history of infection with HIV, hepatitis B or hepatitis C. If there was a positive history of treated hepatitis B or hepatitis C, the viral load must have been undetectable per quantitative polymerase chain reaction and/or nucleic acid testing • Patients with detectable cerebrospinal fluid malignant cells or known brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases • History or presence of non-malignant CNS disorder, such as seizure disorder, cerebrovascular ischaemia/haemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement • Presence of any indwelling line or drain. Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, were permitted • History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months before enrolment • History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months before enrolment

	• History of autoimmune disease requiring systemic immunosuppression and/or systemic disease-modifying agents within the previous 2 years • History of anti-CD19 or CAR T-cell therapy or history of prior randomisation in ZUMA-7
Settings and locations where data were collected	All patients were to receive an axi-cel infusion at a healthcare facility, followed by daily monitoring at a healthcare facility for at least 7 days to monitor for signs and symptoms of CRS and neurological events, unless otherwise required by country regulatory agencies. Alternatively, if deemed appropriate by the investigator, patients could be hospitalised to receive their axi-cel infusion and were observed for CRS and neurological events in the hospital setting. If a patient was hospitalised, they should not be discharged from the hospital until all axi-cel-related non-haematological toxicities resolved to Grade 1 or lower, or returned to the baseline value. If deemed appropriate by the investigator, patients could be discharged with non-critical and clinically stable or improving toxicities (e.g. renal insufficiency), even if the event severity was higher than Grade 1. Patients were to remain in the hospital for ongoing axi-cel-related fever, hypotension, hypoxia, or ongoing neurological events that were higher than Grade 1 or if deemed necessary by the investigator
Trial drugs	**Axi-cel arm:** Approximately one hour before the axi-cel infusion, the pre-infusion medications acetaminophen (650 mg PO or equivalent) and diphenhydramine (12.5 mg PO or IV or equivalent) were to be administered. Axi-cel was administered as a single IV infusion of CAR-transduced autologous T-cells at a target dose of 2×10^6 anti-CD19 CAR T-cells/kg, but may have been dosed at a minimum of 1×10^6 anti-CD19 CAR T-cells/kg. For patients weighing > 100 kg, a maximum flat dose of axi-cel at 2×10^8 anti-CD19 CAR T-cells was to be administered. **SOC arm:** Patients were to be treated with platinum-based second-line combination chemotherapy regimens, including R-ICE, R-ESHAP, R-GDP, R-DHAP or R-DHAX. If a patient demonstrated adequate disease response (CR or PR) after two or three cycles of chemotherapy and collected a sufficient number of CD34+ stem cells, HDT and auto-SCT may have been initiated. Before HDT, G-CSF was to be administered to mobilise stem cells from the bone marrow to the periphery, after which peripheral blood progenitor cells were to be collected by leukapheresis to a minimum target of 2×10^6 CD34+ haematopoietic stem cells per kg body weight. The HDT conditioning regimen was to consist of combination high-dose chemotherapy with or without TBI. Commonly used high-dose regimens include BEAM or CBV. After HDT, the CD34+ haematopoietic stem cells were to be reinfused to rescue haematopoiesis.

Concomitant medication	• Investigators were allowed to prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (e.g. G-CSF) and routine anti-emetic prophylaxis, except those medications listed below • Treatment for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation (TBI for HDT was allowed for the SOC arm), high-dose corticosteroid (other than those allowed in the protocol for either arm), and other investigational agents were prohibited, except as needed for the treatment of disease progression after treatment with axi-cel or SOC • In the axi-cel arm, corticosteroid therapy at a pharmacological dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs were to be avoided for 7 days before leukapheresis and 5 days before axi-cel administration. Systemic corticosteroids were not to be administered as premedication to patients for whom CT scans with contrast are contraindicated (i.e. patients with contrast allergy or impaired renal clearance). Such patients were to undergo MRI with contrast and non-contrast CT scans instead. Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after axi-cel administration, unless used to manage axi-cel-related toxicities. Other medications that might have interfered with the evaluation of axi-cel, such as non-steroidal anti-inflammatory agents, were also to be avoided for the same period unless medically necessary
Primary outcome	• EFS (with progression events and censoring) per blinded central assessment, defined as the time from randomisation to the earliest date of disease progression per the Lugano Classification[45], commencement of new lymphoma therapy, death from any cause, or a best response of SD up to and including the response on the Day 150 assessment after randomisation
Other outcomes used in the economic model/specified in the scope	**Key secondary endpoints:** • ORR per blinded central assessment, defined as the incidence of either a CR or a PR by the Lugano Classification[45] • OS, defined as the time from randomisation to death from any cause **Additional secondary endpoints:** • EFS (with progression and censoring events) per investigator disease assessment • PFS (with progression and censoring events) per investigator disease assessment, defined as the time from randomisation to disease progression per the Lugano Classification[45] or death from any cause • DOR per blinded central assessment, defined as the time from first response to disease progression per the Lugano Classification[45] or death from any cause • mEFS, defined the same way as EFS, except that having SD as the best response by the Study Day 150 assessment was not to be considered as an event

	Exploratory endpoints: • TTNT, defined as the time from randomisation to the earliest date of commencement of new lymphoma therapy (including axi-cel retreatment and subsequent SCT) or death from any cause **Safety and PRO endpoints:** • Incidence of AEs and clinically significant changes in safety laboratory test values, including antibodies to axi-cel • HRQL, as measured by the EORTC QLQ-C30 and EQ-5D-5L Disease assessments occurred on Days 50, 100 and 150 after randomisation, followed by every 3 months until 2 years of follow-up, and then every 6 months until 5 years of follow-up.
Pre-planned subgroups	Selected efficacy and safety endpoints were performed in subgroups defined by baseline covariates, including response to frontline therapy (primary refractory, relapse ≤ 6 months of initiation of frontline therapy versus relapse > 6 and ≤ 12 months of initiating frontline therapy) and AAIPI (0–1 versus 2–3)

Key: AAIPI, age-adjusted International Prognosis Index; ABC, activated B-cell; AE, adverse event; auto-SCT; autologous stem cell transplant; BEAM, carmustine (BCNU), etoposide, ara-C, melphalan; CAR, chimeric antigen receptor; CBV, cyclophosphamide, BCNU, etoposide; CNS, central nervous system; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; EBV+, Epstein-Barr virus-positive; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; FL, follicular lymphoma; GCB, germinal centre B-cell; G-CSF, granulocyte colony-stimulating factor; HDT, high-dose therapy; HGBL, high-grade B-cell lymphoma; HIV, human immunodeficiency virus; HRQL, health-related quality of life; IV, intravenous; LBCL, large B cell lymphoma; mEFS, modified event-free survival; MRI, magnetic resonance imaging; NOS, not otherwise specified; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-DHAX, rituximab, dexamethasone, oxaliplatin, high-dose cytarabine; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SD, stable disease; SOC, standard of care; TBI, total body irradiation; TTNT, time to next therapy.
Source: ZUMA-7 CSR[44]

B.2.3.1. Baseline characteristics

Table 6 provides a summary of baseline characteristics, including demographic and clinical characteristics.

The characteristics of the patients at baseline were generally balanced between the two treatment groups.[1] The median age was 59 years and 30% of the patients were 65 years of age or older. In total, 74% of patients had primary refractory disease, with 26% experiencing relapse ≤ 12 months after the initiation or completion of frontline therapy. Almost half of patients (45%) had a high sAAIPI with two or three risk factors and the majority (79%) had stage III or IV disease. Differences of ≥ 10%

were observed between the axi-cel and SOC arms for sex (male: 61% versus 71%, respectively) and extranodal disease ([redacted] versus [redacted], respectively).[44]

Table 6: Baseline characteristics of patients in ZUMA-7

Characteristic, n (%)	Axi-cel (N = 180)	SOC (N = 179)	Overall (N = 359)
Age			
Median, years (range)	58 (21–80)	60 (26–81)	59 (21–81)
Mean, years (SD)	[redacted]	[redacted]	[redacted]
≥ 65, n (%)	51 (28)	58 (32)	109 (30)
Male, n (%)	110 (61)	127 (71)	237 (66)
Ethnicity[a], n (%)			
American Indian or Alaska Native	0 (0)	1 (1)	1 (< 1)
Asian	12 (7)	10 (6)	22 (6)
Black	11 (6)	7 (4)	18 (5)
Native Hawaiian or other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Hispanic or Latino ethnic group[a], n (%)			
Yes	10 (6)	8 (4)	18 (5)
No	167 (93)	169 (94)	336 (94)
Not reported	3 (2)	2 (1)	5 (1)
ECOG performance status[b], n (%)			
1	85 (47)	79 (44)	164 (46)
Disease stage, n (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	146 (82)	285 (79)
sAAIPI[c], n (%)			
2 or 3	82 (46)	79 (44)	161 (45)
Molecular subgroup according to central laboratory[d], n (%)			
Germinal centre B-cell-like	109 (61)	99 (55)	208 (58)
Activated B-cell-like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing data	28 (16)	41 (23)	69 (19)
Response to frontline therapy at randomisation, n (%)			
Primary refractory disease	133 (74)	131 (73)	264 (74)
Relapse ≤ 12 months after the initiation or completion of frontline therapy	47 (26)	48 (27)	95 (26)

Characteristic, n (%)	Axi-cel (N = 180)	SOC (N = 179)	Overall (N = 359)
Disease type according to central laboratory, n (%)			
DLBCL[e]	126 (70)	120 (67)	246 (69)
High-grade B-cell lymphoma, not otherwise specified	0 (0)	1(1)	1 (< 1)
High-grade B-cell lymphoma, including rearrangement of MYC with BCL2 or BCL6 or both	31 (17)	25 (14)	56 (16)
Not confirmed or missing data	18 (10)	28 (16)	46 (13)
Other	5 (3)	5 (3)	10 (3)
Disease type according to the investigator, n (%)			
Large B-cell lymphoma, not otherwise specified	110 (61)	116 (65)	226 (63)
T-cell- or histiocyte-rich large B-cell lymphoma	5 (3)	6 (3)	11 (3)
Epstein-Barr virus-positive DLBCL	2 (1)	0 (0)	2 (1)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)
High-grade B-cell lymphoma, including rearrangement of MYC with BCL2 or BCL6 or both	43 (24)	27 (15)	70 (19)
Primary cutaneous diffuse large B-cell lymphoma, leg type	1 (1)	0 (0)	1 (< 1)
Other	0 (0)	3 (2)	3 (1)
Extranodal disease, n (%)			
Yes	[redacted]	[redacted]	[redacted]
Prognostic marker according to central laboratory, n (%)			
High-grade B-cell lymphoma, double- or triple-hit	31 (17)	25 (14)	56 (16)
Double-expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Not applicable	74 (41)	70 (39)	144 (40)
Missing data	3 (2)	15 (8)	18 (5)
CD19+ status on immunohistochemical testing[f], n (%)	144 (80)	134 (75)	278 (77)
Bone marrow involvement[g], n (%)	17 (9)	15 (8)	32 (9)
Elevated lactate dehydrogenase level[h], n (%)	101 (56)	94 (53)	195 (54)

Characteristic, n (%)	Axi-cel (N = 180)	SOC (N = 179)	Overall (N = 359)
Median tumour burden, mm^2 (range)	2,123 (181–22,538)	2,069 (252–20,117)	2,118 (181–22,538)

Key: DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; sAAIPI, second-line age-adjusted International Prognosis Index; SD, standard deviation; SOC, standard of care.
Notes: [a] Ethnicity group were determined by the investigator. [b] ECOG performance status scores were assessed on a 5-point scale, with a score of 0 indicating no symptoms and higher scores indicating greater disability. A score of 1 indicates that the patient is ambulatory but restricted from strenuous activity. [c] Values are the sAAIPI at randomisation, which were similar to the sAAIPI according to the investigator as entered into the clinical database. The sAAIPI is used to assess prognostic risk based on various factors after adjustment for patient age and extranodal status at the time of diagnosis of refractory disease. Risk categories are assessed as low (0 factors), intermediate (1 factor), or high (2 or 3 factors). [d] The molecular subgroup as assessed by the investigator was as follows: germinal centre B-cell-like in 96 patients (53%) in the axi-cel group, 84 (47%) in the SOC group, and 180 (50%) overall; non-germinal centre B-cell-like in 47 (26%), 54 (30%), and 101 (28%), respectively. The molecular subgroup was not assessed in 37 patients (21%) in the axi-cel group, 41 (23%) in the SOC group, and 78 (22%) overall. [e] The definition of diffuse large B-cell lymphoma according to the central laboratory included cases of incomplete evaluation that were caused by inadequate sample amount or sample type, for which further classification of the subtype was not possible. Diffuse large B-cell lymphoma, not otherwise specified, according to the World Health Organization 2016 definition, is also included. [f] CD19 staining was not required for participation in the trial. Testing was conducted by the central laboratory. [g] The data shown were as collected on the diagnosis history case-report form. [h] An elevated lactate dehydrogenase level was defined as a level that was above the upper limit of the normal range according to the local laboratory. [i] Tumour burden was determined based on the sum of product diameters of the target lesions, according to the Cheson criteria, and was assessed by the central laboratory.
Source: Locke et al. 2021[1]; ZUMA-7 CSR[44]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 7 provides a summary of the statistical analysis for ZUMA-7.

The study was primarily designed to investigate the EFS in patients with r/r DLBCL treated with axi-cel or SOC, with a hypothesised target of 50% improvement in the median EFS time for axi-cel compared with SOC.[44] Approximately 350 patients were to be randomised (175 patients per treatment group) to achieve approximately 90% power at the 1-sided 2.5% significance level to detect a 50% improvement in EFS. To preserve the overall significance level, statistical testing of the primary and key secondary efficacy endpoints followed a hierarchical scheme:[44]

- EFS was to be tested at the primary analysis using a log-rank test stratified by randomisation factors to test the null hypothesis of no difference in EFS

- Conditional on a statistically significant improvement in EFS, ORR was to be tested at the time of the primary EFS analysis. ORR was to be tested with a stratified Cochran-Mantel-Haenszel (CMH) test using randomisation factors
- Conditional on a statistically significant improvement in EFS and ORR, OS was to be tested up to three times:
  - The first interim analysis of OS was to be tested at the time of the primary EFS analysis
  - The second interim analysis of OS was to be tested when approximately 160 deaths had been observed, or no later than four years after the first patient was randomised
  - The primary analysis of OS was to be tested when approximately 210 deaths had been observed, or no later than five years after the first patient was randomised

The primary analysis was planned to occur when all patients had the opportunity to be followed for the Month 9 disease assessment (i.e. the Month 9 timepoint had passed for all patients) and 250 EFS events had been observed by blinded central assessment.[44] This submission presents data from the primary analysis of EFS with a data cut-off date of 18 March 2021. The median potential follow-up time was 24.9 months, and the median actual follow-up time was [redacted] months. [1, 44] The full analysis set (FAS) was used for the primary efficacy analysis. An algorithm included in the statistical analysis plan (SAP) was to be used to impute partial or missing event dates.

Table 7: Summary of statistical analyses for ZUMA-7

Hypothesis objective	Axi-cel will prolong EFS compared with SOC in adult patients with r/r DLBCL. The hypothesised treatment effect corresponds to a 50% improvement in the median EFS time.
Statistical analysis	**Main analyses** Stratified Cox regression models were used to provide the estimated HR and two-sided 95% CIs for axi-cel relative to SOC. The Breslow method was used to handle the ties for the Cox regression models. Kaplan–Meier plots, estimates and two-sided 95% CIs were generated, and the number of patients censored or having events was summarised. For ORR, the patient incidence of objective response and best response was calculated. Two-sided 95% CIs were calculated with the Clopper–Pearson method and the 95% CI for the difference in ORR was calculated with the Wilson's

	score method with continuity correction. ORR was compared between treatment groups with the Cochran–Mantel–Haenszel test, adjusting for stratification factors. **Sensitivity analyses** Four sensitivity analyses were planned for EFS and mEFS: • Sensitivity analysis 1: progression events that occur between scheduled assessments will be moved forward to the next scheduled assessment after the observed progression • Sensitivity analysis 2: progression events that occur between scheduled assessments will be moved backward to the last scheduled assessment before progression • Sensitivity analysis 3: EFS events that occur after more than one missed disease assessment visit will be censored at the last evaluable disease assessment before the observed progression • Sensitivity analysis 4: patients in the axi-cel arm who undergo auto-SCT while in an axi-cel-induced response are imputed to have an EFS event at the time of auto-SCT A sensitivity analysis was planned for PFS and DOR where patients in the axi-cel group who underwent SCT while in an axi-cel-induced response were imputed to have a PFS event at the time of SCT. Sensitivity analyses of OS were to be conducted using the RPSFT model and IPCW to address the confounding effect of treatment switching. Concordance between per investigator and per blinded central assessment were to be summarised
Analysis sets	**FAS:** all randomised patients. Patients were analysed by the protocol therapy to which they were randomised.
	Safety analysis set: all randomised patients who received at least one dose of axi-cel or SOC immunochemotherapy as protocol therapy. Patients were analysed by the protocol therapy received.
	Safety analysis set – auto-SCT: patients who were randomised to the SOC group and who underwent transplant as part of protocol therapy.
	QoL analysis set: patients in the FAS who had baseline measurements and at least one completed post-randomisation measurement through to Study Day 150.
	Retreatment analysis set: patients treated with axi-cel as the study treatment who received any dose of axi-cel as retreatment.
	Subgroup analysis set: subgroup analyses of selected efficacy and safety endpoints may have been performed for the baseline covariates.
Sample size, power calculation	The primary analysis was planned to occur when all patients had the opportunity to be followed for the Month 9 disease assessment and 250 EFS events by blinded central assessment had been observed. The study was sized to

	achieve approximately 90% power at the 1-sided 2.5% significance level to detect a 50% improvement in EFS. The minimum effect size that could be determined to be statistically significant is an EFS HR of 0.79, or a 27% relative improvement in EFS. It was anticipated that the event goal would be achieved if 350 patients were randomised (175 patients per arm) and would occur approximately 31 months after the first patient was randomised.
Data management, patient withdrawals	**EFS:** patients alive, in response, and with no new therapy were to be censored at the last evaluable disease assessment. Patients with no evaluable disease assessment by the Study Day 150 assessment were considered as not having an EFS event, and the EFS event time was to be censored at the randomisation date. The EFS event time for patients in the axi-cel group who underwent auto-SCT in the absence of any documented progression or new lymphoma therapy were to be censored on the day of auto-SCT. For patients in the SOC group, TBI, HDT, and auto-SCT that occurred while the patient was in response from protocol-specified immunochemotherapy were not to be considered as an EFS event. The EFS event time for patients in the SOC group who were alive, progression-free, and had no new lymphoma therapy were to be censored at the last evaluable disease assessment date. At the time of the interim analysis of EFS, patients who did not have the opportunity to be followed to the Study Day 150 disease assessment and who did not have an EFS event were to be censored at the last evaluable disease assessment before Study Day 150. **PFS and DOR:** patients not meeting the criteria for progression or death by the analysis data cut-off date were to be censored at their last evaluable disease assessment date. Patients who received subsequent new lymphoma therapy (with the exception of HDT, TBI for HDT, and auto-SCT while in a protocol therapy-induced response) in the absence of documented progression were to have DOR censored at the last evaluable disease assessment before the commencement of the new lymphoma therapy. Auto-SCT or allo-SCT that occurred while a patient was in response from a protocol-specified therapy was not to be considered as an event. These patients were to be censored at the last evaluable disease assessment before the auto-SCT or allo-SCT for patients in the axi-cel group, and were to be censored at the last evaluable disease assessment date for patients in the SOC group.
Key: auto-SCT, autologous stem cell transplant; allo-SCT, allogenic stem cell transplant; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival; FAS, full analysis set; HDT, high-dose therapy; HR, hazard ratio; IPCW, inverse probability of censoring weights; mEFS, modified event-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RPSFT, rank preserving structural failure time; SOC, standard of care; TBI, total body irradiation. **Source:** ZUMA-7 CSR[44]	

B.2.4.1. Patient disposition data

At the data cut-off date (18 March 2021), 359 patients with primary refractory or early relapse DLBCL intended for transplant were enrolled, of which 180 patients were randomised to the axi-cel group and 179 patients were randomised to the SOC group.[1] Among the patients in the axi-cel group, 178 (99%) underwent leukapheresis and 170 (94%) received axi-cel. Six patients received neither lymphodepleting chemotherapy nor axi-cel, and two patients received lymphodepleting chemotherapy but not axi-cel for the following reported reasons:

- Adverse events (AEs; n = 4)
- Death (n = 2)
- Disease progression (n = 1)
- Other reason (n = 1)

Axi-cel was successfully manufactured for all the patients who underwent leukapheresis, and 65 patients (36%) received bridging therapy with glucocorticoids while awaiting axi-cel.[1] Among the 170 patients who received axi-cel, the median time from randomisation to leukapheresis was [redacted] days (range: [redacted]), the median time from leukapheresis to delivery of axi-cel to the study site was [redacted] days (range: [redacted]) and the median time from leukapheresis to axi-cel administration was [redacted] days (range: [redacted]).[44] Overall, the median time from randomisation to axi-cel infusion was 29 days (IQR: 27–34).[1] After axi-cel treatment, [redacted] patients who had a response and later progressed were retreated with axi-cel.[44]

Among the patients in the SOC group, 168 (94%) received platinum-based chemotherapy (R-ICE, 84 [50%]; R-ESHAP, 5 [3%]; R-GDP, 42 [25%]; R-DHAP/R-DHAX, 37 [22%]), and 64 (36%) received high-dose chemotherapy and underwent auto-SCT (including two patients who underwent auto-SCT outside the protocol).[1]

The CONSORT diagrams for the ZUMA-7 study are presented in Appendix D.

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

A quality assessment of the ZUMA-7 study was conducted using the NICE checklist; the full details of this checklist are provided in Appendix D.

The study was approved by the institutional review board and independent ethics committee and was conducted according to Good Clinical Practice. Overall, the study is considered to be a methodologically robust and high-quality study with a comprehensive approach to patient allocation, control of confounding factors, and an overall low risk of bias.

The ZUMA-7 study required open-label treatment due to the autologous cellular therapy nature of axi-cel. Although the primary analysis included a blinded central assessment to minimise bias, this open-label design did result in a small proportion (< 5%) of patients who were randomised to the SOC arm withdrawing consent before receiving treatment. They were therefore immediately censored in the time-to-event analyses that were conducted according to the intention-to-treat principle.

Disease assessments were conducted in line with recommended and accepted classification systems. The outcomes that were measured reflected established trial outcomes within the DLBCL setting and those relevant to patients and healthcare providers. Importantly, the ZUMA-7 study provides applicable data to the intended use of axi-cel in clinical practice and the decision problem under appraisal. This is further discussed in Section B.2.13.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. Primary efficacy endpoint

B.2.6.1.1. EFS per central assessment

At the time of the data cut-off (18 March 2021), [redacted] EFS events by blinded central assessment occurred for [redacted] patients ([redacted]%) in the axi-cel group and [redacted] patients ([redacted]%) in the SOC group.[44] Axi-cel treatment was superior to SOC, with a stratified hazard ratio (HR) of 0.40 (95% confidence interval [CI]: 0.31, 0.51; p < 0.001; see Figure 6).[1]

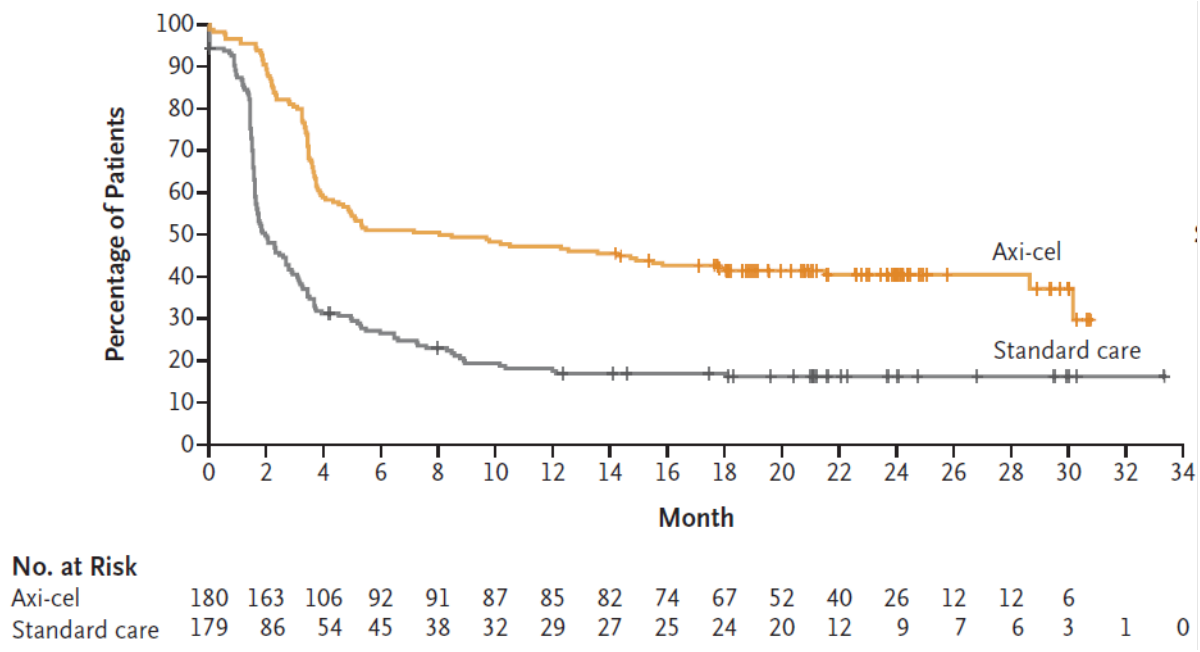
The median EFS was significantly longer in the axi-cel group (8.3 months; 95% CI: 4.5, 15.8) than in the SOC group (2.0 months; 95% CI: 1.6, 2.8).[1] The estimated EFS at 24 months was 41% (95% CI: 33, 48) in the axi-cel group compared with 16% (95% CI: 11, 22) in the SOC group (Appendix L).[1] The median follow-up time for EFS

using the reverse Kaplan–Meier method was [redacted] months in the axi-cel group and [redacted] months in the SOC group.[44]

The most common EFS events in either the axi-cel or SOC groups were disease progression ([redacted]% and [redacted]%, respectively), new lymphoma therapy ([redacted]% and [redacted]%, respectively) and death from any cause ([redacted]% and [redacted]%, respectively).[44]

Findings of the EFS sensitivity analyses were supportive of and consistent with results for the primary analysis of EFS (Appendix L).

Figure 6: Kaplan–Meier plot for EFS as per central assessment, FAS



Key: EFS, event-free survival; FAS, full analysis set.
Source: Locke et al. 2021.[1]

B.2.6.2. Key secondary efficacy endpoints

B.2.6.2.1. ORR per central assessment

The ORR for patients in the axi-cel group was 83% (n = 150/180) compared with 50% (n = 90/179) for patients in the SOC group, with a difference between treatment groups of 33% (see Table 8).[1] The odds ratio comparing axi-cel with the SOC group was significantly in favour of axi-cel (OR: [redacted], 95% CI: [redacted], [redacted]; p [redacted]).[44] CR rates in the axi-cel and SOC groups were 65% (n = 117/180) and 32% (n = 58/179), respectively, and partial response (PR) rates were 18% (n = 33/180) and 18% (n = 32/179), respectively.[1]

Improvement of response after the first evaluable disease assessment per central assessment occurred in both the axi-cel and SOC groups: improvement from PR to CR occurred for [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively; improvement from SD to CR occurred for [redacted] patients ([redacted]%) and [redacted] patient ([redacted]%), respectively; and improvement from SD to PR occurred for [redacted] patients ([redacted]%) and [redacted] patient ([redacted]%), respectively.[44]

Table 8: Summary of ORR and best overall response per central assessment, FAS

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

Key: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; FAS, full analysis set; ORR, objective response rate; PR, partial response; sAAIPI; second-line age-adjusted International Prognostic Index
Notes: Response assessments per Lugano Classification.[45] A one-sided p-value from the CMH test is presented. Undefined/no disease included patients who were found to have no disease at baseline or follow-up by central assessment but had disease by investigator assessment. Not evaluable disease assessments were performed but no conclusion could be made.
Source: Table 14. ZUMA-7 CSR[44]; Locke et al. 2021[1]

B.2.6.2.2. ORR per investigator assessment

ORR per investigator assessment had a high concordance with central assessment (overall [redacted]%; κ = [redacted]; 95% CI: [redacted], [redacted]; see Appendix L).[44]

A summary of ORR, best overall response and concordance with central assessment is provided in Appendix L.

B.2.6.2.3. OS

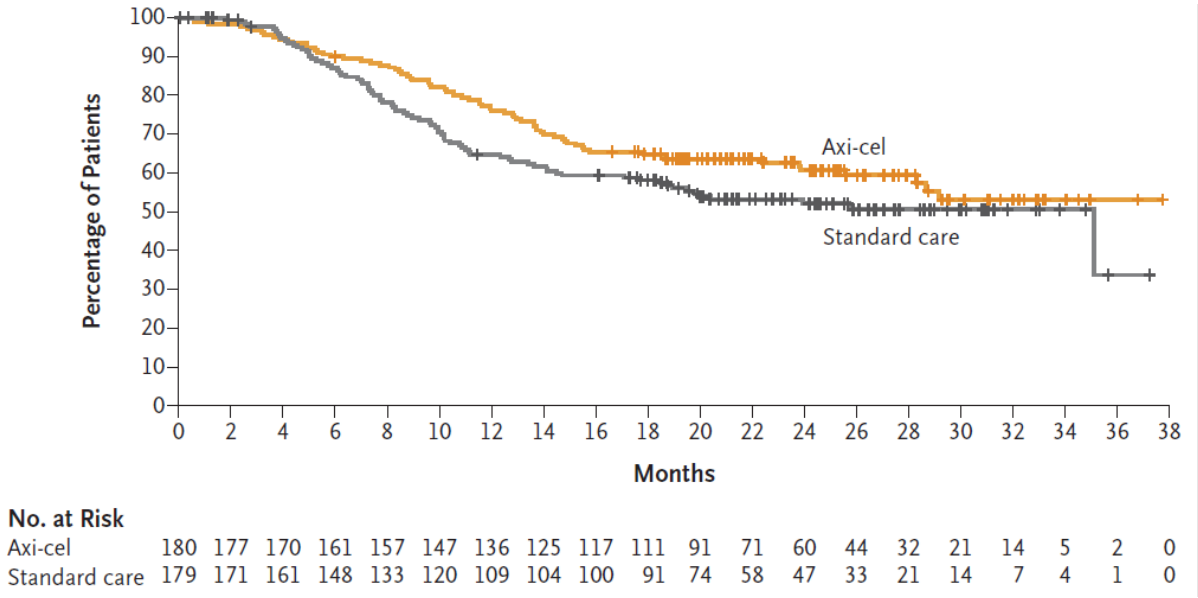
At the time of analysis, 72 deaths in the axi-cel group (40%) and 81 deaths in the SOC group (45%) were reported.[1] The median OS, evaluated as an interim analysis, was not reached (95% CI: 28.3 months, not estimable [NE]) in the axi-cel group and was 35.1 months (95% CI: 18.5, NE) in the SOC group (see Figure 7). No statistically significant difference between the treatment groups was observed (HR: 0.73; 95% CI: 0.53, 1.01; p = 0.054).

In the interim analysis, the estimated OS at 2 years was 61% in the axi-cel group and 52% in the SOC group.[1] The median follow-up time for OS using the reverse Kaplan–Meier method was [redacted] months in the axi-cel group and [redacted] months in the SOC group.[44]

A total of 56% of the patients in the SOC group received subsequent cellular immunotherapy off-protocol.[1] OS outcomes are therefore augmented and reflect a treatment sequence that includes CAR T-cell therapy at third- or later-line settings. To address the confounding effect of off-protocol treatment switching, sensitivity analyses of OS that adjusted for crossover were conducted. Results from the sensitivity analysis showed a difference in OS in favour of axi-cel (HR: 0.58; 95% CI: 0.42, 0.81; see Figure 8) with the rank-preserving structural failure time (RPSFT) method. An additional analysis, which was conducted using the inverse probability of censoring weights model, showed a stratified HR of 0.70 (95% CI: 0.46, 1.05).

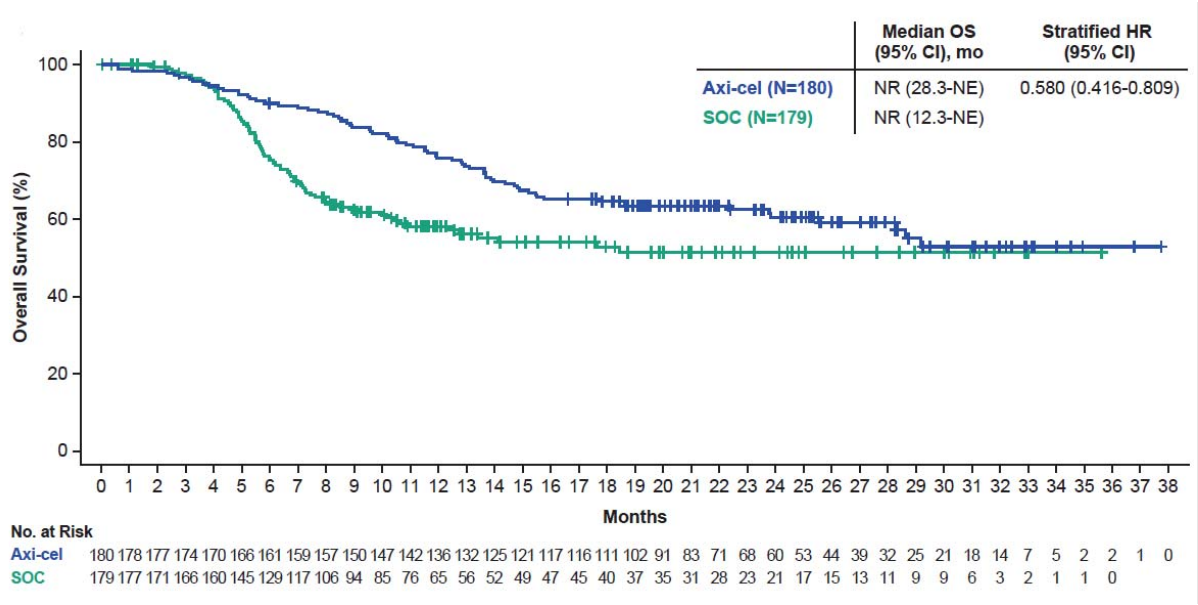
A summary of the pre-planned sensitivity analyses is provided in Appendix L. Further post-hoc sensitivity analyses that consider NICE recommendations for adjusting survival estimates in the presence of treatment switching were conducted for the economic modelling and are presented in Section B.3.3.4.1.

Figure 7: Kaplan–Meier plot for OS, FAS



Key: FAS, full analysis set; OS, overall survival.
Source: Locke et al. 2021[1]

Figure 8: Kaplan–Meier plot of OS – sensitivity analysis using RPSFT model, FAS



Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NE, not estimable; NR, not reached; OS, overall survival; RPSFT, rank-preserving structural failure time; SOC, standard of care.
Source: Locke et al. 2021.[1]

B.2.6.3. Additional secondary efficacy endpoints

B.2.6.3.1. EFS per investigator assessment

At the time of the data cut-off (18 March 2021), [redacted] investigator-assessed EFS events occurred for [redacted] patients ([redacted]%) in the axi-cel group and [redacted] patients ([redacted]%) in the SOC group.[44] Axi-cel treatment was superior to SOC, with a stratified HR of [redacted] (95% CI: [redacted], [redacted]; see Figure 9).

The median EFS was significantly longer in the axi-cel group ([redacted] months; 95% CI: [redacted], [redacted]) than the SOC group ([redacted] months; 95% CI: [redacted], [redacted]).[44] The estimated EFS at 24 months was [redacted]% (95% CI: [redacted], [redacted]) in the axi-cel group compared with [redacted]% (95% CI: [redacted], [redacted]) in the SOC group (see Appendix L). The median follow-up time for EFS using the reverse Kaplan–Meier method was [redacted] months in the axi-cel group and [redacted] months in the SOC group.

The most common EFS events in either the axi-cel or SOC group were disease progression ([redacted]% and [redacted]%, respectively), new lymphoma therapy ([redacted]% and [redacted]%, respectively) and death from any cause ([redacted]% and [redacted]%, respectively).[44]

EFS per investigator assessment had a high concordance with central assessment (overall [redacted]%; κ = [redacted]; 95% CI: [redacted], [redacted]; see Appendix L).[44]

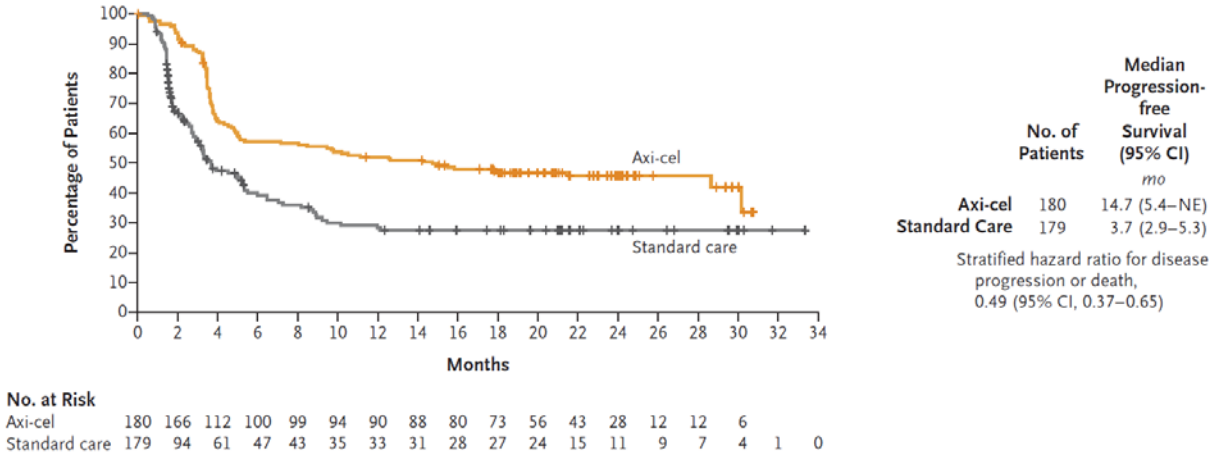
Figure 9: Kaplan–Meier plot for EFS per investigator assessment, FAS

Key: CI, confidence interval; EFS, event-free survival; FAS, full analysis set; HR, hazard ratio; SOCT, standard of care therapy.
Source: Figure 10. ZUMA-7 CSR.[44]

B.2.6.3.2. PFS per investigator assessment

The median PFS was 14.7 months (95% CI: 5.4, NE) in the axi-cel group and 3.7 months (95% CI: 2.9, 5.3) in the SOC group (HR: 0.49; 95% CI: 0.37, 0.65; see Figure 10).[1] The estimated PFS at 24 months was 46% (95% CI: 38, 53) in the axi-cel group and 27% (95% CI: 20, 35) in the SOC group (Appendix L).[1] The median follow-up time for PFS using the reverse Kaplan–Meier method was [redacted] months (95% CI: [redacted], [redacted]) in the axi-cel group and [redacted] months (95% CI: [redacted], [redacted]) in the SOC group.[44]

Figure 10: Kaplan–Meier plot for PFS per investigator assessment, FAS



Key: CI, confidence interval; FAS, full analysis set; mo, months; NE, not estimable; PFS, progression-free survival.
Source: Locke et al. 2021.[1]

B.2.6.3.3. PFS per central assessment

PFS results per central assessment were consistent with those per investigator assessment. A summary of PFS per central assessment is provided in Appendix L.

B.2.6.3.4. DOR per central assessment

The median time to first objective response for patients who achieved a CR or PR per central assessment in the axi-cel group (n = 150/180) or the SOC group (n = 90/179) was [redacted] months (range: [redacted]) and [redacted] months (range: [redacted]), respectively (see Appendix L).[44] The median DOR in all responders for the axi-cel group was [redacted] months (95% CI: [redacted], [redacted]) compared with [redacted] months (95% CI: [redacted], [redacted]) for the SOC group (stratified HR: [redacted]; 95% CI: [redacted], [redacted]; see Figure 11). The median follow-up time for DOR using the reverse Kaplan–Meier method was [redacted] months (95% CI: [redacted], [redacted]) in the axi-cel group and [redacted] months (95% CI: [redacted], [redacted]) in the SOC group.

The proportion of responding patients with an ongoing response at the time of data cut-off (18 March 2021) was [redacted] in the axi-cel group compared with [redacted] in the SOC group.[44] The estimated percentage of responding patients who remained in response at 24 months was [redacted]% (95% CI: [redacted], [redacted]) in the axi-cel group compared with [redacted]% (95% CI: [redacted], [redacted]) in the SOC group (see Appendix L).

Among patients who had a best overall response of CR in the axi-cel group (n = 117/180) and SOC group (n = 58/179), the median DOR was [redacted] months (95% CI: [redacted], [redacted]) and [redacted] (95% CI: [redacted], [redacted]), respectively, with median follow-up times using the reverse Kaplan–Meier method of [redacted] months (95%CI: [redacted], [redacted]) and [redacted] months (95% CI: [redacted], [redacted]), respectively.[44] The proportion of complete responders with an ongoing CR at the time of data cut-off (18 March 2021) was [redacted] in the axi-cel group compared with [redacted] in the SOC group.[44] The estimated percentage of complete responders who remained in CR at 24 months was [redacted] (95% CI: [redacted]) in the axi-cel group compared with [redacted] (95% CI: [redacted]) in the SOC group (Appendix L).

A sensitivity analysis was planned in which patients in the axi-cel group who underwent stem cell transplant (SCT) while in an axi-cel-induced response were imputed to have a PFS event at the time of SCT. [redacted].[44]

Figure 11: Kaplan–Meier plot for DOR per central assessment, FAS

[redacted]

Key: CI, confidence interval; DOR, duration of response; FAS, full analysis set; HR, hazard ratio; NE, not estimable; SOCT, standard of care therapy.
Notes: One-sided p-value from log rank test is presented.
Source: Figure 15. ZUMA-7 CSR.[44]

B.2.6.3.5. DOR per investigator assessment

DOR results per investigator assessment were consistent with those per central assessment. A summary of DOR per investigator assessment is provided in Appendix L.

B.2.6.3.6. mEFS per central assessment

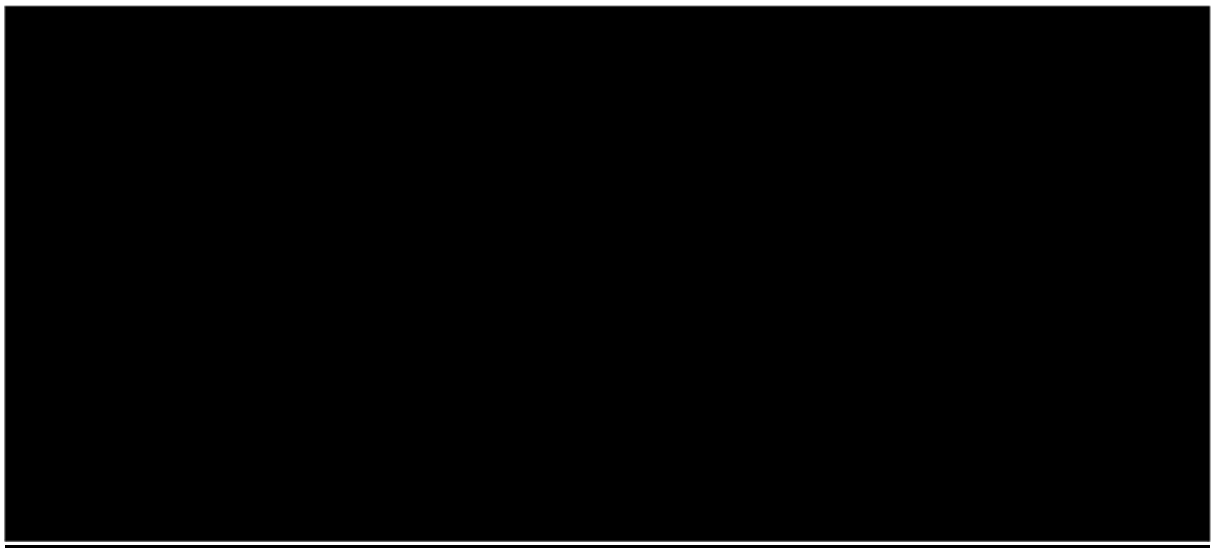
At the time of data cut-off (18 March 2021), [redacted] mEFS events by central assessment occurred for [redacted] patients ([redacted]%) in the axi-cel group and [redacted] patients ([redacted]%) in the SOC group.[44] Axi-cel treatment was superior to SOC, with a stratified HR of [redacted] (95% CI: [redacted], [redacted]; p [redacted]; see Figure 12).

The median mEFS was significantly longer in the axi-cel group ([redacted] months; 95% CI: [redacted], [redacted]) than the SOC group ([redacted] months; 95% CI: [redacted], [redacted]).[44] The estimated EFS at 24 months was [redacted]% (95% CI: [redacted], [redacted]) in the axi-cel group compared with [redacted]% (95% CI: [redacted], [redacted]) in the SOC group (Appendix L). The median follow-up time for EFS using the reverse Kaplan–Meier method was [redacted] months in the axi-cel group and [redacted] months in the SOC group.

The most common EFS events in either the axi-cel or SOC group were disease progression ([redacted]% and [redacted]%, respectively), new lymphoma therapy ([redacted]% and [redacted]%, respectively) and death from any cause ([redacted]% and [redacted]%, respectively).[44]

Findings of the sensitivity analyses were supportive of and consistent with results for mEFS per central assessment (see Appendix L).

Figure 12: Kaplan–Meier plot for mEFS per central assessment, FAS



Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mEFS, modified event-free survival; NE, not estimable; SOCT, standard of care therapy.
Source: Figure 18. ZUMA-7 CSR.[44]

B.2.6.3.7. mEFS per investigator assessment

mEFS results per investigator assessment were consistent with those per central assessment. A summary of mEFS per investigator assessment is provided in Appendix L.

B.2.6.4. Exploratory endpoint

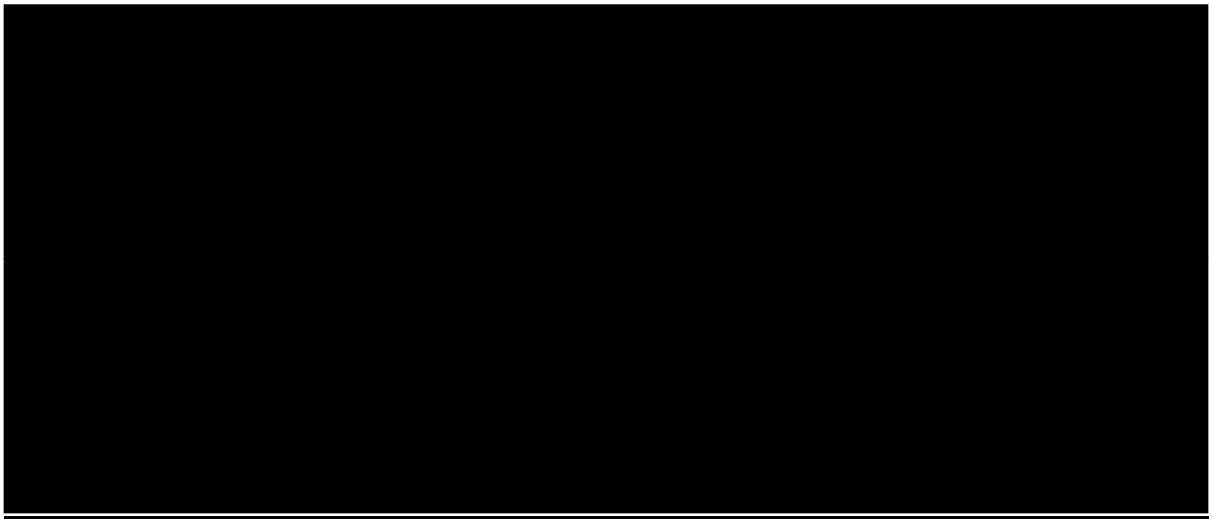
B.2.6.4.1. Time to next therapy

Time to next therapy (TTNT) events occurred for [redacted] patients ([redacted]%) in the axi-cel group and [redacted] patients ([redacted]%) in the SOC group.[44] Axi-cel treatment was superior to SOC, with a stratified HR of [redacted] (95% CI: [redacted], [redacted]; p [redacted]; see Figure 13).

The median TTNT was significantly longer in the axi-cel group ([redacted] months; 95% CI: [redacted], [redacted]) than the SOC group ([redacted] months; 95% CI: [redacted], [redacted]).[44] At the time of data cut-off (18 March 2021), [redacted] of patients in the axi-cel group compared with [redacted] of the SOC group were alive and had not received subsequent therapy. The estimated number of patients who were event-free at 24 months was [redacted]% (95% CI: [redacted], [redacted]) in the axi-cel group compared with [redacted]% (95% CI: [redacted], [redacted]) in the SOC group

(Appendix L). The median follow-up time for EFS using the reverse Kaplan–Meier method was [redacted] months in the axi-cel group and [redacted] months in the SOC group.

Figure 13: Kaplan–Meier plot of TTNT, FAS



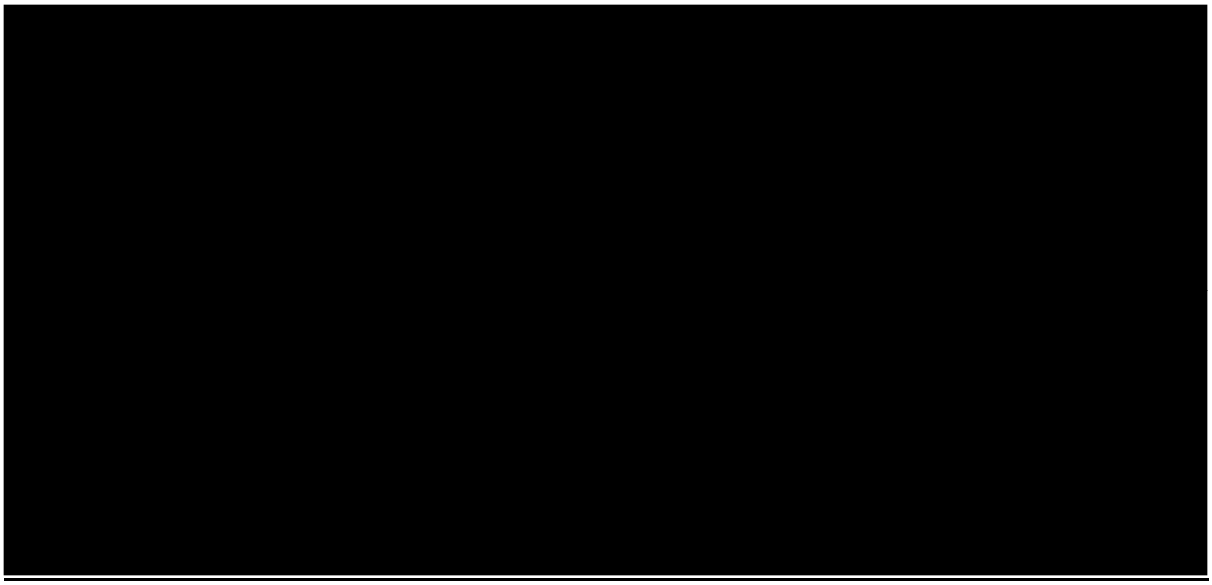
Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; NE, not estimable; SOCT, standard of care therapy; TTNT, time to next treatment.
Source: Figure 21. ZUMA-7 CSR.[44]

B.2.6.5. HRQL

B.2.6.5.1. EORTC QLQ-C30

At screening, the mean EORTC QLQ-C30 Global Health Status scores for evaluable patients in the quality of life (QoL) analysis set were comparable in the axi-cel (mean: [redacted]) and SOC group (mean: [redacted]; Figure 14).[44] At Study Day 50, almost half of evaluable patients reported worsening scores in both the axi-cel (mean: [redacted]) and SOC groups (mean: [redacted]). Scores in the axi-cel group rebounded at Study Day 100 (mean: [redacted]), while those in the SOC group declined (mean: [redacted]). At this point there was a statistically significant and clinically meaningful difference in the mean change of scores in favour of axi-cel (estimated difference: [redacted]; 95% CI: [redacted], [redacted]; adjusted p [redacted]; see Appendix L). This difference was also statistically significant at Study Day 150 (estimated difference: [redacted]; 95% CI: [redacted], [redacted]; adjusted p = [redacted]). Mean estimated scores for the axi-cel group had returned to or exceeded scores at screening by Study Day 100 versus at Month 9 for the SOC group.

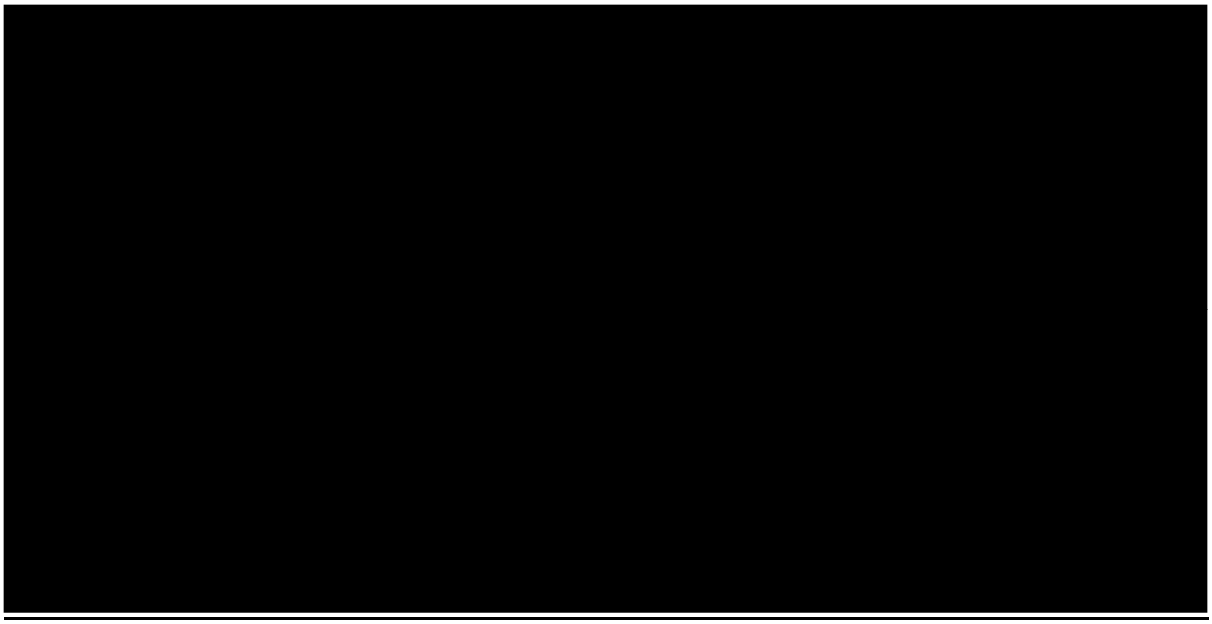
Figure 14: Mean (95% CI) EORTC QLQ-C30 Global Health Status scores over time by treatment group, QoL analysis set



Key: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; QoL, quality of life.
Source: Figure 22. ZUMA-7 CSR.[44]

At screening, the mean EORTC QLQ-C30 physical functioning scores for evaluable patients in the QoL analysis set were comparable in the axi-cel (mean: [redacted]) and SOC groups (mean: [redacted]; Figure 15).[44] At Study Day 50, the majority of evaluable patients reported worsening scores in both treatment arms. Starting at Study Day 100, scores for both treatment groups rebounded. There was a statistically significant and clinically meaningful difference in the mean change of scores from screening to Study Day 100 in favour of axi-cel (estimated difference: [redacted]; 95% CI: [redacted], [redacted]; adjusted p [redacted]; Appendix L). Mean estimated scores for the axi-cel group had returned to or exceeded scores at screening by Study Day 150 versus at Month 12 for the SOC group.

Figure 15: Mean (95% CI) EORTC QLQ-C30 Physical Functioning scores over time by treatment group, QoL analysis set



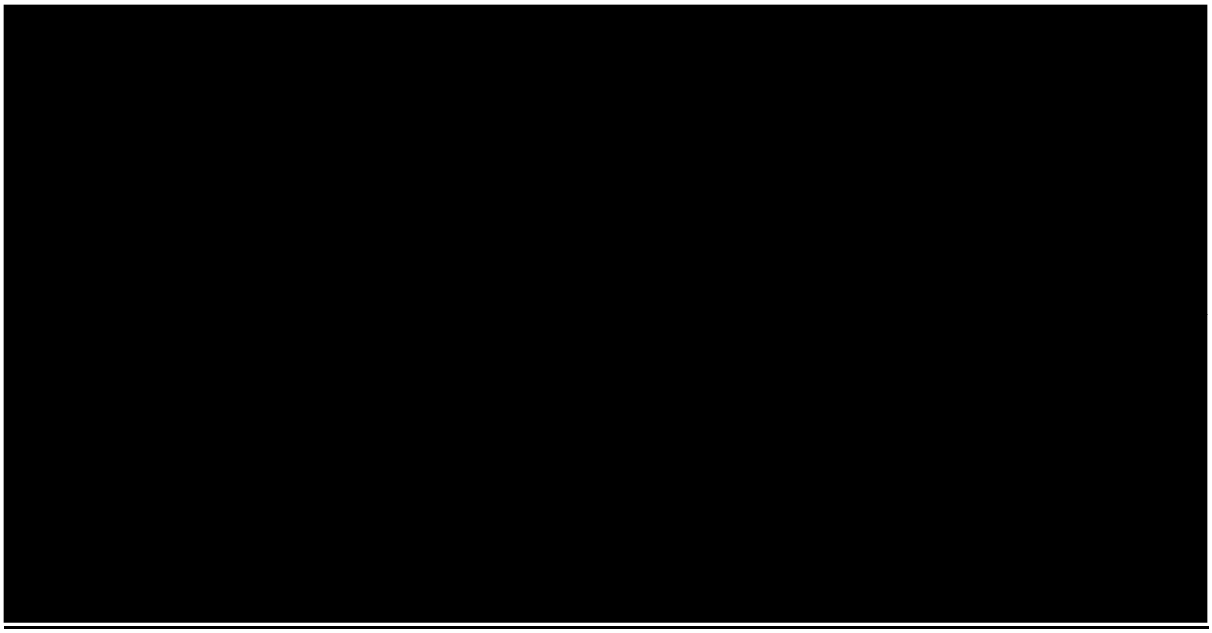
Key: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; QoL, quality of life.
Source: Figure 24. ZUMA-7 CSR.[44]

Statistically significant differences in several EORTC QLQ-C30 measures were found between patients treated with axi-cel and those treated with SOC. Treatment with axi-cel resulted in more favourable outcomes in terms of: nausea and vomiting, diarrhoea, insomnia, and appetite loss measures at Day 100; role functioning at Day 100 and Day 150; and social functioning, fatigue, and dyspnoea measures at Day 100, Day 150, and Month 9 (see Appendix L).[44]

B.2.6.5.2. EQ-5D-5L

The mean visual analogue scale (VAS) score reported by evaluable patients in the axi-cel and SOC groups were comparable at screening (and , respectively; see Figure 16).[44] There was a statistically significant and clinically meaningful difference in the mean change of scores for the EQ-5D-5L VAS from screening in favour of axi-cel at Study Day 100 (estimated difference: ; 95% CI: , ; adjusted p) and Study Day 150 (estimated difference: ; 95% CI: , ; adjusted p = ; see Appendix L).

Figure 16: Mean (95% CI) EQ-5D-5L VAS scores over time by treatment group, QoL analysis set



Key: CI, confidence interval; QoL, quality of life; VAS, visual analogue scale.
Source: Figure 26. ZUMA-7 CSR.[44]

The mean EQ-5D-5L index score was [redacted] at screening for patients who received axi-cel and [redacted] for patients who received SOC (Figure 17).[44] At Study Day 50, many evaluable patients in both the axi-cel and SOC groups reported worsening scores ([redacted]% and [redacted]%, respectively). The estimated mean difference in scores changing from screening was statistically significant and clinically meaningful at Day 100 in favour of axi-cel ([redacted]; 95% CI: [redacted], [redacted]; adjusted p = [redacted]; see Appendix L).

Figure 17: Mean (95% CI) EQ-5D-5L index scores over time by treatment group, QoL analysis set

Key: CI, confidence interval, QoL, quality of life.
Source: Figure 29. ZUMA-7 CSR.[44]

B.2.7. Subgroup analysis

The subgroup analysis demonstrated consistent survival benefits with axi-cel over SOC. EFS, ORR, OS, PFS and mEFS outcomes were generally comparable with those observed in the overall population.

Results of the covariate analysis of EFS consistently showed axi-cel superiority over SOC in most subgroups, including patients with high-risk features such as HGBL (including double- or triple-hit lymphomas), relapsed or primary refractory disease and being ≥ 65 years of age.

A summary of results for the analysed subgroups is provided in Appendix E.

B.2.8. Meta-analysis

The main evidence for the use of axi-cel in the second-line treatment of DLBCL is from ZUMA-7. Therefore, no meta-analysis is required.

B.2.9. Indirect and mixed treatment comparisons

ZUMA-7 provides head-to-head data for the relevant comparator to the decision problem being addressed. Therefore, no indirect or mixed treatment comparisons have been performed.

B.2.10. Adverse reactions

B.2.10.1. Safety summary

Table 9 presents an overview of the safety data up to the data cut-off date (18 March 2021).

All patients experienced at least one AE of any grade. AEs of Grade 3 or higher occurred in 155 patients (91%) who received axi-cel and 140 patients (83%) who received SOC. Serious AEs of any grade occurred in 85 patients (50%) who received axi-cel and in 77 patients (46%) who received SOC.[1]

Seven patients (4%) died due to AEs in the axi-cel group, only one of which was considered by the investigators to be related to axi-cel (the treatment caused the hepatitis B virus to be reactivated).[1] Of the two patients (1%) in the SOC group who died because of AEs, both deaths were considered by the investigators to be related to high-dose chemotherapy (cardiac arrest and acute respiratory disease).

Table 9: Overall summary of treatment-emergent adverse events, SAS

n (%)	Axi-cel (N = 170)	SOC (N = 168)
Any TEAE	170 (100)	168 (100)
Worst Grade ≥ 3	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]
Worst Grade 5, excluding PD	[redacted]	[redacted]
Any serious TEAE	85 (50)	77 (46)
Worst Grade ≥ 3	72 (42)	67 (40)
Worst Grade 5	[redacted]	[redacted]
Worst Grade 5, excluding PD	[redacted]	[redacted]
Any treatment-related TEAE	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]
Worst Grade 5, excluding PD	[redacted]	[redacted]

n (%)	Axi-cel (N = 170)	SOC (N = 168)
Any serious treatment-related TEAE	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]
Worst Grade 5, excluding PD	[redacted]	[redacted]
Any TE neurological event	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Any serious TE neurological event	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Any TE CRS	157 (92)	NA
Worst Grade ≥ 3	11 (6)	NA
Any serious TE CRS	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Any TE hypogammaglobulinaemia	19 (11)	1 (1)
Worst Grade ≥ 3	[redacted]	[redacted]
Any TE cytopenia	[redacted]	[redacted]
Worst Grade ≥ 3	[redacted]	[redacted]
Any TE infection	70 (41)	51 (30)
Worst Grade ≥ 3	24 (14)	19 (11)
Worst Grade 5	[redacted]	[redacted]

Key: AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; PD, progressive disease; SAS, safety analysis set; SOC, standard of care; TE, treatment-emergent; TEAE, treatment-emergent adverse event.
Notes: TEAE includes all AEs with an onset on or after the axi-cel infusion date in the axi-cel group or the first dose of immunochemotherapy in the SOC group. Patients were summarised at their worst CTCAE grade or Lee Grade for CRS. AEs are graded per CTCAE version 4.03 and CRS events are graded according to a modified grading system proposed by Lee and colleagues.[46] For the axi-cel group, treatment-related TEAEs include TEAEs that are related to axi-cel. For the SOC group, treatment-related TEAEs include TEAEs that are related to immunochemotherapy, total body irradiation (given as part of conditioning for autologous stem cell transplant), high-dose therapy and autologous stem cell transplant. Grade 5 AEs were included in the table only when the value was non-zero. The preferred term for progressive disease was B-cell lymphoma. [a] One patient with a Grade 5 TEAE of B-cell lymphoma was not reported as an SAE by the investigator. [b] Another patient in the axi-cel group had a Grade 5 TEAE of progressive multifocal leukoencephalopathy that was deemed by the investigator to be related to lymphodepleting chemotherapy. This event is not included here because 'treatment-related' refers to events related to axi-cel or SOC.
Source: Table 33. ZUMA-7 CSR[44]; Locke et al. 2021.[1]

B.2.10.2. Common AEs

Table 10 presents the most common treatment-emergent adverse events (TEAEs) occurring in ≥ 10% of patients in either treatment group.

The most common TEAEs of any grade in the axi-cel group were: pyrexia (158 patients; 93%); neutropenia and hypotension ([redacted] patients each; [redacted]%); anaemia, fatigue and diarrhoea (71 patients each; 42%); headache (70 patients; 41%); nausea (69 patients; 41%), sinus tachycardia (58 patients; 34%); and a decreased neutrophil count ([redacted] patients; [redacted]%).[1, 44] The most common TEAEs of any grade in the SOC group were: nausea (116 patients; 69%); anaemia (91 patients; 54%); fatigue (87 patients; 52%); diarrhoea (66 patients; 39%); a decreased platelet count ([redacted] patients; [redacted]%); constipation (58 patients; 35%); and vomiting (55 patients; 33%).

The most common Grade 3 or higher TEAEs in the axi-cel group were: neutropenia ([redacted] patients; [redacted]%), anaemia (51 patients; 30%) and a decreased neutrophil count ([redacted] patients; [redacted]%).[1, 44] The most common Grade 3 or higher TEAEs in the SOC group were anaemia (65 patients; 39%), a decreased platelet count ([redacted] patients; [redacted]%) and a decreased neutrophil count ([redacted] patients; [redacted]%). The most common non-haematological worst Grade 3 or higher TEAEs were: hypophosphatemia (31 patients; 18%), encephalopathy (20 patients; 12%) and hypotension (19 patients, 11%) for the axi-cel group; and hypophosphatemia (21 patients, 13%) for the SOC group.

Table 10: Incidence of TEAEs occurring in ≥ 10% of patients in either treatment group, SAS

	Axi-cel (N = 170)		SOC (N = 168)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any TEAE, n (%)	170 (100)	155 (91)	168 (100)	140 (83)
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Anaemia	71 (42)	51 (30)	91 (54)	65 (39)
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)
Diarrhoea	71 (42)	4 (2)	66 (39)	7 (4)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)
Decreased neutrophil count	[redacted]	[redacted]	[redacted]	[redacted]
Decreased platelet count	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	44 (26)	10 (6)	49 (29)	11 (7)
Constipation	34 (20)	0 (0)	58 (35)	0 (0)
Vomiting	33 (19)	0 (0)	55 (33)	1 (1)

	Axi-cel (N = 170)		SOC (N = 168)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)
Decreased white blood cell count	[redacted]	[redacted]	[redacted]	[redacted]
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)
Hypophosphataemia	45 (26)	31 (18)	29 (17)	21 (13)
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Chills	47 (28)	1 (1)	14 (8)	0 (0)
Cough	42 (25)	1 (1)	18 (11)	0 (0)
Dizziness	36 (21)	2 (1)	21 (13)	1 (1)
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased lymphocyte count	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	4 (2)	4 (2)	46 (27)	46 (27)
Hypoxia	37 (22)	16 (9)	13 (8)	7 (4)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]	[redacted]	[redacted]
Increased alanine aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	44 (26)	2 (1)	1 (1)	0 (0)
Confusional state	40 (24)	9 (5)	4 (2)	0 (0)
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Increased aspartate aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]
Aphasia	36 (21)	12 (7)	0 (0)	0 (0)
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy	29 (17)	20 (12)	2 (1)	0 (0)
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]
Hiccups	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinaemia	19 (11)	0 (0)	1 (1)	0 (0)
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]

	Axi-cel (N = 170)		SOC (N = 168)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**

Key: AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Notes: TEAEs include all AEs with an onset on or after the axi-cel infusion date in the axi-cel group or the first dose of immunochemotherapy in the SOC group. Multiple incidences of the same AE in one patient are counted once at the worst grade for each patient. Preferred terms are sorted in descending order of total frequency across both treatment arms. AEs are coded using MedDRA version 23.1 and graded per CTCAE version 4.03. Grade 5 AEs were included in the table only when the value was non-zero. Investigators were instructed to record fever separately from neutropenia if the fever was attributed to CRS.
Source: Table 34. ZUMA-7 CSR[44]; Locke et al. 2021.[1]

B.2.10.3. Treatment-related AEs

Table 11 presents the most common treatment-related TEAEs occurring in ≥ 10% of patients in either treatment group.

In the axi-cel and SOC groups, [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively, had treatment-related TEAEs; [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%), respectively, experience Grade 3 or higher treatment-related AEs.[44] The most common worst Grade 3 or higher treatment-related AEs in the axi-cel group were: pyrexia ([redacted] patients; [redacted]%); hypotension ([redacted] patients; [redacted]%); and headache and sinus tachycardia ([redacted] patients each; [redacted]%). The most common worst Grade 3 or higher treatment-related AEs in the SOC group were: nausea ([redacted] patients; [redacted]%); anaemia ([redacted] patients; [redacted]%); and fatigue ([redacted] patients; [redacted]%).

Table 11: Incidence of treatment-related TEAEs occurring in ≥ 10% of patients in either treatment arm, SAS

	Axi-cel (N = 170)		SOC (N = 168)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any treatment-related TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Decreased platelet count	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]
Increased alanine aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Decreased lymphocyte count	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Hiccups	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinaemia	[redacted]	[redacted]	[redacted]	[redacted]

	Axi-cel (N = 170)		SOC (N = 168)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; auto-SCT, autologous stem cell transplant; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; SOCT, standard of care therapy; TEAE, treatment-emergent adverse event.
Notes: For the axi-cel group, treatment-related TEAEs include TEAEs that are related to axi-cel. For the SOC group, treatment-related TEAEs include TEAEs that are related to immunochemotherapy, total body irradiation (given as part of conditioning for auto-SCT), high-dose therapy and auto-SCT. TEAEs include all AEs with an onset on or after the axi-cel infusion date in the axi-cel group or the first dose of immunochemotherapy in the SOC group. Multiple incidences of the same AE in one patient are counted once at the worst grade for each patient. Preferred terms are sorted in descending order of total frequency across both treatment arms. AEs are coded using MedDRA version 23.1 and graded per CTCAE version 4.03. Investigators were instructed to record fever separately from neutropenia if the fever was attributed to CRS.
Source: Table 35. ZUMA-7 CSR.[44]

B.2.10.4. AEs of special interest

B.2.10.4.1. Neurological events

Table 12 presents neurological events following treatment with axi-cel and SOC.

Neurological events occurred in 102 patients (60%) who received axi-cel and in 33 patients (20%) who received SOC. Neurological events of Grade 3 or higher occurred in 36 patients (21%) and one patient (1%), respectively.[1] No deaths related to neurological events occurred.

The most common worst Grade 3 or higher treatment-emergent neurological events in the axi-cel group were encephalopathy (20 patients; 12%), aphasia (12 patients; 7%) and confusional state (nine patients; 5%).[1] One patient (1%) in the SOC group had a Grade 3 or higher treatment-emergent neurological event of delirium. The most common serious treatment-emergent neurological events of any grade in the axi-cel group were encephalopathy ([redacted] patients; [redacted]%), aphasia ([redacted] patients; [redacted]%) and confusional state ([redacted] patients; [redacted]%), and the only serious neurological event in the SOC group was encephalopathy.[44]

The median time to the onset of neurological events was 7 days (range: [redacted]) in the axi-cel group and 23 days (range: [redacted]) in the SOC group, and the median duration was 9 days (range: 1–817) and 23 days (range: [redacted]), respectively.[1, 44] At

the data cut-off date, two patients had ongoing neurological events; one patient who received axi-cel had Grade 2 paraesthesia and Grade 1 memory impairment, and one patient who received SOC had Grade 1 paraesthesia.[1]

Table 12: Summary of treatment-emergent neurological events occurring in ≥ 5% of patients in either treatment group, SAS

Preferred term	Axi-cel (N = 170)		SOC (N = 168)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any TE neurological event, n (%)	102 (60)	36 (21)	33 (20)	1 (1)
Type of neurological event, n (%)				
Tremor	44 (26)	2 (1)	1 (1)	0 (0)
Confusional state	40 (24)	9 (5)	4 (2)	0 (0)
Aphasia	36 (21)	12 (7)	0 (0)	0 (0)
Encephalopathy	29 (17)	20 (12)	2 (1)	0 (0)
Paraesthesia	8 (5)	1 (1)	14 (8)	0 (0)
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]
Agitation	[redacted]	[redacted]	[redacted]	[redacted]
Mental state changes	[redacted]	[redacted]	[redacted]	[redacted]
Hypoaesthesia	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; TE, treatment-emergent; TEAE, treatment-emergent adverse event.
Notes: TEAEs include all AEs with an onset on or after the axi-cel infusion date in the axi-cel group or the first dose of immunochemotherapy in the SOC group. Multiple incidences of the same AE in one patient are counted once at the worst grade for each patient. Preferred terms are sorted in descending order of total frequency across both treatment arms. AEs are coded using MedDRA version 23.1 and graded per CTCAE version 4.03. Neurological events are identified using a modified search strategy based on Topp 2015.
Source: Table 36. ZUMA-7 CSR[44]; Locke et al. 2021.[1]

B.2.10.4.2. Cytokine release syndrome

Cytokine release syndrome (CRS) is an AE induced by the activated T-cells upon engagement with the CD19 target, so it is considered to be related to treatment with CAR T-cell therapy. In ZUMA-7, the severity of CRS was graded according to a modification of the grading system proposed by Lee et al.[46]

Table 13 presents CRS events and the most common symptoms of CRS (occurring in ≥ 5% of patients) following treatment with axi-cel. CRS occurred in 157 patients (92%) who received axi-cel, of whom 11 (6%) had worst Grade 3 or higher CRS. No

deaths related to CRS occurred.[1] The most common symptoms of CRS worst Grade 3 or higher were hypotension (18 patients; 11%), pyrexia (14 patients; 9%) and hypoxia (13 patients; 8%). The most common serious CRS symptoms by any grade were pyrexia ([redacted] patients; [redacted]%), hypotension ([redacted] patients; [redacted]%) and hypoxia ([redacted] patients; [redacted]%).[44]

The median time to the onset of CRS was 3 days (range: 1–10) after the infusion, and the median duration was 7 days (range: 2–43). At the data cut-off date, all the CRS events were resolved.[1]

Table 13: Summary of treatment-emergent CRS and CRS symptoms occurring in ≥ 5% of patients in the axi-cel group, SAS

Event, n (%)	Any grade	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Any CRS event[a]	157 (92)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRS symptoms by preferred term[b]						
Pyrexia	155 (99)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	68 (43)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinus tachycardia	49 (31)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chills	38 (24)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	32 (20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased transaminases	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TE, treatment-emergent; TEAE, treatment-emergent adverse event.
Notes: TEAEs include all AEs with an onset on or after the axi-cel infusion date in the axi-cel group or the first dose of immunochemotherapy in the SOC group. Multiple incidences of the same AE in one patient are counted once at the worst grade for each patient. Preferred terms are sorted in descending order of frequency count in the Any Grade column. [a] Overall CRS is graded according to a modified grading system proposed by Lee and colleagues.[46] Percentages are calculated using the total number of patients in the axi-cel group of the analysis set as the denominator; [b] Individual CRS symptoms are coded using MedDRA version 23.1 and graded per CTCAE version 4.03. Percentages are calculated using the number of patients with any TE CRS of any grade. Grade 5 AEs were included in the table only when the value was non-zero.
Source: Table 37. ZUMA-7 CSR[44]; Locke et al. 2021.[1]

B.2.10.4.3. Cytopenia events

Table 14 presents cytopenia events following treatment with axi-cel and SOC.

The most common Grade 3 or higher cytopenia events in the axi-cel group were thrombocytopenia ([redacted] patients; [redacted]%), neutropenia ([redacted] patients; [redacted]%) and anaemia ([redacted] patients; [redacted]%).[44] The most common Grade 3 or higher cytopenia events in the SOC group were thrombocytopenia ([redacted] patients; [redacted]%), neutropenia ([redacted] patients; [redacted]%) and anaemia ([redacted] patients; [redacted]%). No patients had Grade 5 CRS.

Prolonged cytopenia events of Grade 3 or higher that were present at or after 30 days after the initiation of definitive therapy (from receipt of the axi-cel infusion or first dose of high-dose chemotherapy) occurred in 49 patients (29%) who received axi-cel, [redacted] patients ([redacted]%) in the overall SOC group, and in 12 of 62 patients (19%) in the SOC group who underwent auto-SCT (see Appendix F).[1, 44]

Table 14: Summary of treatment-emergent cytopenia events in either treatment group, SAS

	Axi-cel (N = 170)		SOC (N = 168)	
Event, n (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any cytopenia events	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased platelet count	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased haemoglobin	[redacted]	[redacted]	[redacted]	[redacted]
Macrocytic anaemia	[redacted]	[redacted]	[redacted]	[redacted]

	Axi-cel (N = 170)		SOC (N = 168)	
Event, n (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Decreased haematocrit	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.
Notes: Multiple incidences of the same AE in one patient are counted once at the worst grade for each patient. Preferred terms are sorted in descending order of Any Grade frequency count in the overall column. AEs are coded using MedDRA version 23.1 and graded per CTCAE version 4.03. Events (neutropenia, thrombocytopenia, or anaemia) with onset on or after therapy day 0 are summarised. Therapy day 0 is defined as the day the patient received the first axi-cel infusion or first dose of immunochemotherapy. Thrombocytopenia was identified with SMQ Haematopoietic Thrombocytopenia (narrow). Neutropenia includes the preferred terms 'febrile neutropenia', 'neutropenia', and 'decreased neutrophil count'. Anaemia was identified with SMQ Haematopoietic Erythropenia (broad). Investigators were instructed to record fever separately from neutropenia if the fever was attributed to cytokine release syndrome
Source: Table 38. ZUMA-7 CSR.[44]

B.2.10.4.4. Infections

Infections were experienced by 70 patients (41%) in the axi-cel group and 51 patients (30%) in the SOC group, of which 24 patients (14%) and 19 patients (11%) had worst Grade 3 or higher infections, respectively. [1] [redacted] patients ([redacted]%) in the axi-cel group and [redacted] patients ([redacted]%) in the SOC group had worst Grade 4 infections.[44] [redacted] patients ([redacted]%) in the axi-cel group had a Grade 5 infection ([redacted] patients with COVID-19, [redacted] with progressive multifocal leukoencephalopathy, [redacted] with hepatitis B reactivation and [redacted] with sepsis). [redacted] in the SOC group experienced a Grade 5 infection.

The most common infections in the axi-cel group were: unspecified ([redacted] patients; [redacted]%); viral infections ([redacted] patients; [redacted]%); bacterial infections ([redacted] patients; [redacted]%); upper respiratory tract infections ([redacted] patients, [redacted]%); and opportunistic infections ([redacted] patients; [redacted]%).[44] The most common infections in the SOC group were: unspecified ([redacted] patients; [redacted]%); bacterial infections ([redacted] patients; [redacted]%); and viral infections ([redacted] patients; [redacted]%).

The most common worst Grade 3 or higher treatment-emergent infections by preferred term (excluding COVID-19) were pneumonia ([redacted] patients; [redacted]%) and upper respiratory tract infection ([redacted] patients; [redacted]%) in the axi-cel group, and pneumonia and sepsis ([redacted]; [redacted]%) in the SOC group.[44] COVID-19 infections were reported as TEAEs for [redacted] patients ([redacted]%) in the axi-cel group, all of whom had worst

Grade 3 or higher, and [redacted] in the SOC group had a Grade 1 COVID-19 infection.

B.2.10.4.5. Hypogammaglobulinaemia

Hypogammaglobulinaemia includes preferred terms of hypogammaglobulinaemia and decreased blood immunoglobulin G. The severity of an event was graded by the investigator.[44]

Hypogammaglobulinaemia during treatment occurred in 19 patients (11%) who received axi-cel and in one patient (1%) who received SOC; all the events were Grade 1 or 2.[1]

A summary of hypogammaglobulinaemia TEAEs are presented in Appendix F.

B.2.10.5. Concomitant medications

Among patients who received axi-cel, [redacted] patients ([redacted]%) received corticosteroids (with or without tocilizumab), [redacted] patients ([redacted]%) were treated with tocilizumab (with or without corticosteroids) and [redacted] patients ([redacted]%) were treated with corticosteroids and tocilizumab.[44] [redacted] patients ([redacted]%) were treated with vasopressors and [redacted] patients ([redacted]%) were treated with immunoglobulins.

B.2.10.6. Safety overview

The safety profile observed in ZUMA-7 was manageable and generally consistent with the safety profile of axi-cel treatment as a third-line therapy for patients with r/r DLBCL (ZUMA-1) and real-world use of axi-cel, as summarised in Table 15. Since the approved access of axi-cel and tisa-cel through the CDF in NHS England, clinicians are increasingly comfortable with toxicity management for this CD19-directed CAR T-cell therapy class.

Table 15: TEAEs observed in patients receiving CAR T-cell therapy

	Clinical trials		Real-world use	
Study	**ZUMA-7**	**ZUMA-1**	**Nastoupil et al. 2020**	**Kuhnl et al. 2020**
Population (n)	DLBCL (170)	DLBCL, TFL, PMBCL (108)	DLBCL, TFL, PMBCL (298)	DLBCL, TFL, TMZL, TLPL, TNLPHL, PMBCL (133)
Any TEAE	100%	100%	-	-
Worst Grade ≥ 3	91%	98%	-	-
Any TE CRS	92%	93%	91%	93%
Worst Grade ≥ 3	6%	11%	7%	9%
Any TE neurological event	[redacted]	67%	69%	43%[a]
Worst Grade ≥ 3	[redacted]	32%	31%	19%[a]

Key: AE, adverse event; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; TE, treatment-emergent; TFL, transformed follicular lymphoma; TLPL, transformed lymphoplasmacytic lymphoma; TMZL, transformed marginal zone lymphoma; TNLPHL, transformed nodular lymphocyte-predominant Hodgkin lymphoma.
Note: Patient populations across clinical trials and real-world settings from which data are presented are highly heterogeneous. [a] Reported as the number of patients who experienced immune effector cell-associated neurotoxicity syndrome.
Source: Table 33. ZUMA-7 CSR[44]; Locke et al. 2021[1]; Locke et al. 2019[47]; Nastoupil et al. 2020[48]; Kuhnl et al. 2020.[49]

As recommended in the SmPC for axi-cel (Appendix C), patients should be monitored for the first 10 days following infusion for signs and symptoms of potential CRS, neurological events and other toxicities. After the first 10 days, the patient can be monitored at the physician's discretion, but patients should remain within proximity of a qualified clinical facility for at least 4 weeks following infusion. At least one dose of tocilizumab in the event of CRS and emergency equipment must be available prior to axi-cel infusion, and 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 MHRA (Medicines & Healthcare products Regulatory Agency) Central Alerting System, suitable alternative measures to treat CRS instead of tocilizumab must be available before infusion takes place.

Blood counts should be monitored after axi-cel infusion and patients should also be monitored for signs and symptoms of infection before, during and after axi-cel

infusion (and treated appropriately). Prophylactic antimicrobials should be administered according to standard institutional guidelines. Immunoglobulin levels should also be monitored after treatment with axi-cel and managed using infection precautions, antibiotic prophylaxis and immunoglobulin replacement.

A recent review summarised the latest data on potential late or prolonged effects of CAR T-cell therapy, including prolonged cytopenia events, hypogammaglobulinaemia, late neurological effects, late immune-related adverse events, second cancers, late infections and cardiac toxicities.[50] Very few late or prolonged effects presented after one year following treatment, which suggests that the available safety data from ZUMA-7 (providing 24.9 months of potential follow-up) will have captured any such event. Conversely to what has been reported for stem cell transplants, this review also reported that HRQL in long-term survivors is comparable to that of the general population, although this conclusion is based on limited data.

B.2.11. Ongoing studies

The ZUMA-7 study is ongoing with follow-up through to 60 months; the potential follow-up represented in the submission is 25 months. No other studies are investigating axi-cel in adults with primary refractory or early relapse DLBCL who are intended for transplant.

A Phase II study investigating axi-cel as a second-line therapy in patients with r/r B-cell NHL who are non-candidates for transplant is currently recruiting (ALYCANTE; NCT04531046), with primary data estimated to be available in May 2022.[51] This study is sponsored by the Lymphoma Academic Research Organisation and therefore Gilead has no early sight of data or access to patient-level data from this study.

B.2.12. Innovation

Axi-cel is a personalised, transformative, single-infusion medicine in which the patient's own T-cells are engineered to target and kill cancer cells. Axi-cel was the first of the breakthrough class of CAR T-cell therapies to receive European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approval,

and its innovative nature is well established and accepted across the healthcare community.

Axi-cel transformed the DLBCL management pathway[52] and now offers a second step change through earlier use in primary refractory or early relapse DLBCL patients intended for transplant. Providing access to axi-cel at first relapse would increase the number of patients receiving definitive therapy in the second-line setting, and thus improve cure rates specific to this patient population with high unmet need and a poor prognosis. Data from ZUMA-7 clearly demonstrate this with a three-fold increase in the number of patients receiving definitive therapy and a 2.5-fold increase in the number of patients living event-free for at least 2 years.[1] While data that would robustly allow quantification of the improved cure rate with second-line CAR T-cell therapy use versus third- or later-line CAR T-cell therapy use are not available to date, clinical experts felt that an approximate 10% improvement as observed in unadjusted OS analyses of ZUMA-7 (where several patients in the SOC arm went on to receive CAR T-cell therapy in the third- or later-line setting) was not 'unreasonable'.[29] Support for advancing axi-cel positioning such that patients have access to CAR T-cell therapy when they are likely to have lower tumour burden and comorbidities, and higher T-cell and general fitness, is strong across the clinical community.[29, 30, 42, 43]

While the main health-related benefits of axi-cel will be captured in the quality-adjusted life years (QALY) calculation, the true extent of the benefit associated with cure is likely to have been underestimated, including the emotional benefit of hope that receiving a potentially curative treatment option can provide.[53] Additional benefits associated with a single-infusion medicine compared with multiple cycles of immunochemotherapy followed by HDT and auto-SCT include reduced impact on the daily lives of patients and their carers, and capacity benefits to health services. These benefits may not be captured in the QALY calculation.

Anecdotal reports of the emotional consequences of auto-SCT are not captured in clinical trial safety outcomes, which include symptoms aligned to post-traumatic stress disorder.[54] Emotional consequences of treatment are not formally captured in the QALY calculation, but with no similar reports of these consequences of CAR T-

cell therapy, this could represent a significant health-related benefit of axi-cel to patients, carers and healthcare services alike.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Principal findings from the clinical evidence

The ZUMA-7 trial supports previous trial observations (Table 3) that only a minority of primary refractory or early relapse DLBCL patients intended for transplant go on to receive definitive therapy with current second-line SOC, and that the associated overall cure rate in this population remains low. It also shows the potential benefit of axi-cel in improving definitive therapy and cure rates, with three times as many patients randomised to axi-cel receiving definitive therapy, and 2-3 times as many patients living event-free for at least 2 years versus SOC.[1]

ZUMA-7 was designed to reflect the future decision-making process at first relapse in clinical practice, with patients intended for transplant enrolled and randomised to follow the current second line SOC pathway or the potential CAR-T service pathway. Despite intent, only 36% of patients randomised to SOC in ZUMA-7 actually went onto receive definitive treatment with HDT plus auto-SCT following re-induction therapy .[1] In contrast, axi-cel was successfully manufactured for 100% of patients who underwent apheresis and 94% of patients randomised to axi-cel received definitive treatment. The overall 2-year EFS rates were 16% in the SOC group versus 41% in the axi-cel group.

The percentage of patients with a response to axi-cel was significantly greater than in the SOC group (83% versus 50%; $p < 0.001$) and a CR was observed in twice as many patients (65% versus 32%).[1] At the time of analysis (median follow-up of 24.9 months), [redacted] of responding patients had an ongoing response to axi-cel treatment compared with [redacted] of patients who had an ongoing response to SOC.[44] In the interim survival analysis, the estimated 2-year OS rate was 61% in the axi-cel group versus 52% in the SOC group, notably, with subsequent cellular immunotherapy received off-protocol in 56% of patients); 29% of patients in the axi-cel group died from progressive disease compared with 36% of patients in the SOC group.[1] In a world without CAR T-cell therapy available in the third- or later-line setting, we would

expect survival to be significantly lower than observed in the SOC arm of ZUMA-7; this is further discussed in Section B.2.13.3.

B.2.13.2. Strengths and limitations of the evidence base

ZUMA-7 is the first and largest RCT investigating the efficacy and safety of CAR T-cell therapy versus current second line SOC for primary refractory or early relapse DLBCL patients intended for transplant. ZUMA-7 provides robust data that is directly relevant to the decision problem being addressed, that is, should patients eligible for intensive therapy at first relapse be treated with re-induction therapy for potential HDTauto-SCT or axi-cel? Data clearly demonstrate that the current pathway of care is lacking and that axi-cel offers a much higher chance of receiving definitive therapy at this crucial stage than current SOC and thus an associated higher chance of cure (see above).We should be aiming to treat patients with the most effective therapies at the earliest stage in their treatment pathway, and there is strong support for advancing axi-cel positioning across the clinical community.[29, 30, 42, 43]

The primary analyses of ZUMA-7 provide more than two years of potential follow-up. Although these data are still relatively immature given the curable disease setting, two years is considered a significant and clinically meaningful milestone in r/r DLBCL.[43] Clinical experts estimate that 95% of patients living event-free at 2 years will achieve long-term remission, and that most patients who would relapse after CAR T-cell therapy or auto-SCT would have done so by this 2-year timepoint.[29] This has been formally explored in the de novo DLBCL setting. A prospective study demonstrates that patients with DLBCL who were treated with immunochemotherapy and who were living event-free at 2 years had an equivalent OS to that of the age- and sex-matched general population.[55] Applying the estimated 95% long-term remission rates to the 2 year EFS rates observed in the ZUMA-1 trial suggests that 38% of patients treated with axi-cel in the second-line setting will be cured, compared with 15% of patients treated with current second-line care.

As noted in Section B.2.12, robust data quantifying the improved cure rate with second-line versus third- or later-line use are not available to date. However, unadjusted OS analyses of ZUMA-1 provide some insight into this potential benefit, taking into consideration that over half of patients who were randomised to the SOC arm went on to receive subsequent cellular immunotherapy. In the interim analyses,

we observe an approximate 10% improvement in 2-year OS (61% vs 52%), but the immaturity of the data prevents us from drawing longer-term conclusions.[1] With the requisite caveat around heterogeneity of patient populations and naïve comparisons, a similar difference is observed between 2-year OS rates of the axi-cel arms of ZUMA-7 and ZUMA-1 (61% vs 50%).[56]

In recognition of the current uncertainty around the longer-term benefit with axi-cel treatment in the second-line setting, we acknowledge that axi-cel is likely to be a CDF candidate. With interim funding through the CDF, earlier access to axi-cel would be available for a patient population with a high unmet need and a poor prognosis. This would happen alongside ongoing data collection, which will robustly assess the cost-effectiveness of axi-cel in this second-line treatment setting.

B.2.13.3. Applicability of clinical evidence to practice

The primary endpoint of ZUMA-7, EFS, is an established endpoint that classes a best 'response' of SD and new therapy commencement prior to radiographic disease progression as an event, alongside radiographic disease progression and death. This is the most clinically relevant endpoint in a curable disease setting where stable disease is not an acceptable outcome, and where patients with a suboptimal response to treatment will be moved onto a new therapy for potential cure at the earliest opportunity.[29, 43, 57] In comparison, PFS data collected are subject to informative censoring, as patients who receive a new therapy before disease progression (and who are then censored in PFS analyses) are not random and directly relate to patient prognosis, which may lead to bias.[58] Using EFS in appraisals of potentially curative treatment has previously been deemed appropriate for decision-making.[59]

EFS is also the most representative endpoint for cure in this setting. It is shown to be a valid surrogate endpoint for OS in haematological malignancy across several correlation analyses identified through systematic literature review (SLR).[60] In DLBCL specifically, the correlation between EFS and OS was found to be stronger than the correlation between PFS and OS in a large-scale surrogacy analysis that was based on 30 clinical trials and 47 retrospective studies.[61] Exploratory analyses of OS by EFS status in the ZUMA-1 trial (third- or later-line axi-cel treatment for r/r DLBCL) further support the usefulness of EFS rates as surrogate endpoints for long-

term OS specific to r/r DLBCL.[56] Significant associations are observed between EFS and HRQL, and between EFS and healthcare resource use.[62, 63]

The target population for reimbursement is aligned to the evidence base supporting the use of axi-cel in the second-line setting. Generally, the ZUMA-7 trial population is also directly applicable to the proposed use of axi-cel in clinical practice, which is for the treatment of primary refractory or early relapse DLBCL patients intended for transplant: a patient population with high unmet need and a poor prognosis for whom clinical experts believe CAR T-cell therapy could play an important role.[29, 30, 42, 43] However, as is often the case in a clinical trial versus real-world setting, the ZUMA-7 trial population is a select group of primary refractory or early relapse DLBCL patients who would be expected to tolerate and respond well to intensive therapy (i.e. a generally younger, fitter population than the real-world population) despite their generally poor prognosis (74% of patients had primary refractory disease, 45% had a high sAAIPI and 79% had Stage III/IV disease).[29] Trial outcomes may therefore be slightly optimistic compared to outcomes that might be expected in practice. However, this would apply to both arms in equal measure, i.e. to patients randomised to axi-cel or SOC, and therefore comparative effect estimates remain applicable to real-world expectations. There is also close alignment in 2-year EFS estimates from the ZUMA-7 SOC arm (16%) to historical trial 2-year EFS estimates (16-17%) in similar patient groups.[1, 25, 27]

The use of steroid-only bridging therapy as mandated in the ZUMA-7 study may also have been a factor in the selection of patients who entered the study. Bridging therapy was restricted to glucocorticoids to isolate the effects of CAR T-cell therapy as second-line therapy in ZUMA-7 but this may have restricted enrolment of patients with rapidly progressing disease that would otherwise have warranted more aggressive bridging therapy. In clinical practice, bridging therapy with outpatient chemotherapy is expected to be used in approximately two-thirds of patients.[29] While the use of bridging therapy should not have a direct impact on effect estimates and is intended to keep patients stable while axi-cel is being manufactured, it does impact cost estimates and is thus further explored in the economic analysis. As noted above, any impact on effect estimates relating to patient selection would be applied to both arms in equal measure.

The SOC immunochemotherapy regimens used in ZUMA-7 are reflective of those that are most used at first relapse in clinical practice. Although some differences are observed in the proportion of patients receiving each regimen in the trial versus real-world treatment patterns (see Appendix M), clinical experts confirmed that they would expect equivalence in effect across regimens, as demonstrated in historical clinical trials.[29]Gisselbrecht, 2010 #41;Crump, 2014 #81} NICE makes a specific recommendation to consider R-GDP based on equivalent effectiveness and reduced toxicity[64]. The proportion of patients receiving an R-GDP regimen was very similar across the ZUMA-7 SOC group (25%) and real-world data (23%), however clinical experts advised that there is an increasing use of R-GDP in practice as it is possible to administer this regimen in an outpatient setting.[1, 17, 29] Importantly, [redacted]

The high proportion of subsequent cellular immunotherapy use in the SOC group of the ZUMA-7 trial (56% off-protocol treatment switching) should be considered when interpreting the (unadjusted) interim OS analyses. Although CAR T-cell therapy is available in the third- or later-line setting to patients in England, it is currently funded through the CDF, and such treatments should not be considered in a treatment sequence for new technology appraisals according to the NICE position statement on this topic.[65] There is also arguably a narrower window of opportunity to select patients for CAR T-cell therapy in the real-world setting vs a clinical trial environment such that the proportion of patients receiving subsequent cellular immunotherapy in the ZUMA-7 SOC arm is higher than we would expect in practice.[30]Aligning to NICE recommendations, post-hoc sensitivity analyses that adjust OS estimates for subsequent CAR T-cell therapy use in the SOC arm of ZUMA-7 are used in the cost-effectiveness base case (see Section B.3.3.4.1).

In a world without CAR T-cell therapy available in the third- or later-line setting, we would expect OS to be significantly lower than observed in the (unadjusted) interim OS analyses in the SOC arm of ZUMA-7. Indeed, OS estimates in the SOC arm were higher than observed in historical trials conducted before CAR T-cell therapies

were introduced at third- or later-lines. For example, the 2-year OS rate in patients with primary refractory or early relapse DLBCL in the ORCHARRD study was 31%, and the 2-year OS rate in patients with primary refractory DLBCL in the SCHOLAR-1 study was 24% (Table 3).[24, 27] Clinical experts agreed that patient survival in a world without CAR T-cell therapy would be significantly lower, and that patients who relapse after current second-line care would follow a steep downward trajectory, with EFS and OS curves estimated to align by 5 years at the latest, perhaps even as early as by 1 year in the primary refractory or early relapse poor risk patient cohort.[29, 30]

B.2.13.4. Service implications

Axi-cel is already reimbursed for the treatment of adult patients with r/r DLBCL and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy. NHS England service provision for CAR T-cell therapies are well established, and there is no or very minimal impact on further site qualification, patient referral or management expected with the advancement of axi-cel in the clinical care pathway. Approval of axi-cel for earlier use would have an impact on patient numbers, but plans are already in place to increase the number of CAR T-cell therapy centres throughout 2022.

B.2.13.5. Axi-cel as an end-of-life therapy

Primary refractory or early relapse DLBCL patients intended for transplant have a poor prognosis with current second-line care, and in the absence of CAR T-cell therapy, these patients are not expected to survive beyond 2 years. Data supporting axi-cel as an end-of-life therapy in this population are summarised in Table 16.

Clinical experts agree with these data and state that in a world without CAR T-cell therapy, patients who relapse after current second-line care would follow a steep downward trajectory, with EFS and OS curves estimated to align by 5 years at the latest, perhaps even as early as by 1 year in the primary refractory or early relapse poor risk patient cohort.[29, 30]

Table 16: End-of-life criteria

Criterion	Data available	Reference in submission
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Current standard-of-care survival estimates for primary refractory or early relapse patients intended for transplant in ORCHARRD: Median months = ~9 2-year OS = 31%	Section B.1.3.2 Table 3
	Current care survival estimates for primary refractory patients in SCHOLAR-1: Median months = 7.1 2-year OS = 24%	Section B.1.3.2 Table 3
	Current care survival estimates for refractory or relapse ≤ 12 months of auto-SCT in SCHOLAR-1: Median months = 6.3 2-year OS = 20%	Section B.1.3.2 Table 3
	Current care survival estimates from economic modelling in the absence of CAR T-cell therapy: Median months = [redacted] 2-year OS = [redacted]	Section B.3.3.4.3 Table 25
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	Axi-cel survival estimates from ZUMA-7: Median months = not reached despite [redacted] months follow-up for OS using the reverse Kaplan–Meier method 2-year OS = 61%	Section B.2.6.3.3
	Axi-cel survival estimates from economic modelling: Median months = [redacted] 2-year OS = [redacted] Survival gain with axi-cel vs current standard-of-care in the absence of CAR T-cell therapy: Median months = [redacted] Incremental LYG = [redacted]	Section B.3.3.4.3 Table 25 Section B.3.7.1 Table 52
Key: CAR, chimeric antigen receptor; NHS, National Health Service; OS, overall survival.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic search was conducted to identify existing published cost-effectiveness studies in adults ≥ 18 years of age with r/r DLBCL after first-line therapy only. Full details of the search methods and results are presented in Appendix G. The search

identified five modelling studies conducted across various geographies.[66-70] Only one study was conducted in the UK and thus can be considered relevant to decision-making in England.[70] This study is summarised in Table 17.

Table 17: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Wang et al.[70]	2017	UK-based CEA using discrete event simulation	67.8	NR	£18,096, £18,396 and £18,396 for 5-year, 15-year and lifetime time horizons, respectively.	NR

Key: CEA cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; NR, not reported; QALYs, quality-adjusted life years; UK, United Kingdom.

Furthermore, a search of the NICE website identified four previous single technology appraisals for adults with r/r DLBCL. These are:

- TA649: Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma[2]
- TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma[71]
- TA559: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies[52]
- TA567: Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies[72]

Modelling approaches for the two CAR T-cell therapy appraisals (TA559 and TA567) are summarised in Table 18. Although these consider a later-line population than the current appraisal, TA559 and TA567 were used as a basis for the modelling approach, inputs and assumptions.

Table 18: Summary of previous TAs of CAR T-cell therapies in DLBCL

	TA559	TA567
Year	2019	2019
Summary of model	Partitioned survival model with three health states (PF, PD, death). PFS and OS modelled independently	Partitioned survival model with three health states (PF, PD, death). Model also included a decision tree element for the tisagenlecleucel arm. PFS and OS modelled independently
Patient population	DLBCL and primary mediastinal B-cell lymphoma after two or more systemic therapies (third-line)	r/r DLBCL after two or more systemic therapies (third-line)
Average age (years)	56	54
Time horizon	Lifetime	Lifetime
Treatment waning effect	Not applied	Not applied
Source of efficacy data	Axi-cel – ZUMA-1 SOC – SCHOLAR-1	Tisagenlecleucel – JULIET and Schuster SOC – HMRN and CORAL
Source of utilities	ZUMA-1 EQ-5D-5L crosswalked to EQ-5D-3L values	JULIET SF-36 study via a mapping exercise
Source of costs	Standard cost sources used (i.e. NHS Reference Costs, PSSRU, BNF and eMIT). Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	Standard cost sources used (i.e. NHS Reference Costs, PSSRU, BNF and eMIT). Where costs were not reported in these sources, cost inputs were sourced from appropriate literature
QALYs (intervention, comparator)	NR	NR
Costs (currency, intervention, comparator)	NR	NR
ICER (cost per QALY gained)	NR	£42,991–£55,403 (with commercial agreement)
FAD outcome	Recommended for use within the Cancer Drugs Fund	Recommended for use within the Cancer Drugs Fund

Key: BNF, British National Formulary; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; eMIT, electronic market information tool; FAD, final appraisal determination; HMRN, Haematological Malignancy Research Network; ICER, incremental cost-effectiveness ratio; NR, not reported; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; PSSRU, Personal and Social Services Research Unit; QALY, quality-adjusted life year; SF-36, Short Form Health Survey-36; SOC, standard of care; TA, technology appraisal.

B.3.2. Economic analysis

B.3.2.1. Patient population

In line with the ZUMA-7 trial, the patient population considered in this analysis is adults with primary refractory or early relapse (≤ 12 months) DLBCL after 1 systemic therapy who are intended for transplant.

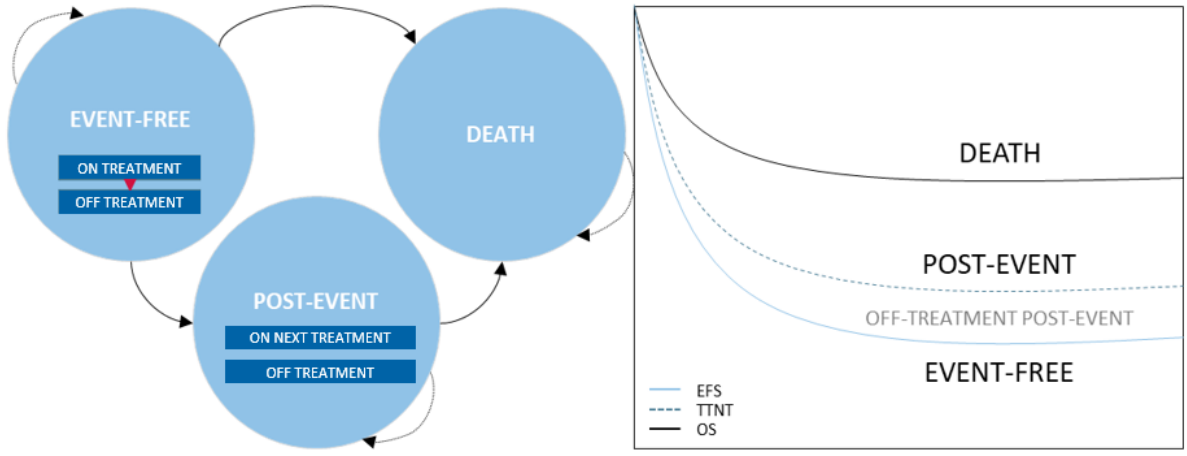
Population characteristics in the model are aligned with those of the ZUMA-7 trial population; the mean age at baseline is 57.2 and the proportion female is 34%.

Section B.2.3.1 provides further details on the baseline characteristics of ZUMA-7 participants. and Section B.2.13.3 discusses the applicability of ZUMA-7 evidence to clinical practice.

B.3.2.2. Model structure

A de novo cost-effectiveness model was developed in Microsoft Excel®. As health economic experts highlighted a preference for a simpler model structure, a partitioned survival approach with three health states was specified (Appendix R). The model structure is presented in Figure 18.

Figure 18: Model structure



Key: EFS, event-free survival; OS, overall survival, TTNT, time to next treatment.

As shown in Figure 18, the partitioned survival model has three mutually exclusive health states defined by three stages of the disease:

- Event-free (split into ‘on treatment’ and ‘off treatment’ states)
- Post-event (split into ‘on next treatment’ and ‘off treatment’ states)
- Death

All outcomes are modelled independently of each other with transitions between health states derived directly from OS, EFS and time to next treatment (TTNT) projections. As shown in Figure 18, the proportion of patients who are dead in each model cycle is estimated by one minus estimated survival (1-OS), the proportion of those in the post-event state is estimated by the area between OS and EFS projections (OS-EFS), and the proportion in the event-free state is the area under the EFS curve. The TTNT curve is used to further partition the post-event health state into those receiving and not receiving subsequent treatment, thus is important in determining post-event treatment costs.

The choice to capture EFS in the model structure rather than PFS was driven by several factors. EFS is the primary endpoint of the ZUMA-7 trial (for which the trial is powered) and defined as the time until disease progression, initiation of a next line of therapy or death. As outlined in Table 1 and Section B.2.13.2, EFS is the most clinically relevant endpoint for DLBCL given the curative intent of treatment. In DLBCL it is common practice to move patients to the next line of therapy in this setting if their best response is stable disease, given the severe nature of the condition. Furthermore, the use of the alternative outcome, PFS, would be biased by informative censoring[58] as, for the assessment of PFS in ZUMA-7, patients who receive a new treatment are censored if this occurs before progression. As initiation of a new treatment is not random and is related to a patient’s prognosis, this results in an overestimation of PFS as the outcome is reflective of patients with a better prognosis. There is also precedent for the use of EFS as an outcome on which to base a partitioned survival model. The modelling approach for TA554 (tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years),[73] used EFS as again this was the primary endpoint in the key trials. The structure of the company’s model was deemed appropriate for decision-making by the committee.[59]

The partitioned survival model structure is both simple and flexible enough to extrapolate survival using various methods and can incorporate relative efficacy in numerous ways. The approach is considered to reflect the patients' disease pathway in r/r DLBCL and allows for key trial endpoints to be modelled directly (EFS is the primary outcome in ZUMA-7).

Partitioned survival modelling is a widely used and accepted approach in oncology appraisals, particularly for end-stage cancer treatments. It is also consistent with the model structures used for previous CAR T-cell therapies in r/r DLBCL (Table 18). In both prior CAR T-cell therapy appraisals in DLBCL the committee accepted the model structure as appropriate for decision-making.[74, 75] Specifically, the models for TA559 and TA567 incorporated a decision tree to account for costs and outcomes for patients who undergo leukapheresis but do not go on to receive CAR T-cell therapy infusion. This was not required for the current submission as ZUMA-7 is a randomised (rather than single-arm) trial, patient outcomes were measured from randomisation and therefore capture the range of events that can occur before axi-cel infusion. On consultation, clinical experts agreed that the model structure appropriately reflected the disease pathway for r/r DLBCL patients.[29]

B.3.2.2.1. General model settings

The analysis perspective is that of the NHS and Personal Social Services (PSS) in England for costs and direct health effects on individual patients for outcomes, in line with the NICE reference case.[76]

The model uses a 1-month cycle length (30.44 days). A half-cycle correction is applied throughout the model to both costs and health outcomes; to better account for the fact that some (costs) can occur at any point during the cycle, while others (health outcomes) are spread across time.

The analysis assumes a lifetime time horizon (50 years), which is sufficient to capture the plausible maximum life expectancy for the ZUMA-7 ITT population (mean age 57.2 years). Shorter time horizons are explored in the scenario analysis in Section B.3.8.3.

A discount rate of 3.5% per annum is applied to costs and QALYs, as also specified in the NICE reference case. All costs are presented in British pound sterling (GBP) and the cost year is 2021.[76]

General model settings are summarised in Table 19, with features of previous CAR T-cell therapies presented in Table 20 alongside features of the current appraisal. It is important to note that CAR T-cell therapies presented are in the third-line population and thus slightly less fit than patients considered in the current second-line appraisal.

Table 19: General model settings

Aspect	Base case analysis	Justification
Perspective	NHS and PSS	As specified in the NICE reference case[76]
Time horizon	Lifetime	
Discount rate (costs and QALYs)	3.5%	
Currency	GBP	
Cost year	2021	
Key: GBP, British pound sterling; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal and Social Services; QALY, quality-adjusted life year.		

Table 20: Features of the economic analysis

	Previous appraisals (third-line)		Current appraisal (second-line)	
Factor	**TA559 (axi-cel)**	**TA567 (tisagenlecleucel)**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	Lifetime	Long enough to reflect all important differences in costs or outcomes between the technologies being compared, in line with the reference case.[76] Survival benefits for patients treated with axi-cel are only fully captured if a lifetime horizon is used
Treatment waning effect?	Not applied	Not applied	Not applied	CAR T-cell therapies are potentially curative. Mixture cure modelling approach used in base case accounts for a proportion of patients achieving survival outcomes comparable to that of general population
Source of utilities	ZUMA-1 EQ-5D-5L crosswalked to EQ-5D-3L values	JULIET SF-36 study via a mapping exercise	ZUMA-7 EQ-5D-5L crosswalked to EQ-5D-3L values for pre-event states. Utilities from previous NICE appraisals applied for post-event states	EQ-5D data reported directly from patients with utilities based on public preferences is considered the preferred method by NICE[76] Since EQ-5D-5L data in ZUMA-7 were not routinely collected post-event, data from previous NICE appraisals were used instead
Source of costs	NHS Reference Costs, PSSRU, BNF, eMIT. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	NHS Reference Costs, PSSRU, BNF, eMIT. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	NHS Reference Costs, PSSRU, BNF, eMIT. Where costs were not reported in these sources, cost inputs were sourced from appropriate literature	Standard costs sources relevant to NHS England and in line with NICE reference case [76]

Key: BNF, British National Formulary; CAR, chimeric antigen receptor; eMIT, electronic market information tool; PSSRU, Personal and Social Services Research Unit; SF-36, Short Form Health Survey-36; TA, technology appraisal.

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention

The intervention, axi-cel, is implemented in the model as per the expected marketing authorisation, anticipated [redacted], and is reflective of the decision problem described in Section B.1.1.

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. The mechanism of action and process for manufacturing and administering axi-cel is described in Section B.1.2.

Axi-cel is a single-infusion product, for autologous and intravenous use only. Each single-infusion bag contains a target dose of 2 x 10^6 CAR-positive viable T-cells per kg of body weight. Before infusion, all patients will receive lymphodepleting chemotherapy consisting of intravenous cyclophosphamide 500 mg/m^2 and intravenous fludarabine 30 mg/m^2 intravenous on the 5th, 4th and 3rd day before axi-cel infusion, and some patients are treated with bridging chemotherapy.

B.3.2.3.2. Comparator

As described in Section B.1.3.4, patients who are fit enough to tolerate intensive therapy should be offered further multi-agent immunochemotherapy (re-induction therapy) at relapse to try to obtain sufficient response for HDT-auto-SCT consolidation.

Aligned with the control arm of ZUMA-7, the comparator considered within the analysis comprises a basket of the most commonly given treatments for transplant-intended patients at second-line, including platinum-containing salvage chemotherapy (R-ICE, R-ESHAP, R-GDP or R-DHAP) followed by HDT (e.g. BEAM) and auto-SCT in responders.

Clinical expert opinion was sought to determine the regimens given in NHS England, in addition to estimates of the distribution across these regimens.[29] [29]It was stated that the type of chemotherapy regimen use was centre dependent, however both R-ESHAP and R-DHAP was rarely used in England. Clinicians also stated that a lot of centres in England were moving towards using R-GDP, as it is possible to administer

in an outpatient setting, and therefore had the possibility of using less inpatient beds. There was general consensus that R-ICE and R-GDP are the most commonly used regimens in England, therefore an equal split was assumed across these two regimens. In addition, clinicians stated that it is reasonable to assume equal efficacy across all four of the platinum-based chemotherapy regimens, therefore the distribution of use was only expected to affect costs.[29] [29]

Importantly, CAR T-cell therapies, axi-cel and tisagenlecleucel are approved to treat patients with DLBCL after at least two prior therapies (i.e. third-line+). In line with NICE's position statement on the inclusion of CDF-funded treatments as comparators or subsequent therapies [77], third-line CAR T-cell therapies are excluded from this analysis. Further details are provided in Section B.3.3 and Section B.3.5. Other subsequent treatment options, based on the final scope of the previous third-line CAR T-cell therapy appraisals, include nivolumab, pembrolizumab, polatuzumab, lenalidomide, auto-SCT, allo-SCT, and best supportive care (including radiotherapy). However, some of these treatments are given in an experimental setting only, therefore have been excluded from the analysis. Further details are provided in Section B.3.5.[78, 79]

B.3.3. Clinical parameters and variables

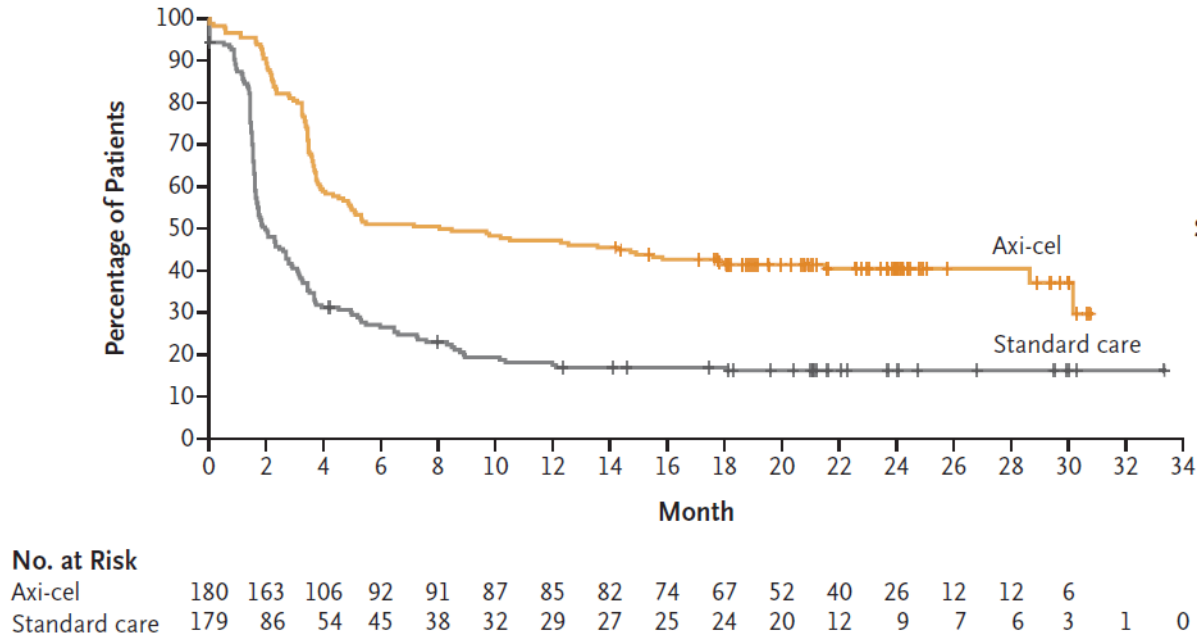
B.3.3.1. Clinical effectiveness data overview

EFS, OS and TTNT expectations for axi-cel and SOC were based on the latest available data for the FAS population of the ZUMA-7 trial (data cut-off date 18 March 2021). The median potential follow-up time was 24.9 months and the median actual follow-up time was [redacted] months.[1, 44]

Previous CAR T-cell therapy appraisals have focussed on the mITT population for the axi-cel arm (i.e. patients receiving CAR T-cell therapy infusion). However, this approach has been critiqued due to the need to determine outcomes for patients who failed to receive treatment due to events occurring prior to infusion, such as death during the manufacturing period, adverse events associated with pre-treatment, or manufacturing failures.[52, 72] Therefore, the FAS population is used to determine outcomes in the current appraisal, providing data for 180 patients receiving infusion with axi-cel and 179 patients receiving SOC.

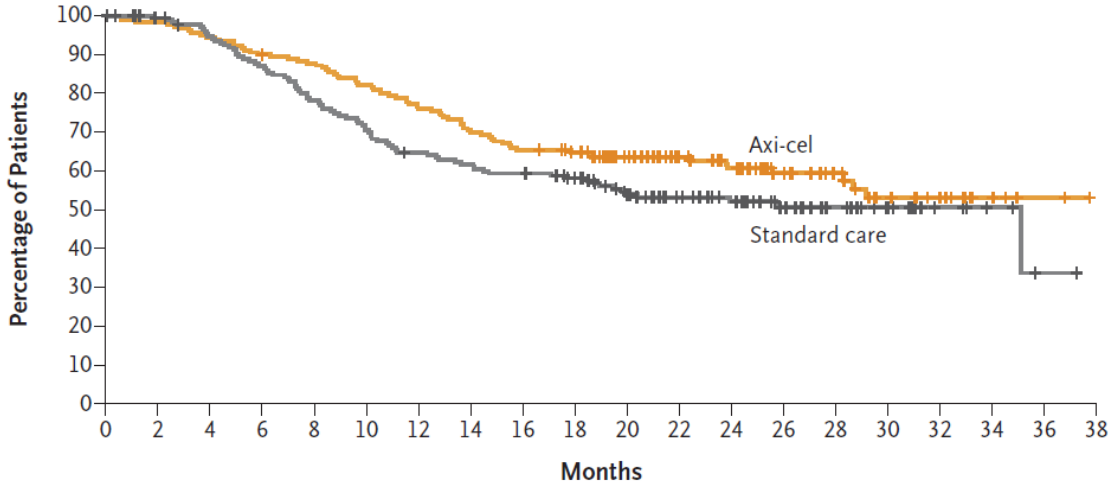
Kaplan–Meier data for EFS, OS and TTNT for both axi-cel and SOC are presented in Figure 19 to Figure 22. Two different Kaplan–Meier data is presented for OS as one shows the mITT population (Figure 20) and the second shows the crossover adjusted Kaplan–Meier data (Figure 21) as this is used in the base case. Extrapolation of trial survival data was required to capture lifetime outcomes following guidance in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs).[80, 81]

Figure 19: Kaplan–Meier plot for EFS as per central assessment, FAS



Key: EFS, event-free survival; FAS, full analysis set.
Source: Locke et al. 2021.[1]

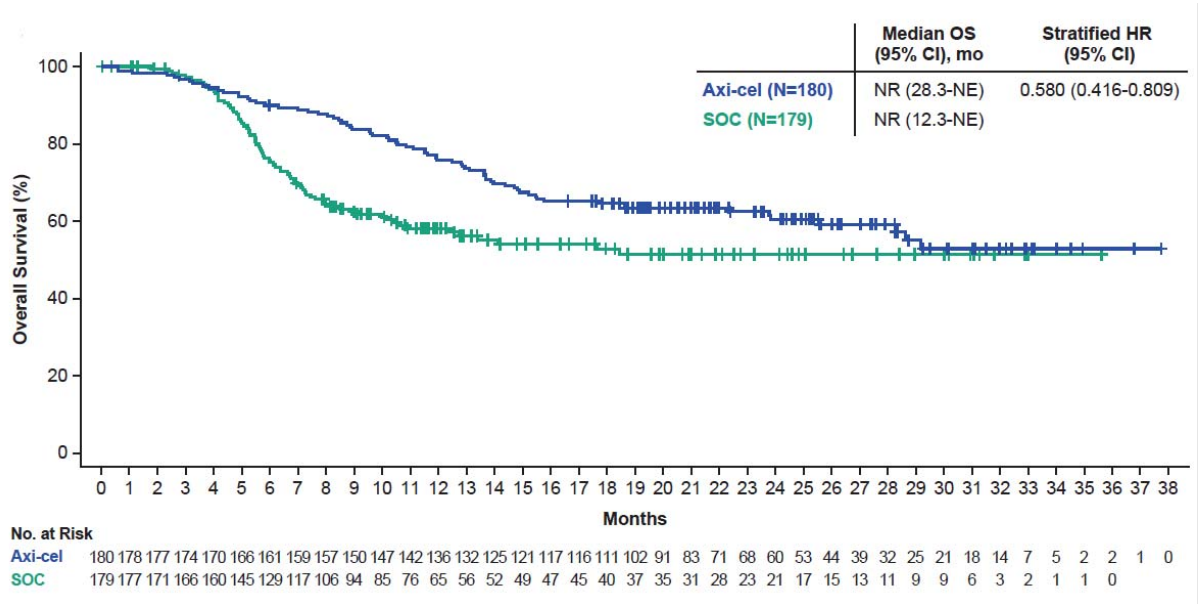
Figure 20: Kaplan–Meier plot for OS, FAS



No. at Risk																			
Axi-cel	180	177	170	161	157	147	136	125	117	111	91	71	60	44	32	21	14	5	2	0
Standard care	179	171	161	148	133	120	109	104	100	91	74	58	47	33	21	14	7	4	1	0

Key: FAS, full analysis set; OS, overall survival.
Source: Locke et al. 2021[1]

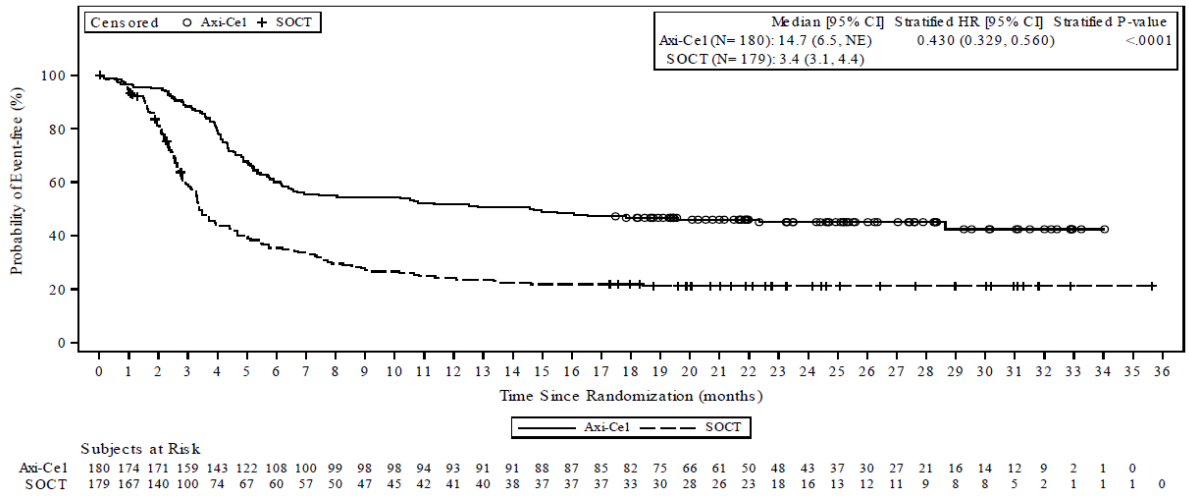
Figure 21: Kaplan–Meier plot of OS – analysis using RPSFT model, FAS



No. at Risk																																		
Axi-cel	180	178	177	174	170	166	161	159	157	150	147	142	136	132	125	121	117	116	111	102	91	83	71	68	60	53	44	39	32	25	21	18	14	7	5	2	2	1	0
SOC	179	177	171	166	160	145	129	117	106	94	85	76	65	56	52	49	47	45	40	37	35	31	28	23	21	17	15	13	11	9	9	6	3	2	1	1	0		

Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; mo, months; NE, not estimable; NR, not reached; OS, overall survival; RPSFT, rank-preserving structural failure time; SOC, standard of care.
Source: Locke et al. 2021[1]

Figure 22: Kaplan–Meier plot for TTNT, FAS



Key: CI, confidence interval; FAS, full analysis set; HR, hazard ratio; NE, not estimable; SOCT, standard of care therapy; TTNT, time to next treatment.
Source: Figure 21. ZUMA-7 CSR.[44]

Despite the relatively short follow-up period and small number of patients at risk, the flattening tails observed in the EFS and OS data suggest a proportion of r/r DLBCL patients at this line experience long-term remission and survival. The following sections illustrate how, in comparison to standard parametric survival approaches described in TSD 14, more flexible 'mixture cure' methodologies as described in TSD 21 better fit both these data and expectation of long-term prospects for patients responding to CAR T-cell therapy. There is also empirical support for the use of mixture cure modelling to extrapolate trial OS estimates with ZUMA-1 data (axi-cel in 3L).[82] Most importantly, validation of predicted survival estimates was performed using data from ZUMA-1 (axi-cel in 3L) and the insights of clinical experts.[29, 56]

Importantly, 56% patients on the SOC arm received subsequent CAR T-cell therapies, which are currently only available to patients in NHS England via the CDF. Aligned with NICE's position statement on this issue,[65] crossover analysis was conducted, in line with guidance from NICE DSU TSD 16.[83] This analysis attempts to remove the confounding effect of subsequent CAR T-cell therapies on SOC survival estimates (see Section B.3.3.4.1). Note that the impact of crossover only affects OS estimates, as treatment switch to subsequent lymphoma therapy was considered an event as per the definition of EFS and TTNT in the ZUMA-7 trial. Here, we present

both crossover adjusted analyses for SOC (base case, in line with NICE guidance) as well as a scenario analysis which uses the unadjusted ITT data. The latter, reflecting the state of the world where subsequent CAR T-cell therapies receive a positive recommendation following reassessment later this year. Crossover adjusted analyses were interpreted within the context of observational datasets for r/r DLBCL patients, prior to the availability of CAR T-cell therapies. Aligned with previous appraisals of CAR T-cell therapies in DLBCL, ORCHARRD and SCHOLAR-1 datasets summarised in Table 3 were used as validation of SOC OS extrapolation.

B.3.3.2. Mixture cure models

NICE TSDs 14 and 21[80, 81] discuss the potential benefits of using more flexible models when standard parametric curves do not provide a good fit to the observed data. Mixture cure models represent an alternative, more flexible approach to modelling EFS, OS and TTNT for axi-cel that can potentially account for more complex hazard functions. The use of these models can be beneficial over standard parametric models 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.

Following NICE TSDs 14 and 21[80, 81], mixture cure models were estimated using the ZUMA-7 patient-level data, for which a logistic regression with maximum likelihood estimation using R and the package `flexsurvcure` was used to model the probability that patients experienced a 'statistical cure'.[84] Associated cure fractions are presented in later sections (B.3.3.3 and B.3.3.4). Applying this survivor fraction splits the ZUMA-7 population into two groups: patients who experience a 'statistical cure' and those who do not. Mortality for 'statistically cured' (hereafter known as 'cured') patients is captured by standardised mortality ratio (SMR)-adjusted age- and gender-matched general population mortality data (derived from UK Life Table data)[85]; for patients in the latter group, risk of progression was defined by the standard parametric survival model fits to ZUMA-7 data as reported in Appendix O.

In line with previous appraisals of CAR T-cell therapies, including the 3L DLBCL appraisals, an SMR of 1.09, derived from the publication by Maurer (2014) was used in the base case to adjust for excess mortality in long-term survivors.[52, 55, 72] Assuming the same excess mortality as per the 3L indication could arguably be

considered a conservative approach, given the better prognosis of less heavily pre-treated patients.

The survival estimates for the overall population treated with a potentially curative intervention is the weighted average of the survival among the 'cured' and 'non-cured' patients. The survival function is described as:

$$S(t) = S^*(t)[p + (1-p)S_u(t)]$$

Where S(t) denotes survival probability at time t, *S** is the survival in the general population associated with background mortality, S_u is the survival probability associated with the excess disease-related risk, and *p* denotes the cure fraction.[86]

The use of mixture cure models is statistically feasible regardless of the intervention used, as the model will determine a cure fraction based on the observed trial data and exogenous mortality data. However, good practice dictates that it should only be used when a "cure" is clinically feasible.

In a recent study looking at the accuracy of different extrapolation techniques in the ZUMA-1 trial (a phase II single-arm study of patients [N=101] given axi-cel in 3L LBCL) found that mixture-cure models were the most accurate models for predicting OS over the long-term.[56] This study fitted spline, mixture cure, non-mixture and single distribution models to the 12-month ZUMA-1 data cut. Extrapolations were then evaluated against the 24-, 36- and 48-month follow-up data using a range of metrics, including AIC and BIC. Single parametric models poorly predicted long-term survival in axi-cel treated patients. Therefore, the use of mixture cure models can be justified in this case.

Mixture cure models have been used for decision making in multiple previous CAR T-cell therapy appraisals, where, similar to this appraisal, the observed data were immature and where there was clinical expectation of a plateau in PFS/OS.[52, 72, 87]

B.3.3.3. Event-free survival analysis

This section details the approaches to modelling EFS for the axi-cel and SOC treatment arms. Patients randomised to the axi-cel arm experience a clear benefit in

terms of EFS in comparison to SOC patients as demonstrated by the HR of 0.398 (95% CI: 0.308, 0.514).

Kaplan-Meier plots and Cox regression results for ZUMA-7 EFS are reported in Appendix O. Although a treatment effect for axi-cel was observed and the proportional hazards assumption seems to be valid, the parallelism between curves was lost towards the end of the log-log plot for EFS. Therefore, the proportional hazards assumption was assumed not to hold for EFS across the entire time horizon and independent survival models have been fitted for axi-cel and SOC as per the NICE DSU guidance.[80]

As specified in NICE TSDs 14 and 21[80, 81], standard parametric distributions and the mixture cure models were fit to each arm of the trial data, as well as spline models. Results for mixture cure models are described in this section, while standard parametric models and spline models are reported in Appendix O.

As described in sections B.3.3.1 and B.3.3.2, a more flexible approach to modelling EFS, mixture cure models, is considered appropriate and would better fit both these data and expectation of long-term prospects for patients responding to CAR T-cell therapy. This approach was validated by UK clinical and health economic experts.[29, 43]

Table 21 reports the cure fraction as estimated by the mixture cure models, derived based on methods described in section B.3.3.2. The cure fractions represent the proportion of patients that experience adjusted general population mortality as determined by data on the pattern of death observed in ZUMA-7. For axi-cel the predicted cure fractions were between 35% and 39% with predicted cure fractions for SOC of between 14% and 16%.

EFS projections for each mixture cure model are presented for axi-cel and SOC in Figure 23 and Figure 24, respectively, with smoothed hazard plots presented in Appendix O. AIC and BIC statistics and landmark survival estimates are presented in Table 22.

B.3.3.3.1. Base case EFS models

For both axi-cel and SOC, results show that the predicted EFS outcomes are very similar across different mixture cure models. Due to similar predictions across all models, the best-fitting models were selected in the base case analysis. These were the log-logistic and exponential models for axi-cel and SOC, respectively.

Alternative EFS curve selection is tested in the scenario analysis.

Table 21: EFS, mixture cure model, implied cure fractions

Model	Implied cure fraction	
	Axi-cel	SOC
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Key: EFS, event-free survival; SOC, standard of care.		

Figure 23: Axi-cel EFS, mixture cure models

[redacted]

Key: EFS, event-free survival; KM, Kaplan–Meier.

Figure 24: SOC EFS, mixture cure models

Key: EFS, event-free survival; KM, Kaplan–Meier; SOC, standard of care.

Table 22: EFS, mixture cure model AIC and BIC statistics and landmark survival estimates

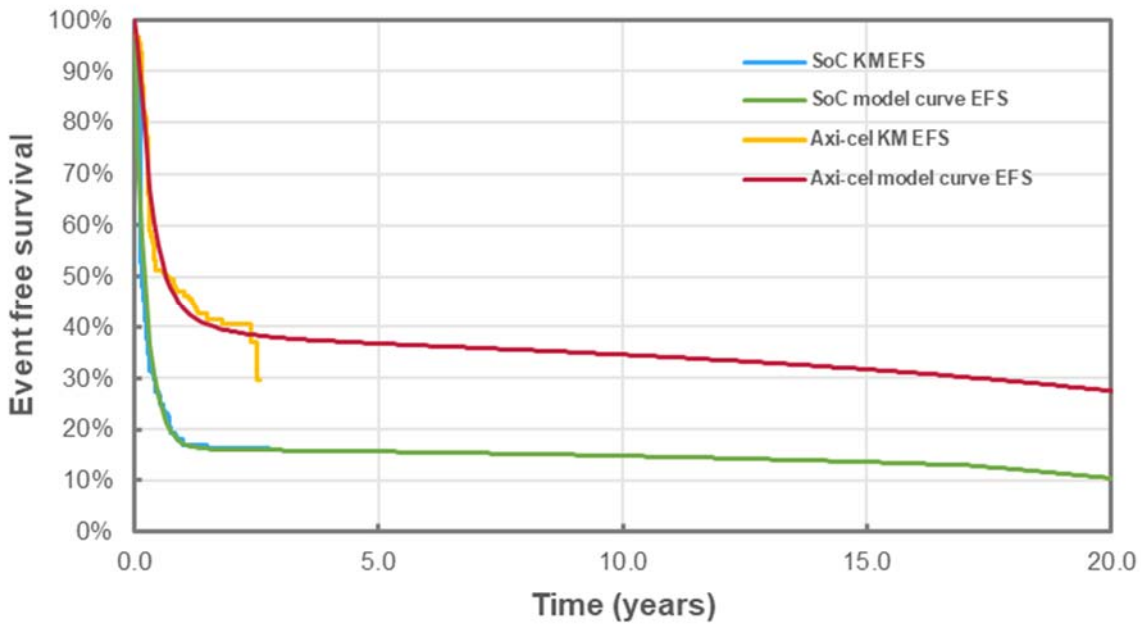
Model	AIC	BIC	Mean EFS	Median EFS	Proportion event-free at…			
					1 year	2 years	3 years	5 years
Axi-cel								
Exponential	813.98	820.36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	814.71	824.29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	814.07	823.65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	816.50	826.08	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	**795.38**	**804.96**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	809.92	822.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SOC								
Exponential	**743.56**	**749.94**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	744.44	754.00	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	745.56	755.12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	780.88	790.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	747.76	757.32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	746.34	759.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; EFS, event-free survival.
Notes: Mean and median values are provided in units of months. Best fitting model in bold.

Figure 25 shows the modelled base case EFS curves for both axi-cel and SOC.

Figure 25: Modelled base case EFS curves



Key: EFS, event free survival; KM, Kaplan-Meier; SOC, standard of care
Note: Axi-cel is modelled using log-logistic mixture-cure model; SOC is modelled using exponential mixture-cure model

B.3.3.4. Overall survival analysis

As discussed in Section B.3.3.1, the interpretation of OS based on data from ZUMA-7 is challenging as a significant proportion of patients on the SOC arm of the trial went on to receive CAR Ts as subsequent therapies. As per NICE guidance, the

model base case attempts to adjust for the impact of subsequent CAR T treatments, however for completeness, unadjusted estimates of OS for SOC patients (as per the ITT population of ZUMA-7) are also presented and reflect a state of the world where subsequent CAR T-cell therapies are routinely commissioned within NHS England.

B.3.3.4.1. Crossover analysis

A significant proportion of patients in the SOC arm of ZUMA-7 went on to receive subsequent CAR T-cell therapies: 56% are estimated to receive, which are currently only available to patients in NHS England via the CDF. Aligned with NICE's position statement on this issue,[65] crossover analysis was conducted, in line with NICE DSU TSD 16,[83] to attempt to adjust survival estimates for SOC patients to remove the confounding effect of subsequent CAR T-cell therapies. Full details of the methods and results of the crossover analyses conducted are presented in Appendix S. Different models were explored. Rank preserving structural failure time models (RPSFTM) results were summarised below. Results from Inverse Probability of Censoring Weighting (IPCW) models were reported in Appendix S. A two-stage model is applicable if there is an identifiable secondary baseline time when patients switch. A suitable secondary baseline could not be identified for this study, since patients switched to cell therapy at various different points. Therefore, the two-stage model is not appropriate in ZUMA-7 given the switching mechanism, and it is not considered.

B.3.3.4.1.1. RPSFTM

As discussed in section B.2.6.3.3, pre-specified analyses using inverse probability of censoring weights and rank preserving structural failure time models (RPSFTM) were explored as part of the ZUMA-7 analyses conducted by KITE, with RPSFT model stratified (HR: 0.58; 95% CI: 0.42, 0.81; see Figure 8). The analysis shows the sensitivity of the treatment effect (hazard ratio) as a result of treatment crossover.

The pre-specified analysis is based on recesoring switchers only. The recommendation around recensoring[88] is to present results both without any recensoring and with full recensoring of all control arm patients, not just recensoring switchers. Further RPSFTM based on censoring is explored and summarised in Table 23.

It is worth noting that there was some evidence of non-proportional hazards in the "no recensoring" and "recensoring switchers only" models, but in the full recensoring analyses the proportional assumptions held. This is likely to be because these first two models exhibit a plateau in the control arm survival after around 18 months, whereas the full recensoring analysis recensors these patients prior to 18m and no plateau is seen.

The model applies the HR based on RPSFTM recensoring (0.425) in the base case analysis.

Table 23 Summary of OS results from ITT and standard RPSFTM analyses (stratified)

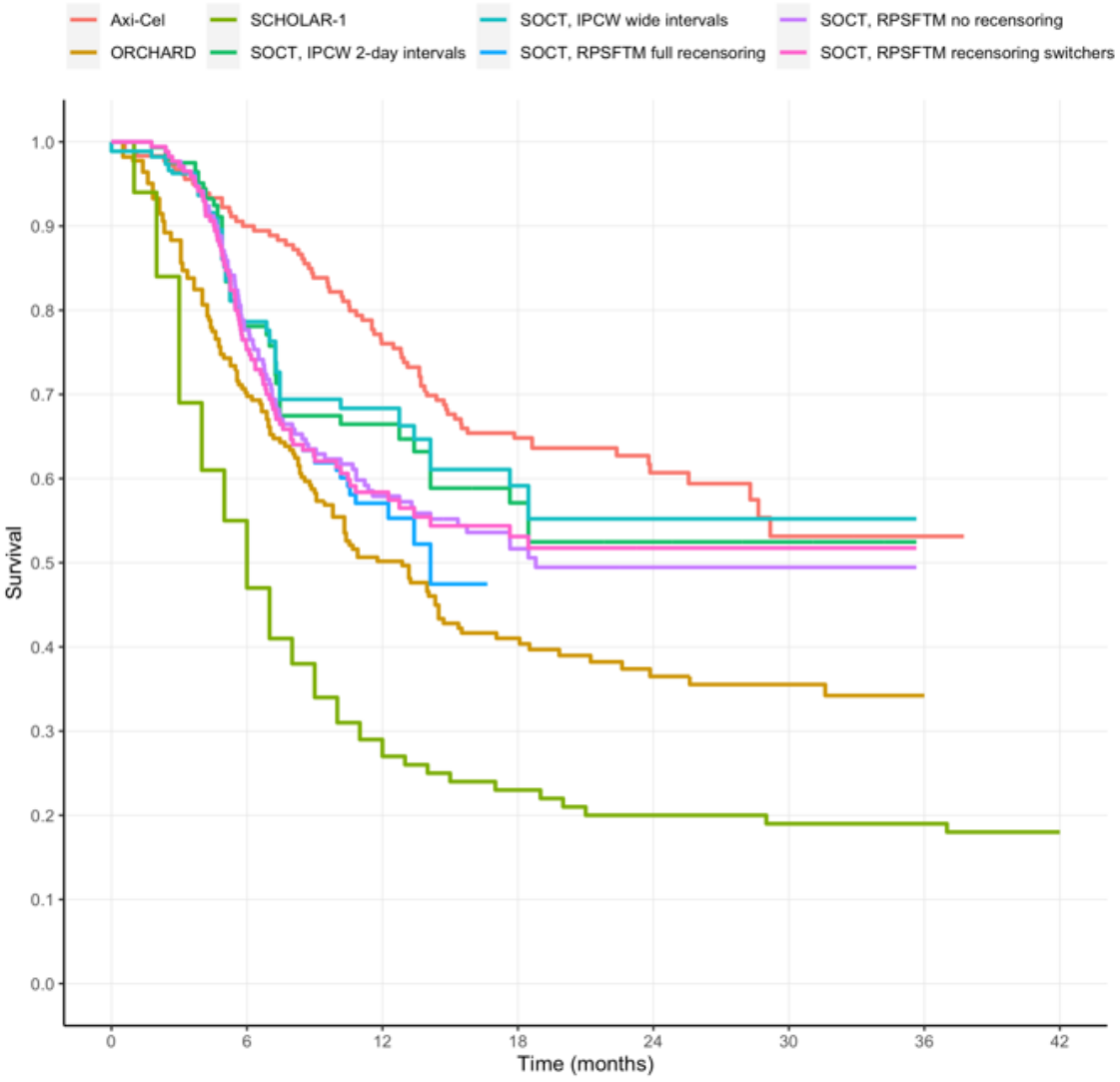
Model	Median (m), Axi-Cel	Median (m), SOC	HR (95% CI)	1-sided p-value
ITT log rank	[redacted]	[redacted]		[redacted]
ITT Cox	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM, no recensoring	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM, recensoring, full analysis	[redacted]	[redacted]	[redacted]	[redacted]
RPSFTM, recensoring switchers only	[redacted]	[redacted]	[redacted]	[redacted]
ITT log rank	[redacted]	[redacted]		[redacted]

Key: NR, not reached; SOC, standard of care

A summary of the crossover adjusted Kaplan–Meier data for SOC is presented in Figure 26. Due to the inherent uncertainty in all methods for adjusting for crossover, it was important to validate analysis outcomes through external datasets and clinical expert consultation. The ORCHARRD and SCHOLAR-1 provide outcomes data for r/r DLBCL patients in the absence of CAR T-cell therapy. As summarised in Table 3, there are differences in the patient and study characteristics of ORCHARRD and

SCHOLAR-1 compared with ZUMA-7. Therefore, the adjusted OS from ZUMA-7 crossover analysis would not completely align with observation from ORCHARRD and SCHOLAR-1. This is further confirmed by clinical experts that the expected OS trend among DLBCL patients eligible for 2L treatments is likely to be between the observation from ORCHARRD and SCHOLAR-1.[29, 43]

Figure 26: OS estimates adjusted for crossover, compared to external datasets



Key: IPCW, inverse-probability-of-censoring weighting; RPSFTM, rank preserving structural failure time model; SOCT, standard of care therapy.

B.3.3.4.2. Mixture cure models

As described in section B.3.3.1 and B.3.3.4.1, the model base case attempts to adjust for the impact of subsequent CAR T treatments, to reflect the current practice

where subsequent CAR T-cell therapies are not routinely commissioned within NHS England. Only the crossover (base case) analysis results are reported in this section. Results from ITT population are described in Appendix Q.

This section details the approaches to modelling OS for the axi-cel and SOC treatment arms. Kaplan-Meier plots and Cox regression results for ZUMA-7 OS are reported in Appendix O, showing that the proportional hazards assumption was not held for OS. Independent survival models have been fitted for axi-cel and SOC as per the NICE TSD14.[80]

Following the guidance from NICE TSDs 14 and 21,[80, 81] standard parametric distributions, mixture cure models and spline models were fit to each arm of the trial data. Results for mixture cure models are described in this section, while standard parametric models and spline models are reported in Appendix O.

As described previously in sections B.3.3.1 and B.3.3.2, mixture cure models is considered appropriate and would better fit both these data and expectation of long-term prospects in OS for patients responding to CAR T-cell therapy. This approach was validated by clinical and health economic experts.[29, 43 29]

The cure fraction, reported in Table 24, is derived based on methods described in section B.3.3.2. For axi-cel the predicted cure fractions were between 24% and 54% and predicted cure fractions for SOC between 32% and 49%.

OS extrapolation for each mixture cure model are presented for axi-cel and SOC in Figure 27 and Figure 28, respectively, with smoothed hazard plots presented in Appendix O. AIC and BIC statistics and landmark survival estimates are presented in Table 25.

B.3.3.4.3. Base case OS models

For both axi-cel and SOC, the log-logistic, generalized gamma and log-normal models provide the best statistical fit based on AIC/BIC.

As described in Section B.3.3.4.1, clinical experts expected that in the absence of CAR T-cell therapies, SOC OS would likely be falling somewhere between ORCHARRD (as presented) and SCHOLAR-1, with a survival plateau similar to that

of EFS at ~20%. Clinical experts further indicated that SOC OS and EFS are likely to converge by 5 years.[29] Table 25 and Figure 28 show that at 5 years, the predicted SoC OS by two of the best fitting models (log-logistic and log-normal) would not reflect this clinical expectation. Therefore, log-logistic and log-normal models are not considered due to lack of clinical plausibility.

It is worth noting that the base case analysis described in this section and presented in Figure 28 has taken into account the crossover adjustment in the SOC arm, as described in section B.3.3.4.1. The model base case applied the HR based on the RPSFTM full recensoring analysis (HR=0.425). This is different to the pre-specified analysis from ZUMA-7 (see section B.2.6.3.3, B.3.3.4.1.1 and Figure 8) where the analysis is for RPSFTM, recensoring with switchers only (HR=0.58). The crossover adjustment is not relevant for the axi-cel arm.

For axi-cel arm, published evidence reports sustained plateau in long-term OS. Based on the most recent ZUMA-1 data, 44% of patients treated with axi-cel at 3L were still alive 4 years later, supporting the emerging plateau in ZUMA-7 OS.[56]

There is also empirical support for the use of mixture cure modelling to extrapolate trial OS estimates. A recent study using five years' worth of follow-up data from ZUMA-1 demonstrated that cure models, when fitted to 'immature' OS data, most accurately and reliably predicted long-term survival of axi-cel treated DLBCL patient versus spline based and standard parametric models, the latter of which substantially underestimated lifetime survival. [82]

In the base case, generalized gamma mixture cure model is selected for axi-cel as it provided the best statistical fit and had the most clinical plausibility and the HR relative to axi-cel is used in the SOC arm.

Alternative OS curve selection is tested in the scenario analysis.

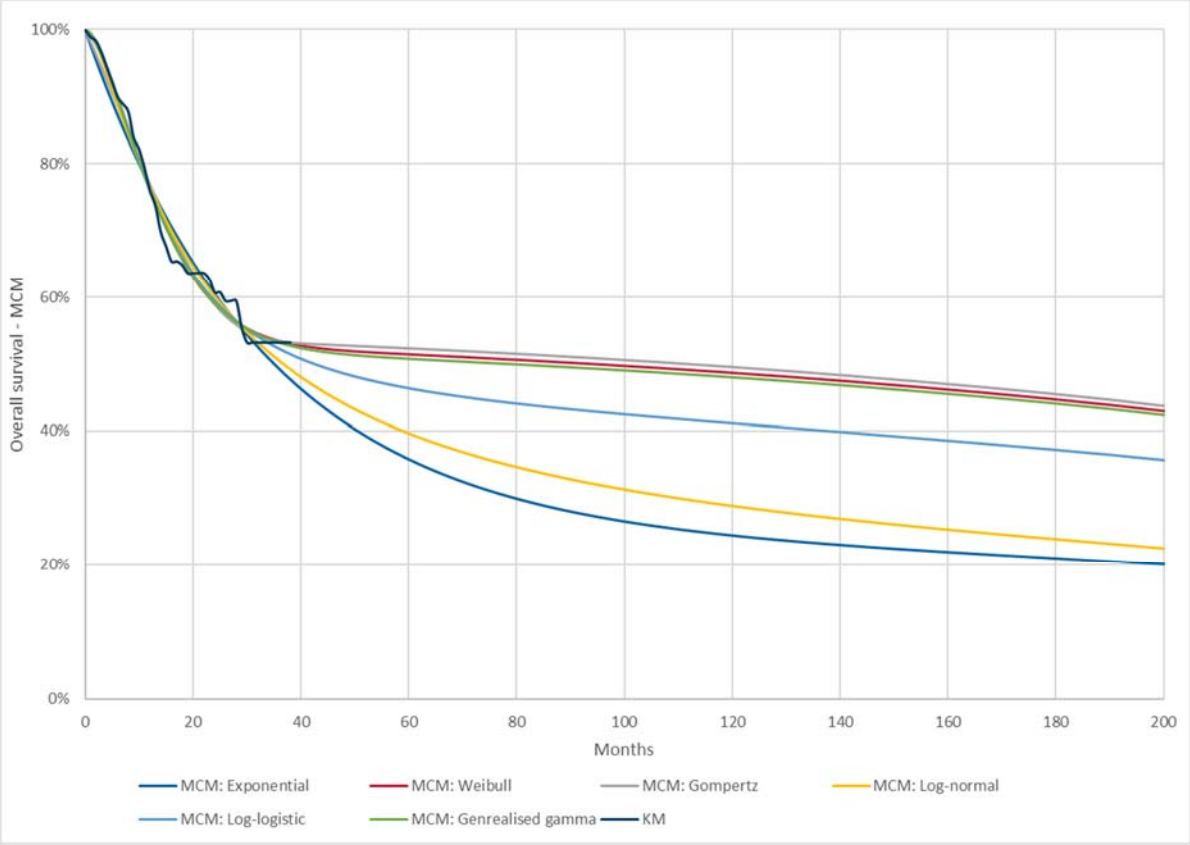
Clinicians agreed that despite the crossover adjustment, the modelled survival for the SOC arm predicted optimistic outcomes for patients who will not receive subsequent cell therapy in third line setting. In order to address this, a separate scenario analysis was also included to explore SOC OS and EFS converging at 5 years.

Table 24 : Axi-cel OS, implied cure fractions

Model	Implied cure fractions	
	Axi-cel	SOC
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]

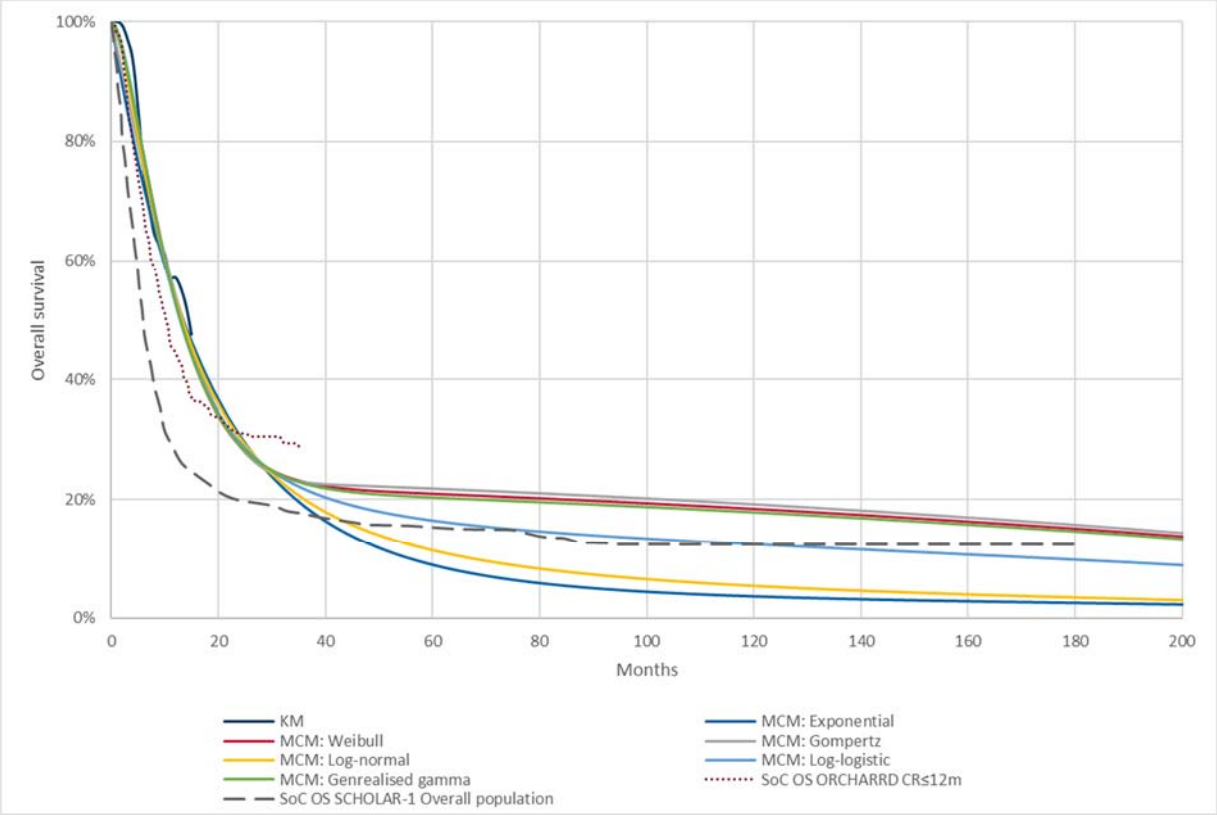
Key: NA, not applicable; SOC, standard of care
Note: Implied cure fraction for SOC is based on ITT analysis and therefore not relevant in the base case as crossover adjusted curve is selected.

Figure 27 : Axi-cel OS, mixture cure models



Key: KM, Kaplan–Meier; OS, overall survival.

Figure 28 : SOC OS, mixture cure models, crossover



Key: CR, complete response; KM, Kaplan–Meier; OS, overall survival; SOC, standard of care. .
Notes: ORCHARRD data presented for population with the CR≤ 12 months

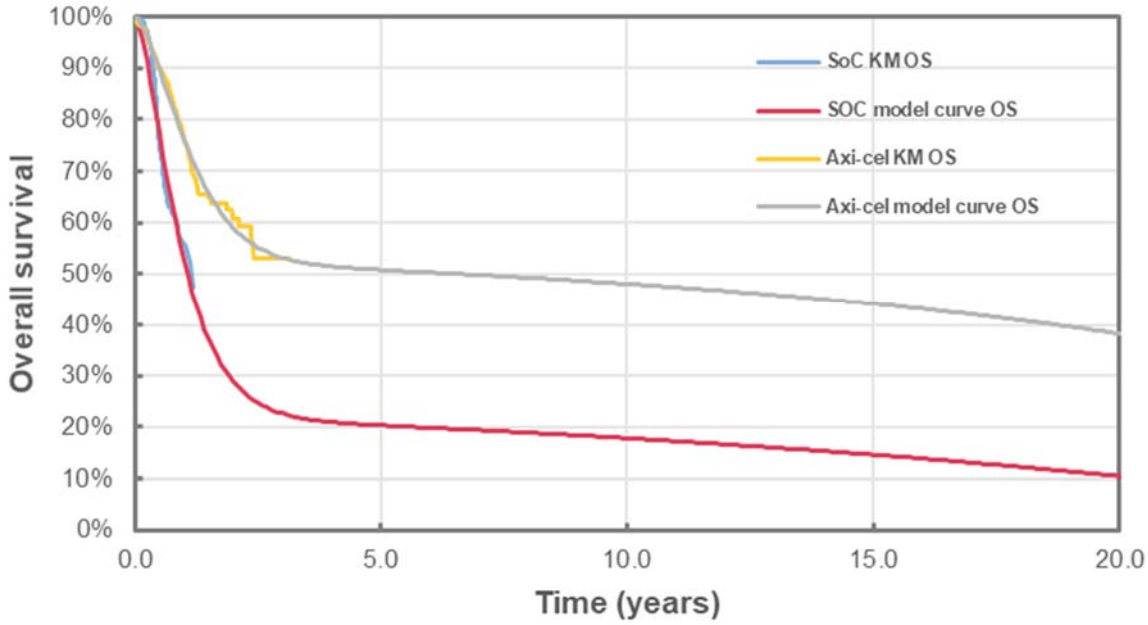
Table 25: OS mixture cure model AIC and BIC statistics and landmark survival estimates, crossover

Model	AIC	BIC	Mean OS	Median OS	Proportion alive at…			
					1 year	2 years	3 years	5 years
Axi-cel								
Exponential	705.60	711.98	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	700.22	709.79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	704.28	713.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	702.73	712.31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	700.00	709.58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	**702.15**	**714.92**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC								
Exponential	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	**N/A**	**N/A**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Published OS for r/r DLBCL patients in the absence of CAR T-cell therapy								
SOC OS ORCHARRD CR≤12m	-	-	-	-	45%	31%	28%	-
SOC OS SCHOLAR-1 Overall population	-	-	-	-	29%	20%	18%	16%

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; CR, complete response; OS, overall survival; SOC, standard of care.
Notes: Mean and median values are provided in units of months. Best fitting model in bold. No AIC or BIC reported for SOC as landmark results are based on hazard ratio applied to axi-cel arm.

Figure 29 shows the modelled base case curves for OS in the axi-cel and SOC arms.

Figure 29: Modelled base case overall survival curves



Key: KM, Kaplan–Meier; OS, overall survival; SOC, standard of care
Note: Axi-cel is modelled using the generalized gamma mixture-cure model; SOC is modelled using the crossover adjusted curve

B.3.3.5. TTNT analysis

This section details the approaches to modelling Time to Next Treatment (TTNT) for the axi-cel and SoC treatment arms. TTNT curves were used in the model to determine the time at which patients receive subsequent therapy costs.

As per the approach for OS and EFS, Kaplan-Meier plots and Cox regression results for TTNT are reported in Appendix O. The parallelism between curves was lost at several timepoints of the log-log plot for TTNT. Therefore, the proportional hazards assumption was assumed not to hold for TTNT across the entire time horizon and independent survival models have been fitted for axi-cel and SoC as per the NICE DSU guidance.[80]

Standard parametric distributions and the mixture cure models were fit to each arm of the trial data. Spline models were not explored. Results for mixture cure models are described in this section, while standard parametric models are reported in Appendix O.

Mixture cure models for axi-cel and SoC TTNT are presented alongside ZUMA-7 TTNT Kaplan–Meier data in Figure 30 and Figure 31, respectively, with cure fractions presented in Table 26. Smoothed hazard plots are presented in Appendix O. AIC/BIC statistics and landmark estimates are presented in Table 27.

B.3.3.5.1. Base case TTNT models

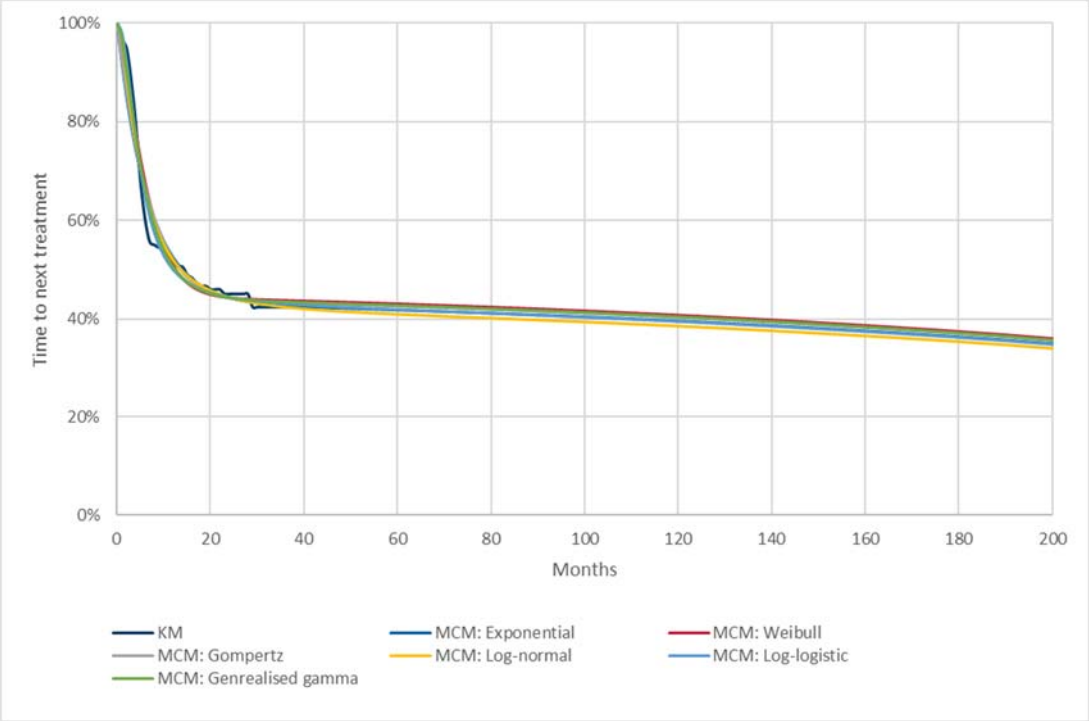
For both axi-cel and SOC, results show that the predicted TTNT overtime are similar across different mixture cure models. Due to similar predictions across all models, the best-fitting models were selected in the base case analysis. The mixture cure models using a Loglogistic function provided the best fit for both axi-cel and SoC. The long-term TTNT extrapolations aligned with feedback from clinical experts.

Alternative TTNT curve selection is tested in the scenario analysis.

Table 26: Axi-cel TTNT, implied cure fractions

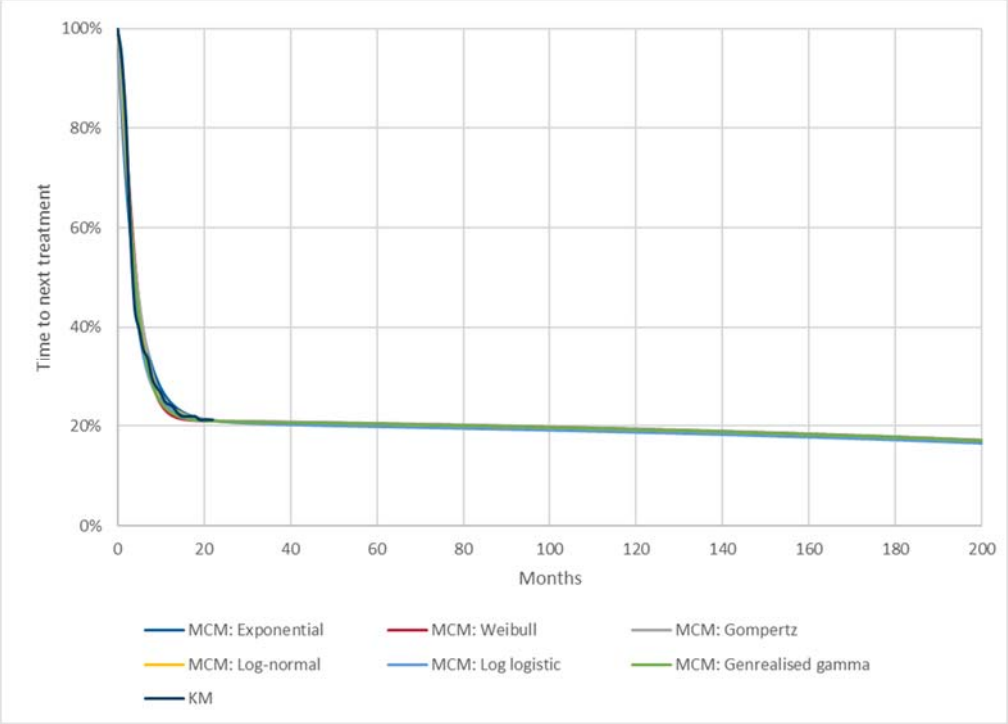
Model	Implied cure fraction	
	Axi-cel	SoC
Exponential	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Key: NA, not applicable; TTNT, Time to Next Treatment; SOC, standard of care.		

Figure 30 : Axi-cel TTNT, mixture cure models



Key: KM, Kaplan–Meier; TTNT, time to next treatment.

Figure 31 : SOC TTNT, mixture cure models



Key: KM, Kaplan–Meier; SOC, standard of care; TTNT, time to next treatment.

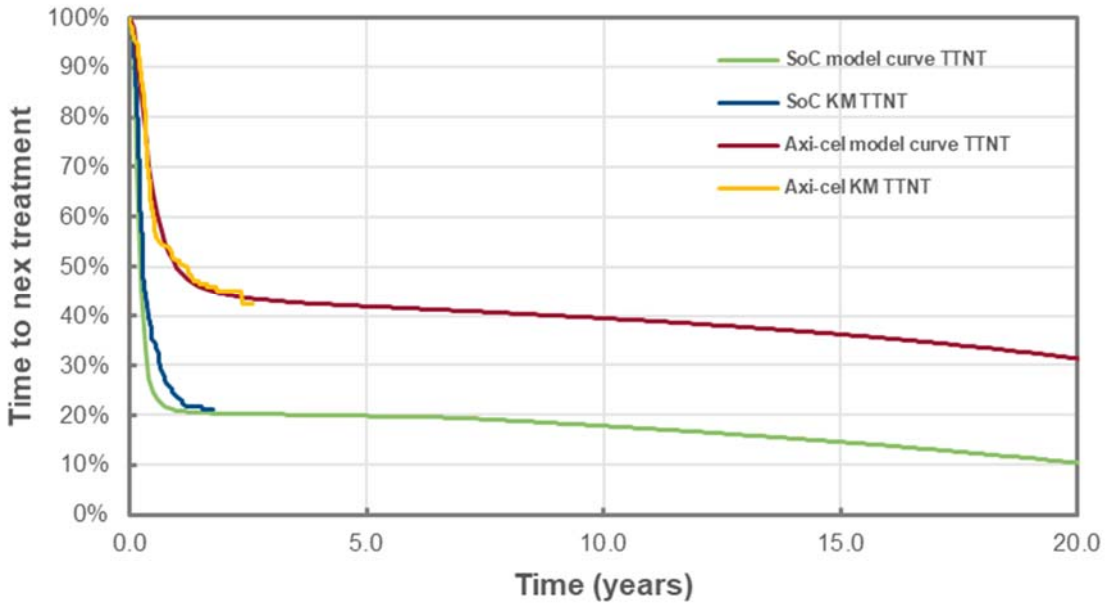
Table 27: TTNT mixture cure model AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Mean TTNT	Median TTNT	Proportion not on next treatment at…			
					1 year	2 years	3 years	5 years
Axi-cel								
Exponential	798.24	804.62	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	790.86	800.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	799.53	809.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	791.85	801.43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	**778.58**	**788.16**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	787.79	800.56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC								
Exponential	821.97	828.35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	801.88	811.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	818.26	827.82	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	798.30	807.86	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	**784.48**	**794.04**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	793.74	806.49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTNT, Time to next treatment
Notes: Mean and median values are provided in units of months. Best fitting model in bold.

Figure 32 shows the modelled TTNT base case curves for both axi-cel and SOC.

Figure 32: Modelled base case TTNT curves



Key: KM, Kaplan–Meier; SOC, standard of care; TTNT, time to next treatment.
Note: Axi-cel is modelled using the log-logistic mixture-cure model; SOC is modelled using the log-logistic mixture-cure model

B.3.3.6. General population mortality

To ensure the hazard of death in the r/r DLBCL population was never less than that of the general population, background mortality was incorporated into the model based on age and sex matched general population mortality estimates from UK National Life Tables published by the Office for National Statistics.[85] The choice of pre-2020 mortality rates was intentional, to ensure that excess mortality associated with COVID-19 was not captured, thus reflecting typical mortality rates for the population receiving axi-cel.

As discussed throughout section B.3.3, an SMR of 1.09 was applied, to general population mortality estimates, to reflect excess mortality experienced by long-term survivors. This approach is aligned with previous technology appraisals for CAR T-cell therapies.[52, 72]

B.3.4. Measurement and valuation of health effects

Section B.1.3.3 describes the negative impact of r/r DLBCL on patients' quality of life.

B.3.4.1. Health-related quality of life data from clinical trials

Health-related quality of life (HRQL) data were collected in the ZUMA-7 QoL analysis set using both the EORTC QLQ-C30 and the EQ-5D-5L. The NICE reference case stipulates that the EQ-5D is the preferred measure of HRQL in adults[76], and as such the EQ-5D results were used to derive utility values in the event-free state of the cost-effectiveness model.

In the axi-cel arm of ZUMA-7, data were collected at screening, the first day of conditioning chemotherapy, the day of axi-cel administration, and Months 2, 3, 5, 9, 12, 15, 18, 21 and 24 after randomisation. In the SOC arm, the data were collected at screening, approximately 5 days after randomisation (during the first cycle of salvage chemotherapy), at the time of disease assessment (assumed to be approximately Day 50/Month 2), the day of transplant for those receiving auto-SCT, and then Day 100 and Day 150 post-randomisation (Months 3 and 5) as well as Months 9, 12, 15, 18, 21 and 24.

Of the 359 patients enrolled in the ZUMA-7 study, 165 in the axi-cel arm and 131 in the SOC arm had baseline HRQL responses and ≥1 follow-up measure and were included for analysis in the ZUMA-7 QoL analysis set.

The health state utility values used in the economic analysis (derived from ZUMA-7 data in the event-free state) are presented in Section B.3.4.5. Notably, patients in the QoL analysis set of ZUMA-7 were not mandated as per the protocol to complete patient reported outcome questionnaires after an EFS event, and as such, data is sparse and potentially biased, introducing both statistical and clinical uncertainty. Details on the sparsity of the data is highlighted in the PRO report (in Appendix T). Therefore, for the base case, the utility for the post-event state is assumed to be equal to the utility derived from the JULIET trial data for tisagenlecleucel in R/R LBCL, as applied in the NICE submission following a mapping exercise.[52, 72] Alternative utility values sourced from the ZUMA-1 trial are explored in scenario analysis.

B.3.4.2. Mapping

As described in Section B.3.4.1, the EQ-5D-5L questionnaire was administered to patients in the ZUMA-7 trial. As recommended by NICE in their updated position statement in October 2019[77], the crosswalk algorithm developed by van Hout et al. (2012) was used to convert EQ-5D-5L scores into EQ-5D-3L utility values.[89]

The resulting EQ-5D-3L utility value of 0.785 was used in the model base case for the event-free health state. Furthermore, utility values for the event-free state were segregated further based on treatment status. This resulted in an "on-treatment" utility of 0.772 for the SOC arm, and for axi-cel patients a lower utility of 0.780. These were derived according to the following criteria:

- Axi-cel on treatment, pre-event: All visits that were after the axi-cel treatment start date and prior to the axi-cel treatment end date or date of event (whichever is sooner)
- SOC on treatment, pre-event: All visits that were after the SOC start date and prior to the SOC treatment end date or date of event (whichever is sooner).

Applying on-treatment specific utility values was explored in a scenario analysis, where they were applied for one month in the axi-cel arm to account for the fact that patients have recently relapsed from first-line treatment (average time between leukapheresis and infusion with axi-cel), and three months in the SOC arm. This approach has been taken in previous models for other CAR T-cell therapies in a third-line setting.[52, 72] Health state utilities in the base case are summarised in Section B.3.4.5.

B.3.4.3. Health-related quality of life studies

In line with the search for economic evaluations (described in Section B.3.1), a systematic search was conducted to identify HRQL evidence in adults with r/r DLBCL after first-line therapy only. The study identification process, search strategies and a description of the included studies is provided in Appendix H.

No studies that reported health state utility values for the population of interest were identified in the search for HRQL evidence, therefore insights were drawn from the

two previous completed NICE single technology appraisals in r/r DLBCL (TA559 and TA567).[52, 72]

In TA559, health state utility values were based on EQ-5D data collected in a safety management cohort of the ZUMA-1 trial (n = 34, with 87 observations) were used in the base case analysis. In TA567, health state utility values were derived from SF-36 data collected in the JULIET study, mapped to EQ-5D. In both TA559 and TA567, health state utilities taken from NICE TA306 were tested in the scenario analysis.

Table 28 presents health state utility values sourced from prior NICE appraisals in patients with r/r DLBCL. The utility values reported in TA559 from the ZUMA-1 study are explored in a scenario analysis.

Table 28: Health state utility values from prior NICE appraisals

NICE TA	Progression free	Progressed disease	Source
TA306 – pixantrone; mean (CI)	0.76 (0.70–0.82)	0.68 (0.6–0.7)	TA178 assessment group
TA559 – axi-cel ; mean (SE)	0.72 (0.03)	0.65 (0.06)	ZUMA-1 EQ-5D
TA567 – tisagenlecleucel; mean (SE)	0.83 (NR)	0.71 (NR)	JULIET EQ-5D (mapped from SF-36)
Key: CI, confidence interval; NR, not reported; SE, standard error; TA, technology appraisal.			

B.3.4.4. Adverse reactions

B.3.4.4.1. Adverse event data

As reported in NICE TA677, clinicians have become increasingly comfortable with toxicity management for CAR T-cell therapies.[87] However, following treatment with axi-cel, it is acknowledged that there may still be short-term impactful Aes. Table 29 presents Grade 3+ Aes that occurred in ≥10% of patients for axi-cel and SOC captured in the cost-effectiveness model, sourced from the ZUMA-7 study.

Table 29: Adverse event data (Grade 3+, ZUMA-7)

Adverse event	Axi-cel	SOC
CRS	[redacted]	[redacted]
Neurologic events	[redacted]	[redacted]
B-cell aplasia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]
Key: CRS, Cytokine release syndrome; SOC, standard of care.		

B.3.4.4.2. Adverse event disutility

Adverse events associated with axi-cel and SOC are expected to occur in the short-term after initial treatment, therefore a one-off QALY decrement is applied in the first model cycle.

Utility decrements for anaemia, febrile neutropenia, neutropenia, platelet count decrease and thrombocytopenia were obtained from the pixantrone submission to NICE.[71] For patients experiencing CRS, it is assumed that patients have a quality of life of zero (i.e. the utility decrement is set to be the negative value of the event-free health state). This is in line with the York study[90], which was the method adopted for the third-line DLBCL axi-cel NICE submission (TA559).[52] Disutilities associated with the remaining AEs were not identified, therefore for each of these AEs, a disutility equal to the maximum of the identified non-CRS AE disutilities was assumed. This is in line with the pixatrone submission to NICE (TA306)[71] as well as the third-line DLBCL axi-cel NICE submission (TA559).[52] The duration of CRS and neurologic events was obtained from ZUMA-7, whilst the remaining duration of adverse events were sourced from ZUMA-1 patient level data, in line with the axi-cel third-line

DLBCL NICE submission (TA559).[52] Table 30 presents the AE disutilities and durations, and their respective data sources.

Table 30: Adverse event disutilities

Adverse event	Utility decrement	Source	Duration (days)	Source
CRS	-0.78	Set to be equal to the utility value in the progression-free health state. Assumption as in the York study.	8.3	ZUMA-7
Neurologic events	-0.15	Assumed equal to the maximum of other, non-CRS AE disutilities in the absence of other data	40.0	
B-cell aplasia	0.00	Assumed to equal zero in line with previous CAR T submissions and York report.[90]	N/A	

Adverse event	Utility decrement	Source	Duration (days)	Source
Anaemia	-0.12	Swinburn et al., 2010[91]	14.1	Analysis of patient-level data from ZUMA-1, in line with NICE TA559[52]
Neutropenia	-0.09	Nafees et al., 2008[92]	46.9	
Hypotension	-0.15	Assumed equal to the maximum of other, non-CRS AE disutilities in the absence of other data	5.3	
Neutrophil count decreased	-0.15		17.2	
Platelet count decreased	-0.11	Tolley et al., 2013[93]	50.5	
White blood cell count decreased	-0.15	Assumed equal to the maximum of other, non-CRS AE disutilities in the absence of other data	40.2	
Hypophosphatemia	-0.15		15.6	
Thrombocytopenia	-0.11	Tolley et al., 2013[93]	63.3	
Lymphocyte count decreased	-0.15	Assumed equal to the maximum of other, non-CRS AE disutilities in the absence of other data	64.0	
Febrile neutropenia	-0.15		6.0	
Encephalopathy	-0.15		9.4	
Key: CRS, Cytokine release syndrome; SOC, standard of care.				

B.3.4.5. Health-related quality of life data used in the cost-effectiveness analysis

As described in Section B.3.4.1 and B.3.4.2, utility values for the event free states are derived using trial-based EQ-5D-5L scores mapped to EQ-5D-3L values. As PRO questionnaires were not administered in ZUMA-7 post-event, it is assumed the progressed disease utility value from the JULIET study (reported in TA567) is applicable to the post-event state (0.710). The progressed-disease utility was used as this health state represents all post-event patients including those that have progressed after 3L treatment. ZUMA-1 utility data were also considered, however given the small number of post-progression observations (<5% of the sample with data), JULIET data were preferred. This is aligned with ERG feedback on TA559.[52]

In line with previous appraisals of CAR T-cell therapies, it is assumed that the health-related quality of life for long-term survivors, remaining event free (for both SOC and axi-cel) would eventually return to that of the age- and gender-matched general population values, reflective of the fact that patients would be effectively cured. Historically, there has been debate around when this may occur. The company submission for TA559 assumed this would happen after 2 years, however this was challenged by the ERG.[52] In this appraisal we assume a more conservative estimate of 5 years, in line with latest committee preferences for CAR T-cell therapies.[87]

General population utility estimates, applied to long-term survivors remaining event free after 5 years, were obtained from national publications for the UK, as shown in Table 31.[94]

Table 31: UK general population utility[94]

Age range	Males	Females
55 to 64	0.833	0.804
65 to 74	0.810	0.760
75+	0.753	0.692

A summary of the utility values applied in the model base case is presented in Table 32.

Table 32: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission	Justification
Health state utility values				
Event free	0.785 (0.01)	0.765 to 0.805	B.3.4.1 and B.3.4.2	The use of HRQL data collected directly from patients using the EQ-5D is consistent with the NICE reference case. Furthermore, mapping from the EQ-5D-5L to the EQ-5D-3L using the algorithm developed by van Hout et al. (2012) is consistent with the latest NICE position statement[77, 89]
Event free, after 5 years	Age-matched general population	N/A	B.3.4.5	In line with prior appraisals of CAR T-cell therapies, and in line with clinical opinion, it is assumed patients who survive beyond five years are considered effectively cured[87]
Post event	0.710 (0.01)	0.685 to 0.735	B.3.4.3	As PRO questionnaires were not administered in ZUMA-7 post-event, it is assumed the progressed disease utility value from the JULIET study (reported in TA567) is applicable to the post-event state[72]

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission	Justification
Utility decrements				
CRS	-0.780 (-0.012)	0.756-0.804	B.3.4.4	The same approach as TA559 was used for disutilities. It was assumed that a utility of zero was applicable to those experiencing CRS, in line with the York report.[90] Where disutilities could not be sourced, a disutility equal to the maximum of the non-CRS adverse event disutilities was assumed.
Neurologic events	-0.150 (-0.03)	0.091-0.209		
B-cell aplasia	0.000 (0.000)	0.000		
Anaemia	-0.120 (-0.024)	0.073-0.167		
Neutropenia	-0.090 (-0.018)	0.055-0.125		
Hypotension	-0.150 (-0.03)	0.091-0.209		
Neutrophil count decreased	-0.150 (-0.03)	0.091-0.209		
Platelet count decreased	-0.110 (-0.022)	0.067-0.153		
White blood cell count decreased	-0.150 (-0.03)	0.091-0.209		
Hypophosphatemia	-0.150 (-0.03)	0.091-0.209		
Thrombocytopenia	-0.110 (-0.022)	0.067-0.153		
Lymphocyte count decreased	-0.150 (-0.03)	0.091-0.209		
Febrile neutropenia	-0.150 (-0.03)	0.091-0.209		
Encephalopathy	-0.150 (-0.03)	0.091-0.209		

Key: DLBCL, diffuse large B-cell lymphoma; EFS event-free survival; HRQL, health-related quality of life; N/A, not applicable; PRO, patient reported outcomes; SOC standard of care; TA, technology appraisal.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

B.3.5.1. Cost and resource use estimates identified in the literature

A systematic search for published healthcare costs and resource use studies for patients with early relapsed or primary refractory DLBCL was conducted alongside the search for published cost-effectiveness studies as detailed in B.3.1 and Appendix G. Full details of the search methods and results are presented in Appendix I.

As with the cost-effectiveness model structure, costs and resource use inputs are largely aligned with prior single technology appraisals of CAR T-cell therapies in DLBCL (TA559 and TA567).

B.3.5.2. Intervention and comparators' costs and resource use

B.3.5.2.1. Axi-cel costs and resource use

For axi-cel, treatment-related costs included in the model are

- Leukapheresis
- Bridging therapy
- Conditioning chemotherapy
- Axi-cel acquisition costs
- Axi-cel infusion and monitoring (hospitalisation)

As described in Section B.2.4.1, in the ZUMA-7 FAS population, [redacted] patients were randomised to the axi-cel arm. Subsequently, [redacted] underwent leukapheresis, [redacted] received bridging therapy, [redacted] received conditioning therapy and [redacted] received axi-cel treatment. A further [redacted] received axi-cel re-treatment.

All axi-cel related costs included in the analysis have been scaled according to these proportions.

Leukapheresis costs

The cost of leukapheresis was obtained from NHS reference costs 2019/2020 and is based on the cost for peripheral blood stem cell harvest and bone marrow harvest for all HRGs. Table 33 details the costs of leukapheresis applied in the model. As discussed previously, [redacted] of patients on the axi-cel arm of ZUMA-7 received leukapheresis, therefore leukapheresis costs were weighted according to this proportion.

Table 33: Unit costs of leukapheresis

Currency code	Setting	Currency description	Cost (SE)
SA43Z	Total HRGs	Peripheral blood stem cell harvest	£1,904.30
SA18Z	Total HRGs	Bone Marrow Harvest	£2,993.81
Total weighted average cost (inflated to 2021)			£2,013.54 (£100.68)
Key: SE, standard error.			

Bridging therapy and conditioning chemotherapy costs

In ZUMA-7, patients were permitted to receive bridging therapy after leukapheresis and up to 5 days before the administration of axi-cel. Bridging therapy was considered for any patient but particularly for those with high disease burden at screening, to maintain stable disease during the manufacturing process.

Bridging therapy in ZUMA-7 consisted of corticosteroid treatment (for example, dexamethasone at a dose of 20 to 40 mg or equivalent, either orally or IV daily for 1–4 days). The choice of corticosteroid and dosing was based on clinical judgement. As discussed previously [redacted] of patients on the axi-cel arm of ZUMA-7 received bridging therapy. On consultation, clinical experts explained that the proportion of patients expected to receive bridging therapy in clinical practice in NHS England was closer to two thirds. Furthermore, rather than oral dexamethasone given in ZUMA-7, it is likely that one or two cycles of R-GDP chemotherapy would be administered in an outpatient setting. Therefore, the model base case was amended to reflect UK

expert opinion, and two thirds of patients received two cycles of R-GDP in an outpatient setting.[29]

Table 34: Bridging therapy cost calculations

Therapy	Dose and route	Doses/ cycle	Drug cost per dose	Admin cost per cycle
R-GDP	See Table 37		£1,447.25	£1,565.12
Total cost (for two cycles)				£6,024.73
Key: R-GDP, rituximab with gemcitabine, dexamethasone, and cisplatin.				

As described in Section B.1.2, patients received lymphodepleting chemotherapy consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous on the 5th, 4th and 3rd day before axi-cel infusion. This is aligned with the anticipated licence for axi-cel. The costs for conditioning chemotherapy were taken from the electronic market information tool (eMIT). In line with previous CAR T-cell therapy appraisals, conditioning chemotherapy was assumed to be administered in the inpatient setting, costs for which are documented in Section B.3.5.2.2. Unit costs for conditioning and bridging therapies are presented in Table 35 with dosing assumptions and final costs presented in Table 36. Final costs were weighted by the proportions receiving bridging and conditioning in ZUMA-7 as documented above.

Table 35: Unit costs conditioning chemotherapy

Therapy	Strength	Form	Pack size	Cost per vial	Source
Cyclophosphamide	500 mg	Vial	1	£8.23	eMIT (2020)
	1000 mg	Vial	1	£13.55	eMIT (2020)
	2000 mg	Vial	1	£27.50	eMIT (2020)
Fludarabine	50 mg	Vial	1	£20.28	eMIT (2020)
Key: eMIT, electronic market information tool.					

Table 36: Conditioning chemotherapy cost calculations

Therapy	Dose and route	Doses/ cycle	Drug cost per dose	Admin cost per cycle*
Fludarabine	30 mg/m^2 IV	3	£29.97	£1,404.35
Cyclophosphamide	500 mg/m^2 IV	3	£16.83	
Total cost			£140.38	

Key: Admin, administration; IV, intravenous.
Notes: 1 x simple outpatient and 2 x subsequent elements of chemotherapy cycle assumed (see Table 38).

Axi-cel acquisition costs

As described in Section B.1.2, axi-cel is administered as a single infusion. The list price of axi-cel is [redacted] including shipping, engineering and generation of the CAR T-cells. Within NHS England, there is a simple PAS discount of [redacted] on the list price of axi-cel, therefore the net cost for a single infusion is [redacted]

As explained above, only [redacted] patients randomised to the axi-cel arm [redacted] went on to receive the axi-cel infusion. Therefore, acquisition costs were weighted accordingly. The final mean acquisition cost applied in the model is [redacted]

A further [redacted] patients on the axi-cel arm of ZUMA-7 received axi-cel re-treatment. Retreatment with axi-cel is not expected to occur in clinical practice in England and does not form part of the expected marketing authorisation therefore costs of axi-cel retreatment are not included.

Axi-cel infusion and monitoring (hospitalisation costs)

Patients receiving CAR T-cell therapies typically require an inpatient stay for ongoing monitoring and management of any potential Aes. The average length of stay for axi-cel patients in ZUMA-7 was [redacted] days.

The cost for the first [redacted] days is assumed to be £7,528.93 based on the values obtained from NHS Reference Costs 2019/20 [SA31A-F [Elective Long Stay] and inflated using the NHS Cost Inflation Index. Given CAR-T hospital stays are typically longer than reported by hospital episode statistics (HES), the length of stay for HES

was estimated by dividing the elective inpatient stay cost (£7,303.97) by the elective inpatient excess bed day cost (£454.13), which resulted in a mean length of hospital stay of 16.08. Therefore, inpatient hospital stay was calculated as £7,528.93, with [redacted] subsequent days costed using £468.12 (based on £454.13 and inflated using the NHS Cost Inflation Index). The total cost for hospitalisation is therefore [redacted]

B.3.5.2.2. Standard of care costs and resource use

As detailed in Section B.3.2.3.2, the SOC arm in the model comprises a basket of treatments, as administered to patients in the control arm of ZUMA-7.

SOC treatment regimens included are R-ICE, R-ESHAP, R-GDP or R-DHAP, followed by high-dose therapy (BEAM) and auto-SCT in responders.

Among the patients in the SOC group in ZUMA-7, 168 patients received platinum-based chemotherapy, with 84 (50%) receiving R-ICE, 5 (3%) receiving R-ESHAP, 42 (25%) receiving R-GDP and 37 (22%) receiving R-DHAP/R-DHAX. The model applies costs for each regimen, multiplied by their expected distribution of use in NHS England Despite the distributions being available from ZUMA-7, clinical expert opinion was sought to determine the distribution over SOC chemotherapy regimens, in order to reflect clinical practice in the NHS in England. As stated in section B.3.2.3.2, clinicians stated that although distribution of chemotherapy regimens was centre dependent, R-ICE and R-GDP were the most commonly used regimens. They also stated that a lot of centres in the UK were moving towards using R-GDP given it was possible to administer in an outpatient setting. In addition, clinicians stated that it is reasonable to assume equal efficacy across the different platinum-based chemotherapy regimens, therefore the distribution of use is only expected to affect costs. As a result, the base case assumed 50% of patients received R-ICE and 50% received R-GDP. A scenario analysis was tested using the trial-based values (see Section B.3.8.3).

Standard of care drug acquisition

Table 37 summarises the posology, formulations and costs, for each SOC therapy. All doses were based on the ZUMA-7 protocol and chemotherapy regimen guidelines from NHS trusts in England.[95-99] The majority of SOC chemotherapy regimens are dosed variably with mean patient weight, body surface area (BSA), and

creatinine clearance based on patients in ZUMA-7. Costs were sourced from eMIT in the first instance as this better reflects the prices paid by hospitals.[100] Where eMIT costs were not available, costs were taken from the Monthly Index of Medical Specialities (MIMS) or the British National Formulary (BNF). [101] Where multiple options were listed for each drug, it was conservatively assumed that the pack providing the cheapest cost per mg would be used in practice. No discounts on SOC drug costs are applied in the model base case.

Table 37. Standard of care chemotherapy acquisition costs

Drug	Defined dose	Vial size/ tablet strength	Pack size	Cost per pack	Source	Vials/tablets per administration	Administrations per cycle	Cost per treatment cycle
R-ICE								£2,742.13
Rituximab	375 mg/m^2	100 mg	2	£349.25	MIMS 2021	1.47	1	£1,387.28
		500 mg	1	£873.15	MIMS 2021	1.00		
Ifosfamide	5 g/m^2	1 g	1	£120.69	eMIT (2021)	0.25	1	£1,209.00
		2 g	1	£234.84	eMIT (2021)	5.02		
Carboplatin	AUC 5	50 mg	1	£3.18	eMIT (2021)	1.00	1	£16.69
		150 mg	1	£6.08	eMIT (2021)	0		
		450 mg	1	£13.51	eMIT (2021)	1.00		
Etoposide	100 mg/m^2	100 mg	1	£3.84	eMIT (2021)	2.12	3	£129.16
		500 mg	1	£9.94	eMIT (2021)	3.51		
R-ESHAP								£1,470.32
Rituximab	375 mg/m^2	100 mg	2	£314.33	MIMS 2021	1.47	1	£1,387.28
		500 mg	1	£785.84	MIMS 2021	1.00		
Etoposide	40 mg/m^2	100 mg	1	£3.84	eMIT (2021)	1.00	4	£15.36
		500 mg	1	£9.94	eMIT (2021)	0		
Cytarabine	2 g/m^2	100 mg	5	£16.07	eMIT (2021)	0.68	1	£22.93
		500 mg	5	£19.48	eMIT (2021)	0.59		
		1 g	1	£6.29	eMIT (2021)	0.24		
		2 g	1	£10.33	eMIT (2021)	1.64		
Cisplatin	25 mg/m^2	50 mg	1	£6.03	eMIT (2021)	0.60	4	£28.80

Drug	Defined dose	Vial size/ tablet strength	Pack size	Cost per pack	Source	Vials/tablets per administration	Administrations per cycle	Cost per treatment cycle
		100 mg	1	£8.97	eMIT (2021)	0.40		
R-GDP								£1,447.25
Rituximab	375 mg/m^2	100 mg	2	£314.33	MIMS 2021	1.47	1	£1,387.28
		500 mg	1	£785.84	MIMS 2021	1.00		
Gemcitabine	1 g/m^2	200 mg	1	£3.18	eMIT (2021)	1.58	2	£40.02
		1 g	1	£10.06	eMIT (2021)	0.36		
		2 g	1	£17.78	eMIT (2021)	0.64		
Dexamethasone	40 mg	2 mg	1	£0.05	eMIT (2021)	20	4	£4.28
Cisplatin	75 mg/m^2	50 mg	1	£6.03	eMIT (2021)	0.40	1	£15.66
		100 mg	1	£8.97	eMIT (2021)	1.48		
R-DHAP								£1,435.30
Rituximab	375 mg/m^2	100 mg	2	£314.33	MIMS 2021	1.47	1	£1,387.28
		500 mg	1	£785.84	MIMS 2021	1.00		
Dexamethasone	40 mg	2 mg	1	£0.05	eMIT (2021)	20	4	£4.28
Cytarabine	2 g/m^2	100 mg	5	£16.07	eMIT (2020)	0.68	1	£22.93
		500 mg	5	£19.48	eMIT (2020)	0.59		
		1 g	1	£6.29	eMIT (2020)	0.24		
		2 g	1	£10.33	eMIT (2020)	1.64		

Drug	Defined dose	Vial size/ tablet strength	Pack size	Cost per pack	Source	Vials/tablets per administration	Administrations per cycle	Cost per treatment cycle
Cisplatin	100 mg/m^2	50 mg	1	£6.03	eMIT (2020)	0.73	1	£20.81
		100 mg	1	£8.97	eMIT (2020)	1.83		

Key: AUC, area under the curve; eMIT, electronic market information tool; MIMS: Monthly Index of Medical Specialties; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab with gemcitabine, dexamethasone, and cisplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOC, standard of care.

Standard of care drug administration

Administration costs for SOC chemotherapy regimens included in the model are presented in Table 38.

Table 38: Chemotherapy administration costs

	Cost	Cost (inflated to 2020/21	Reference	Code/setting
Simple parenteral administration (first attendance)	£295.92	£305.03	NHS reference costs (2019/2020)[102]	SB12Z/DCRDN
More complex parenteral administration (first attendance)	£329.75	£339.91	NHS reference costs (2019/2020)[102]	SB13Z/DCRDN
Prolonged infusion time	£428.26	£441.45	NHS reference costs (2019/2020)[102]	SB14Z/DCRDN
Subsequent administrations of a chemotherapy cycle	£363.37	£374.56	NHS reference costs (2019/2020)[102]	SB15Z/DCRDN
Inpatient bed day	£454.13	£468.12	NHS reference costs (2019/2020)[102]	Weighted average SA31A-F/inpatient

Given that most NHS England regimen guidelines recommend inpatient administration of salvage chemotherapy, the weighted average cost of elective inpatient stays for patients with malignant lymphoma is assumed to capture this cost for all regimens, except for R-GDP which is typically administered in the outpatient setting.[95-99] Treatment duration for each regimen was based on the ZUMA-7 trial.

Table 39 summarises the assumed setting and final administration cost applied for each regimen along with details on how this was calculated.

Table 39: Total costs for administration of each regimen

Chemotherapy regimen	Administration setting	Total administration cost per chemotherapy cycle	Details	Number of 21-day cycles
R-ICE	Inpatient	£1,404.35	• 3 x inpatient bed days	2.25
R-ESHAP	Inpatient	£2,340.59	• 5 x inpatient bed days	2.40
R-GDP	Outpatient	£1,565.12	• 1 x prolonged infusion • 3 x subsequent administrations	2.33
R-DHAP	Inpatient	£1,872.47	• 4 x inpatient bed days	2.22
Key: R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab with gemcitabine, dexamethasone, and cisplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide.				

Other standard of care treatments

As described in Section B.3.2.3.2, patients who respond to initial salvage chemotherapy may be treated with high dose therapy (BEAM) and auto-SCT.

In ZUMA-7, 62 out of 179 (34.6%) patients underwent auto-SCT. The costs for which include stem cell harvest, high dose therapy, reinfusion, and follow-up care.

The costs of stem cell harvest were based on NHS reference costs 2019/2020, and The cost of the auto-SCT procedure was obtained from the NICE National Guideline on Non-Hodgkin's lymphoma (NG52).[103] Both costs were inflated to 2020/21 using hospital and community health services (HCHS) index reported by PSSRU.[104]. Details are provided in Table 40.

Table 40: Stem cell harvest and reinfusion costs

Component	Cost	Cost (inflated)	Reference	Details
Stem cell harvest	£3,021.82	£3,114.89	NHS reference costs (2019/2020)	SA34Z (stem cell harvest) / outpatient
Transplant (reinfusion)	£34,000	£37,735.95	NICE NG52	Non-Hodgkin's lymphoma: diagnosis and management guideline estimate

Before transplant, patients receive conditioning with high dose therapy. In the model it is assumed that the BEAM regimen would be used in line with guidelines.[105] This regimen involves:

- A 300 mg/m^2 infusion of carmustine Day 6 before transplant
- A 200 mg/m^2 infusion of cytarabine every 12 hours, Days 5, 4, 3 and 2 before transplant
- A 200 mg/m^2 infusion of etoposide Days 5, 4, 3 and 2 before transplant
- A 140 mg/m^2 dose of melphalan Day 1 before transplant

Unit costs of drugs were obtained from eMIT or the BNF in line with the treatment protocol and are presented in Table 41. The final calculated cost per BEAM cycle is presented in Table 42. In line with guidelines, is assumed that all drugs are administered via an intravenous infusion on an inpatient basis.[105]

Table 41: Unit costs, BEAM (high dose chemotherapy) regimen

Component	Vial size/tablet strength	Cost per unit	Source
Carmustine	100 mg	£391.24	NICE NG52 – used the estimate of £358.80, and - inflated to 2020/21)
Cytarabine	100 mg	£3.21	eMIT (2021)
	500 mg	£3.90	eMIT (2021)
	1000 mg	£6.29	eMIT (2021)
	2000 mg	£10.33	eMIT (2021)
Etoposide	100 mg	£3.84	eMIT (2021)
	500 mg	£9.94	eMIT (2021)
Melphalan	50 mg	£26.64	BNF (2022)
Key: BNF, British National Formulary; eMIT, electronic market information tool; NICE, National Institute for Health and Care Excellence.			

Table 42: Cost per cycle of BEAM

Component	Dose	Cost per dose	Doses per cycle
Carmustine	300 mg/m^2	£2,412.56	1
Cytarabine	200 mg/m^2	£64.21	8
Etoposide	200 mg/m^2	£48.49	4
Melphalan	140 mg/m^2	£159.44	1
Total cost:			£2,684.70

It is assumed that administration costs related to BEAM therapy would be covered by the auto-SCT procedure costs.

B.3.5.3. Health-state unit costs and resource use

Patients with r/r DLBCL on SOC or CAR T-cell therapies incur the costs for ongoing monitoring/resource use. Resource use frequencies differ for patients before and after an event, thus separate resource use costs are applied to the pre-event and post-event health states. The types of resources used and associated frequencies were based on the previous submission for axi-cel in the third-line DLBCL setting (TA559).[52] A summary of resource use costs and frequencies applied in the model is presented in Table 43.

Table 43: Pre- and post-event healthcare resource use unit costs and frequencies per model cycle

Resource	Unit cost (UK)	Pre-event use (axi-cel and SOC)	Post-event use (axi-cel and SOC)
GP visits	£50.72	0.94	2.50
District nurse	£44.80	1.88	0
CT scans	£283.69	0.11	0.02
Outpatient visits (Months 1 to 6)	£283.86	0.69	1.00
Outpatient visits (Months 7 to 12)	£283.86	0.34	1.00
Outpatient visits (Years 2 to 3)	£283.86	0.20	1.00
Outpatient visits (Years 4 to 5)	£283.86	0.14	1.00
Nurse visits	£44.32	1.88	0
Specialist nurse visits	£155.00	0.32	1.88
Inpatient days	£468.12	0.18	0.16
Full blood counts	£2.61	2.50	0.75
Serum LDH	£2.61	1.50	0.25
Liver function	£1.24	2.50	0.75
Renal function	£1.24	2.50	0.25
Immunoglobulin	£2.61	0.50	0.25
Calcium phosphate	£1.24	0.50	0.75

Key: CT, 131omputerized tomography; GP, General practitioner; LDH, lactate dehydrogenase; SOC, standard of care; UK, United Kingdom.

It is assumed that resource use for SOC and axi-cel patients surviving more than 5 years would be limited. Aligned with the most recent ERG preferences, it is assumed that event-free patients at 5 years would incur the cost of a GP visit every 6 months. This results in a cost of £8.45 per cycle.

B.3.5.4. Adverse reaction unit costs and resource use

Adverse events included in the model were based on the ZUMA-7 trial. The model includes severe (Grade 3 or 4) Aes occurring in ≥10% of subjects in ZUMA-7, or those with a meaningful impact on costs and quality of life. In addition, grade 3 or higher treatment-emergent cytokine release syndrome (CRS) and B-cell aplasia events were included, as these are likely to have high costs. This is in line with the approach taken in TA559. Full details of adverse events based on ZUMA-7 are

included in Section B.2.10. The adverse events accounted for in the model are presented in Table 44.

As stated in Section B.2.10.6, the safety profile observed in ZUMA-7 was manageable and generally consistent with the safety profile of axi-cel treatment as a third line therapy for patients with r/r DLBCL (ZUMA-1) and real-world use of axi-cel.

Table 44: Grade 3+ adverse event rates, ZUMA-7

Adverse event	Incidence	
	Axi-cel	Standard of care
CRS	[redacted]	[redacted]
Neurologic events	[redacted]	[redacted]
B-cell aplasia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Hypophosphatemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]

Adverse event management costs were based on the TA567 (tisagenlecleucel for treating r/r DLBCL) and NHS reference costs 2019/2020[72, 102], and inflated to 2020/21.[104]. These costs are summarised in Table 45. The HRG codes associated with each event were obtained from those preferred by ERGs and appraisal committees from previous submissions to NICE and updated with the latest published costs. Key adverse events with CAR T-cell therapies are cytokine release syndrome and B-cell aplasia. Costs for these Aes are aligned with TA567.

Table 45: Adverse event costs

Adverse event	Cost (inflated)	Source	Details
Cytokine release syndrome	£6,900.54	NHS reference costs (2019/2020)	Based on cost of tocilizumab (PHCD00098 / High Cost Drugs) and ICU stay (XC05Z and XC06Z) lasting 4 days, following the same approach as TA567
Neurologic events	£0	N/A	Not included in other models for CAR T-cell therapies
B-Cell aplasia	£12,136.20	NICE TA567	Assumed cost of receiving IVIG for a duration of 11.4 months including drug costs and administration
Anaemia	£3,687.88	NHS reference costs (2019/2020)	Haemolytic Anaemia, SA03G-SA03H, NEL (weighted average)
Neutropenia	£3,701.96	NHS reference costs (2019/2020)	Other Haematological or Splenic Disorder, SA08G, NEL
Hypotension	£1,580.60	NHS reference costs (2019/2020)	Assumed equal to febrile neutropenia
Neutrophil count decreased	£3,701.96	NHS reference costs (2019/2020)	Assumed equal to neutropenia
Platelet count decreased	£3,515.93	NHS reference costs (2019/2020)	Assumed equal to thrombocytopenia
White blood cell count decreased	£4,227.39	NHS reference costs (2019/2020)	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 2-3, SA31E, NEL
Hypophosphatemia	£515.91	NHS reference costs (2019/2020)	Fluid or Electrolyte Disorders, with Intervention, KC05G-KC05N, NES (weighted average)

Adverse event	Cost (inflated)	Source	Details
Thrombocytopenia	£3,515.93	NHS reference costs (2019/2020)	Thrombocytopenia, SA12G-SA12K, NEL (weighted average)
Lymphocyte count decreased	£3,515.93	NHS reference costs (2019/2020)	Assumed equal to thrombocytopenia
Febrile neutropenia	£1,580.60	NHS reference costs (2019/2020)	Other haematological or Splenic disorders, SA08G-SA08J, NEL and NES (weighted average)
Encephalopathy	£1,055.06	NHS reference costs (2019/2020)	Cerebrovascular Accident, Nervous System Infections or Encephalopathy, AA22C-AA22G, NES (weighted average)
Key: CAR, chimeric antigen receptor; CC, complication and comorbidity; IVIG; intravenous immunoglobulin; NHS, National Health Service; NEL; non-elective long-stay; NES; non-elective short-stay.			

Unit costs were multiplied by incidence to determine mean adverse event costs. These were then applied as one-off costs to both arms at the start of the model time horizon.

Table 46 summarises the one-off adverse event costs applied for both arms.

Table 46: Adverse event costs applied in the model

Adverse event	Cost (£)	
	SOC	Axi-cel
CRS	£0.00	£446.47
Neurologic events	£0.00	£0.00
B-cell aplasia	£0.00	£970.90
Anaemia	£1,426.86	£1,106.36
Neutropenia	£616.99	£1,589.62
Hypotension	£47.04	£176.66
Neutrophil count decreased	£1,035.67	£1,067.04
Platelet count decreased	£983.62	£1,013.42
White blood cell count decreased	£780.05	£1,069.28
Hypophosphatemia	£64.49	£94.08
Thrombocytopenia	£774.34	£289.55
Lymphocyte count decreased	£376.71	£599.78
Febrile neutropenia	£432.78	£37.19
Encephalopathy	£0.00	£124.12
Total one-off AE cost	£6,538.56	£8,584.45
Key: AE, adverse event; CRS, cytokine release syndrome; SOC, standard of care.		

B.3.5.5. Miscellaneous unit costs and resource use

B.3.5.5.1. Subsequent therapy costs

Aligned with NICE guidance, future, related healthcare costs are included in the analysis.[76] Patients receiving 2L treatment for DLBCL are likely to move on to subsequent treatment if the treating clinician determines that response is inadequate. A range of subsequent therapies were included in the model, the distribution over which was informed by ZUMA-7 data and adapted to reflect clinical expert insights into the subsequent therapies received by r/r DLBCL patients in NHS England.[29]

Subsequent therapies from the ZUMA-7 trial are presented in Table 47. Clinical experts outlined that some of the subsequent therapies included in the ZUMA-7 trial were not reimbursed for subsequent lines of therapy in NHS England, including pembrolizumab and nivolumab.[29] In addition, the base case analysis used the crossover adjusted curves for SOC, therefore CAR T-cell therapies are not applicable for the subsequent therapies. Clinical experts were asked to predict subsequent treatments, excluding those that are not reimbursed and where CAR T-cell therapy is not available in further lines, and are presented in Table 48.

Table 47: Subsequent treatments received in ZUMA-7

Subsequent therapy	Axi-cel (%)	SOC (%)
R-chemotherapy	68%	19%
Nivolumab	11%	3%
Pembrolizumab	5%	4%
Pola-BR	20%	13%
R-lenalidomide	14%	13%
Radiotherapy	20%	25%
Allo-SCT	8%	4%
Axi-cel	0%	56%
Liso-cel	0%	4%
Tisagenlecleucel	0%	12%
Auto-SCT	11%	4%

Key: Allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; liso-cel, lisocabtagene maraleucel; N/A, not applicable; pola-BR, polatuzumab vedotin + bendamustine + rituximab; R, rituximab; SOC, standard of care.
Note: Subsequent therapies do not sum to 100% as proportions also include 4L and 5L treatments. In addition, these reflect the proportion of patients receiving subsequent therapy, rather than proportion of patients in the trial.

Table 48: Subsequent treatments applied in the base case (crossover adjusted) analysis

Subsequent therapy	Axi-cel (%)	SOC (%)
R-chemotherapy	25%	30%
Nivolumab	0%	0%
Pembrolizumab	0%	0%
Pola-BR	10%	26%
R-lenalidomide	25%	10%
Radiotherapy	40%	20%
Allo-SCT	5%	5%
Axi-cel	0%	0%
Liso-cel	0%	0%
Tisagenlecleucel	0%	0%
Auto-SCT	11%	8%

Key: Allo-SCT, allogeneic stem cell transplant; auto-SCT, autologous stem cell transplant; liso-cel, lisocabtagene maraleucel; N/A, not applicable; pola-BR, polatuzumab vedotin + bendamustine + rituximab; R, rituximab; SOC, standard of care.
Note: Subsequent therapies do not sum to 100% as proportions also include 4L and 5L treatments

Costs for subsequent therapies not presented elsewhere in this document are shown in Table 49. With total drug and administration costs for each subsequent therapy presented in Table 50.

Table 49: Subsequent therapy unit costs

Subsequent therapy	Vial size/tablet strength	Pack size	Cost per pack / therapy	Source
Nivolumab	40mg	1	£439.00	MIMS (2021)[106]
Pembrolizumab	100mg	1	£2,630.00	MIMS (2021)[106]
Polatuzumab	140mg	1	£11,060.00	MIMS (2021)[106]
Lenalidomide	20mg	21	£4,168.50	BNF (2021)[101]
Radiotherapy	N/A	N/A	£1,673.87	NHS reference costs (2019/2020); code SC41Z; setting – radiotherapy
Allo-SCT	N/A	N/A	£33,543.88 (initial cost, £44,565.92 (follow-up cost)	NHS reference costs (2019/2020); codes SA38A,

Subsequent therapy	Vial size/tablet strength	Pack size	Cost per pack / therapy	Source
				SA39A and SA40Z, total HRG (for initial cost) and UK Stem Cell Strategy Oversight Committee Report for follow-up cost
Axi-cel	N/A	1	[redacted]	Kite/Gilead (2021)*
Tisagenlecleucel	N/A	1	£282,000	NICE TA567[72]
Liso-cel	N/A	1	£282,000	Assumption**

Key: eMIT, electronic market information tool; MIMS, Monthly Index of Medical Specialities; NICE, National Institute for Health and Care Excellence.
Notes: *[redacted] PAS applied. **List price for liso-cel is not available – same list price as for tisagenlecleucel was assumed

Table 50: Subsequent therapy drug and administration costs

Subsequent therapy	Number of cycles	SOC	
		Admin cost	Drug cost
R-chemotherapy	3	£851.47	£1,193.34
Nivolumab	2	£816.00	£5268.00
Pembrolizumab	5	£441.45	£5260.00
Pola-BR	6	£816.00	£13,421.23
R-lenalidomide	4	£679.59	£6,943.06
Radiotherapy	1	£1,673.87*	
Allo-SCT	1	£33,543.88*	£44,565.92**
Axi-cel	1	See Section B.3.5.2.1	See Section B.3.5.2.1
Liso-cel	1	See Section B.3.5.2.1	See Section B.3.5.2.1
Tisagenlecleucel	1	See Section B.3.5.2.1	See Section B.3.5.2.1
Auto-SCT	1	£37,735.95	

Key: allo-SCT, allogeneic stem cell transplant; auto-SCT; autologous stem cell transplant; pola-BR, polatuzumab bendamustine and rituximab; SOC, standard of care.
Notes: * procedure cost, ** follow up cost.

To calculate the costs applied in the model for subsequent therapy, costs were weighted according to the expected proportions receiving each subsequent therapy in clinical practice. Subsequent treatment costs in the model are applied as a one-off

cost at the time of initiation of subsequent therapy based on the TTNT curve. Patients who did not have a TTNT event by 5 years were assumed not to receive subsequent therapy. The duration of treatment is not explicitly modelled for subsequent therapy. Instead, an estimated average number of treatment cycles has been derived for each subsequent therapy based on previously published trial or observational evidence.

B.3.5.5.2. End-of-life costs

End-of-life care costs are applied to the proportion of patients entering the dead state per cycle. The cost for end-of-life care was taken from Round (2015)[107], and inflated to 2021 prices.[104] The final cost applied is £4,884.98.

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

A summary of the variables included in the model, their base case values, and the measurement of uncertainty and distribution is tabulated in Appendix P.

B.3.6.2. Assumptions

Table 51 contains the key assumptions made in the de novo economic model.

Table 51: Key model assumptions

Assumption	Justification
Extrapolations of OS and EFS – axi-cel that are based on mixture cure models	The use of MCM models is beneficial over standard parametric models as CAR T-cell therapies are potentially curative clinically. There is also empirical support for the use of mixture cure modelling to extrapolate trial OS estimates with ZUMA-1 data (axi-cel in 3L).[82] Most importantly, validation of predicted survival estimates was performed using data from ZUMA-1 (axi-cel in 3L) and the insights of clinical experts.[29, 56]
Extrapolations of OS and EFS - SOC that OS would be between OS observed in ORCHARRD and SCHOLAR-1.	There are difference in patient and study characteristics between ZUMA-7, ORCHARRD and SCHOLAR-1. Therefore, the adjusted OS from ZUMA-7 crossover analysis would not completely align with observation from ORCHARRD and SCHOLAR-1. This is further confirmed by clinical experts that the expected OS trend among DLBCL patients eligible for 2L treatments is likely to be

	between the observation from ORCHARRD and SCHOLAR-1.
The distribution of chemotherapy regimens for the SOC arm are assumed to be split equally between R-ICE and R-GDP, with no patients receiving R-ESHAP and R-DHAP.	The distribution of chemotherapy regimens from ZUMA-7 were not reflective of UK clinical practice, and clinicians stated that the type of regimen used is centre dependent, however it was agreed that R-ICE and R-GDP is the most commonly used. As a result, an equal split between R-ICE and R-GDP is assumed for the SOC arm, with no patients receiving R-ESHAP and R-DHAP. Clinicians stated that it is reasonable to assume equal efficacy across the different regimens, therefore the distribution of use is only expected to affect costs.
Quality of life for long-term survivors, remaining in the event-free health state returns to that of the age- and gender-matched general population values after 5 years, reflective of the fact that patients would be effectively cured. This applied to both the axi-cel and SOC arms.	This is in line with previous CAR T appraisals, and the company submission for TA559 assumed this would happen after 2 years, however this was challenged by the ERG.[52] In this appraisal we assume a more conservative estimate of 5 years, in line with latest committee preferences for CAR T-cell therapies.[87]
After 5 years, patients that are in the event-free health state acquire limited monitoring costs.	Previous submissions in CAR T have assumed that no monitoring costs are applied after the assumed cure point, for example, TA559 applied no monitoring costs after 2 years for patients in the progression-free health state. For this analysis, costs were aligned with the most recent ERG preferences where it is assumed that event-free patients at 5 years would incur the cost of a GP visit every 6 months.
Subsequent therapy applied in the model is estimated from clinical experts instead of ZUMA-7.	Given some of the subsequent treatments in the ZUMA-7 trial are not reimbursed for patients, these are not included. In addition, as the crossover adjusted analysis is the base case, subsequent CAR T therapy is not included as a subsequent therapy for SOC.
Key: CAR, chimeric antigen receptor; EFS, event-free survival; OS, overall survival; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab with gemcitabine, dexamethasone, and cisplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOC, standard of care.	

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

The discounted base case results for axi-cel versus SOC are shown in Table 52. With a [redacted] PAS applied, axi-cel is associated with [redacted] incremental life years, [redacted] incremental QALYs, and incremental costs of [redacted] per patient, compared with SOC. The incremental cost-effectiveness ratio (ICER) is £51,996 per QALY gained. Estimates of clinical outcomes compared with trial results and disaggregated results are presented in Appendix J, and summarised and interpreted in B.3.10.

Markov traces over the total model time horizon are presented for axi-cel and SOC in Figure 33 and Figure 34, respectively.

Table 52: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,996
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Figure 33: Lifetime Markov trace for axi-cel

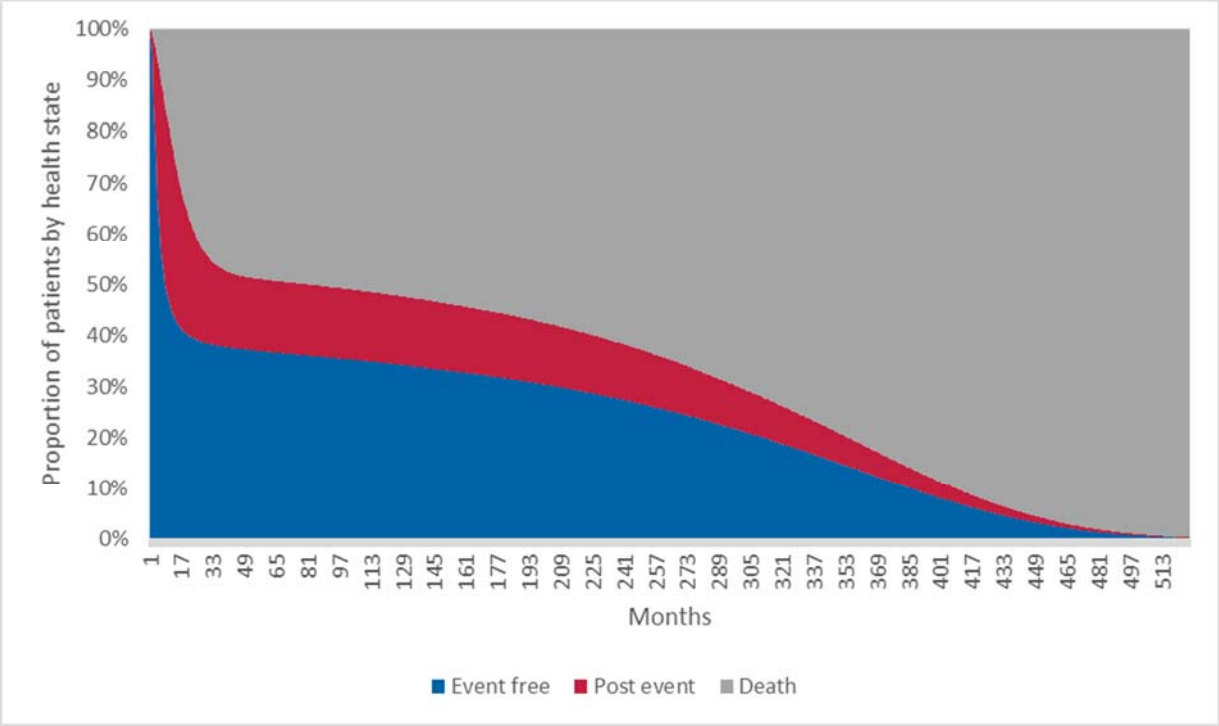
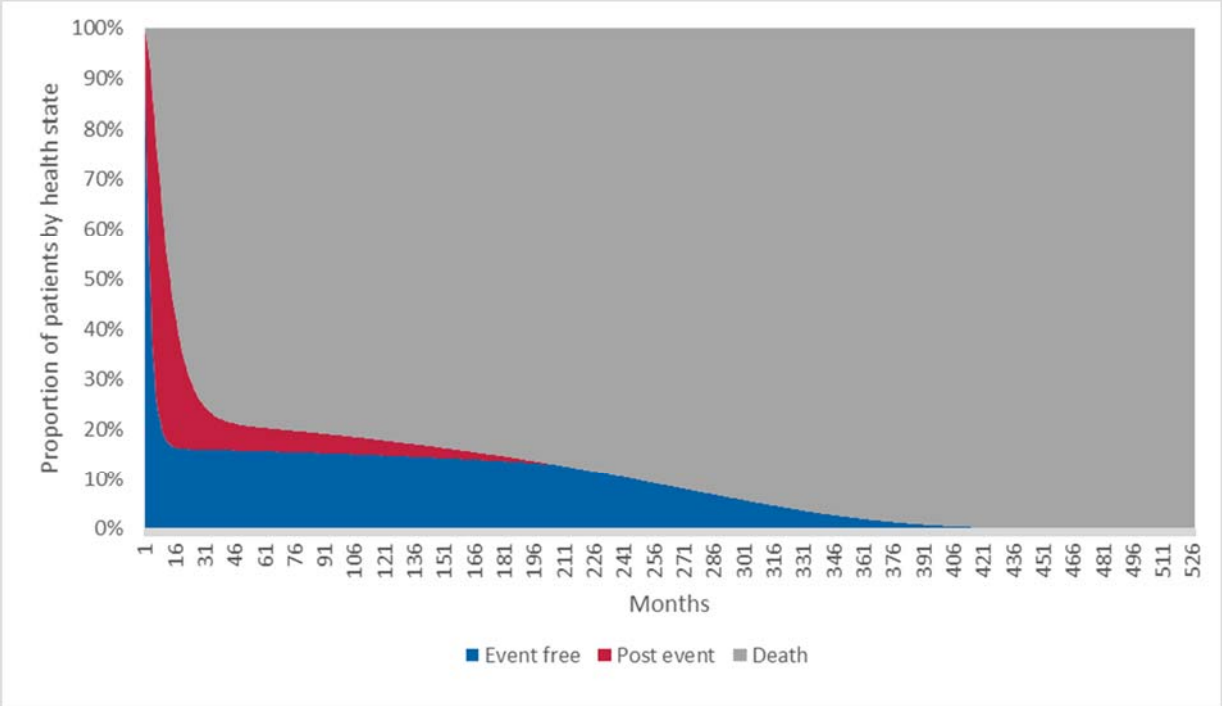


Figure 34: Lifetime Markov trace for SOC

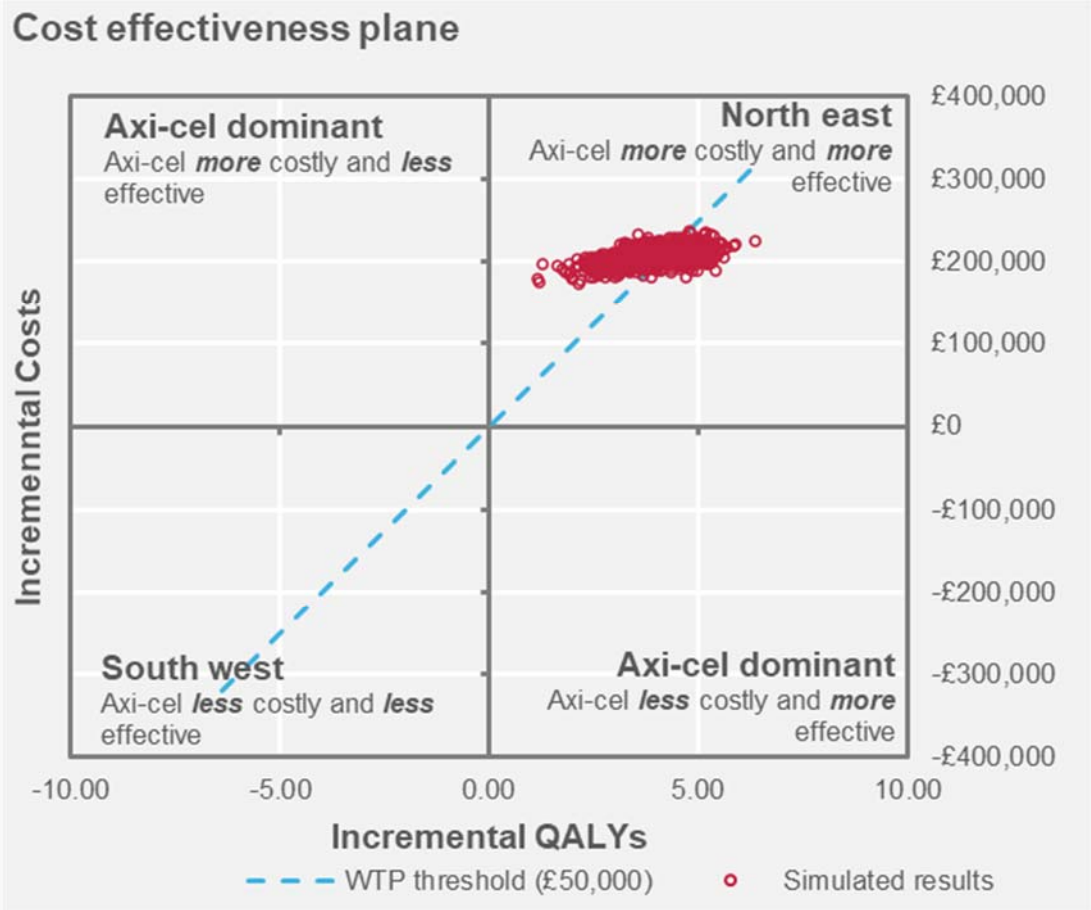


B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning specific parametric distributions and repeatedly sampling mean parameter values. Each parameter was varied according to its associated distribution, and mean model results were recorded. One thousand simulations were run, this was justified by the flattening of the PSA convergence (see Figure 37). The results are presented as the probability of being cost-effective at a willingness-to-pay (WTP) threshold of £50,000 per QALY, to reflect the end-of-life criteria as discussed in B.2.13.5. The PSA cost-effectiveness plane is presented in Figure 35. This shows that all of the iterations fell in the north-east quadrant.

Figure 35: PSA scatter plot at £50,000 threshold



Key: QALYs, quality-adjusted life years, WTP, willingness-to-pay.

The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], giving a probabilistic ICER of £52,669. This is similar to the deterministic changes in costs and QALYs of [redacted] and [redacted], respectively, and ICER of £51,996, resulting in a difference in ICER of approximately 1.3%. the cost-effectiveness acceptability curve is presented in Figure 36. This shows that at a willingness-to-pay threshold of £50,000, the probability of axi-cel being more cost-effective compared to SOC is [redacted]

Figure 36: Cost-effectiveness acceptability curve

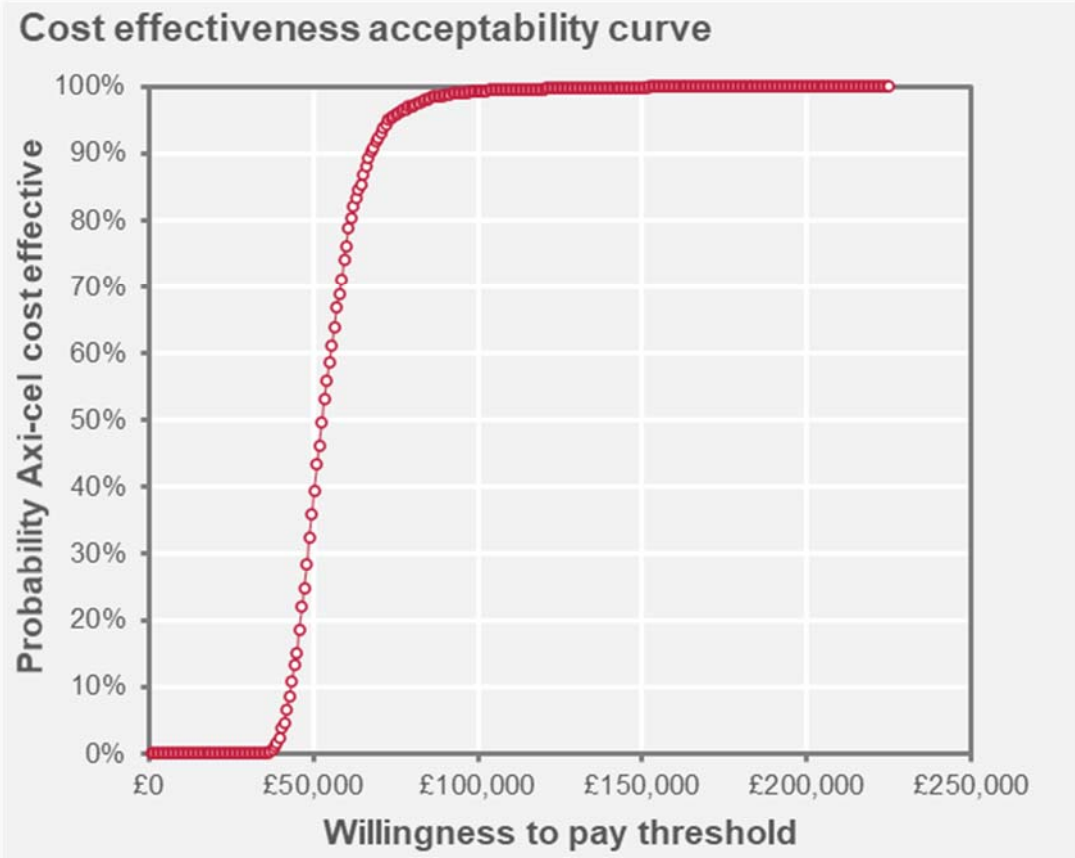
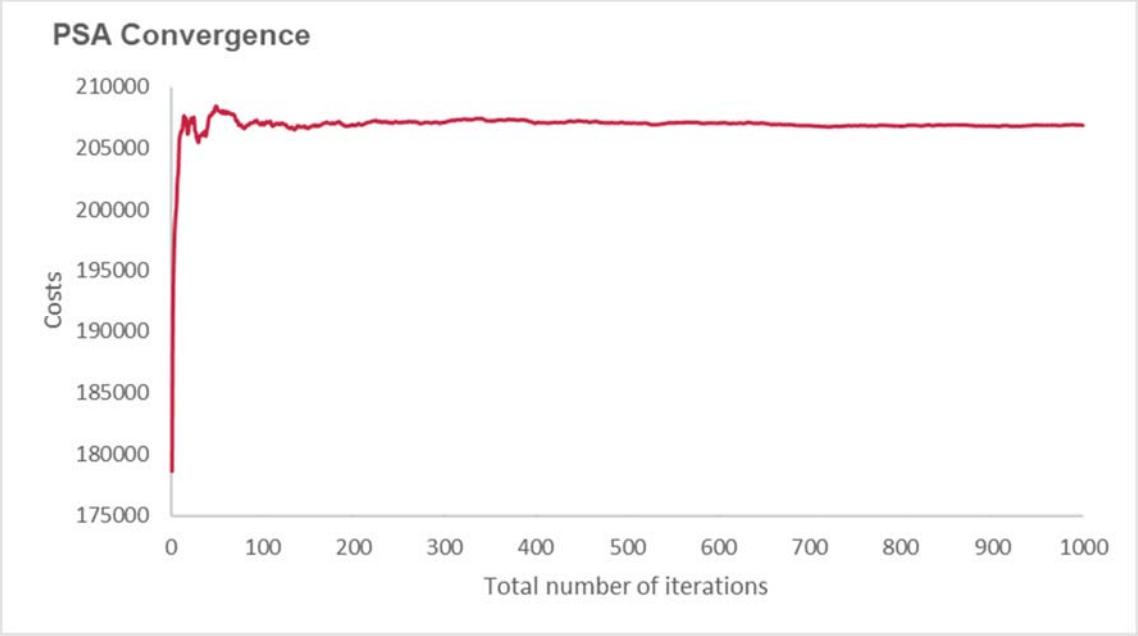


Figure 37: PSA convergence plot

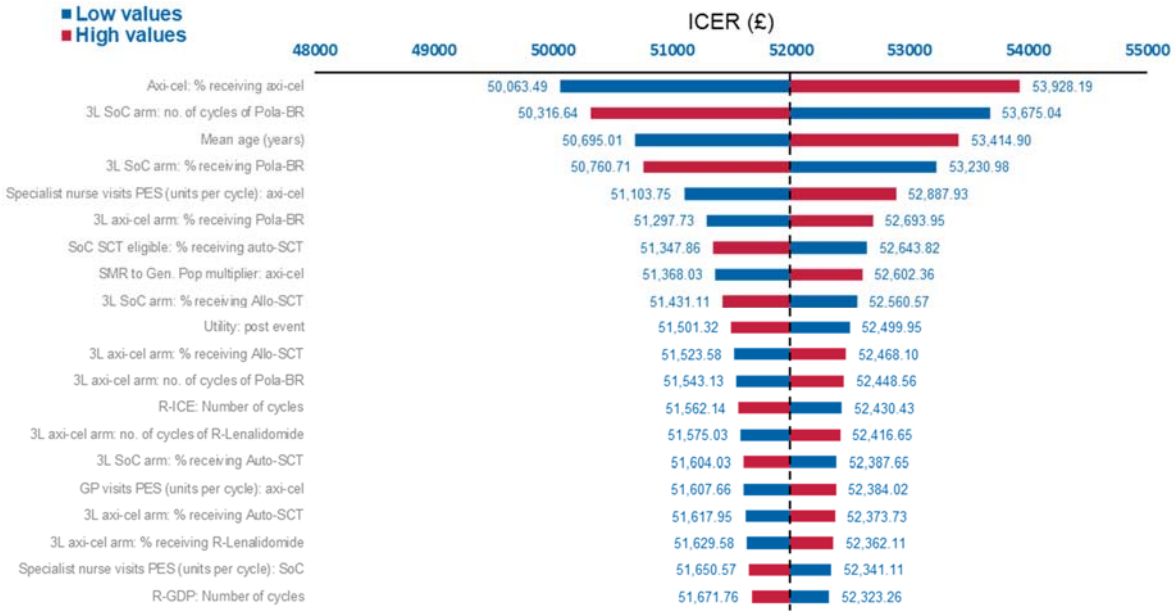


Key: PSA, probabilistic sensitivity analysis.

B.3.8.2. Deterministic sensitivity analysis

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. Confidence intervals were calculated using reported standard errors of the mean, or by calculating a margin of error of 20% around the mean estimate where standard errors were not available or reported, the upper and lower limits of the confidence interval are reported in Appendix P. The top 20 influential parameters on the incremental cost-effectiveness ration (ICER) are presented as a tornado diagram in Figure 38. As shown in the tornado diagram, the three most influential parameters on the model results were the percentage of patients receiving axi-cel, the number of cycles of Pola-BR received in the 3L SoC arm, and the mean patient age (years).

Figure 38: One-way sensitivity analysis, Tornado diagram



B.3.8.3. Scenario analysis

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

- Time horizon: 10- and 20-year time horizons were explored
- Discounting: costs and outcomes were discounted at 1.5%
- Model selection for axi-cel OS: Weibull MCM and log-logistic MCM
- Model selection for axi-cel EFS: Generalised gamma MCM
- Model selection for SOC EFS: Weibull MCM
- SOC OS curve: converges with EFS curve at 5 years in line with clinician opinion
- Utility source: use of ZUMA-1 utility values
- Disutilities: not applying individual disutility to adverse events
- Cure time point: 2- and 7- years
- SOC chemotherapy regimen distribution: use of ZUMA-7 estimates instead of UK clinician estimates
- ITT population analysis (details in Appendix Q)

The results of the scenario analyses are presented below in Table 53.

Table 53: Scenario analyses results

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
Base case	**-**	[redacted]	[redacted]	**£51,996**	**-**
Time horizon = 10 years	50 years	[redacted]	[redacted]	£111,183	113.8%
Time horizon = 20 years		[redacted]	[redacted]	£66,249	27.4%
Discount rates = 1.5%	3.5%	[redacted]	[redacted]	£40,631	-21.9%
Axi-cel OS = Weibull (MCM)	Generalised gamma (MCM)	[redacted]	[redacted]	£51,882	-0.2%
Axi-cel OS = Log-logistic (MCM)		[redacted]	[redacted]	£53,075	2.1%
Axi-cel EFS = Generalised gamma (MCM)	Log-logistic (MCM)	[redacted]	[redacted]	£51,705	-0.6%
SOC EFS = Weibull	Exponential (MCM)	[redacted]	[redacted]	£52,012	0.0%
SOC OS convergence with EFS at 5 years applied	No convergence applied	[redacted]	[redacted]	£49,792	-4.2%
Utility values based on ZUMA-1	Based on ZUMA-7 and JULIET study	[redacted]	[redacted]	£54,144	4.1%

No AE disutilities applied and on-treatment specific utilities applied	AE disutilities included and no on-treatment specific utility applied	[redacted]	[redacted]	£51,973	0.0%
Cure time point = 2 years	5 years	[redacted]	[redacted]	£50,770	-2.4%
Cure time point = 7 years		[redacted]	[redacted]	£52,557	1.1%
Use of ZUMA-7 estimates for SOC distribution	UK clinical expert estimates	[redacted]	[redacted]	£51,953	-0.1%
ITT analysis	Crossover adjusted	[redacted]	[redacted]	£79,034	52.0%
Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality adjusted life year.					

B.3.8.4. Summary of sensitivity analyses results

The key influential drivers of cost-effectiveness results were around parameters that influenced drug acquisition costs, such as percentage of people receiving axi-cel. The scenario analysis that resulted in the biggest deviation from base case results was when the model adopted a shorter time horizon (10 years) as well as the ITT analysis, where OS for the SOC arm was not crossover adjusted. Overall, the sensitivity and scenario analyses explored indicate that under a range of assumptions and across different parameters, the estimated cost-effectiveness of axi-cel is close to the decision-making threshold for end-of-life medicines.

B.3.9. Subgroup analysis

As described in Section B.2.7, the ZUMA-7 primary outcome findings were consistent across pre-planned subgroups, including those defined by baseline demographics, clinical characteristics and treatment history, therefore no subgroup analyses was conducted.

B.3.10. Validation

B.3.10.1. Validation of cost-effectiveness analysis

The models have undergone internal quality checks as well as an external QC process. The model has been “pressure-tested” in advisory board meetings with health economic experts and cost-effectiveness market payers, including review of the ZUMA-7 development plan in second-line LBCL, review of the CEA/BIM methods, model inputs, extrapolation methodology, base case model findings, and scenario analysis results.[29, 43]

The cost-effectiveness model was reviewed and validated against peer-reviewed checklists, in particular the CHEERS 2022 checklist.[108] The cost-effectiveness model was internally quality checked by a health economist and any errors or issues identified were addressed following the quality check. The key assumptions of the model have been validated by UK clinical experts, to ensure that the inputs and assumptions were plausible and relevant to UK clinical practice.

B.3.10.1.1. Validation of Survival Outcomes

Validation of the modelled survival results was explored against the EFS and OS findings from the full analysis set. Modelled EFS outcomes alongside those from the ZUMA-7 full analysis set are provided in Table 54**.** Modelled OS outcomes alongside that of the ZUMA-7 trial are provided in Table 55.

Table 54: Modelled median EFS and ZUMA-7 median EFS (central assessment, investigator-assessed) estimates for axi-cel and SoC

EFS analysis	Axi-cel	SOC
Modelled EFS, median, months	[redacted]	[redacted]
ZUMA-7 EFS, Centrally assessed, median (95% CI), months	8.3 (4.5, 15.8)	2.0 (1.6, 2.8)
ZUMA-7 EFS, Investigator assessed, median (95% CI), months	[redacted]	[redacted]
Key: CI, confidence interval; EFS, event free survival; SOC, standard of care.		

Table 55: Modelled median OS and ZUMA-7 median OS estimates for axi-cel and SoC

OS analysis	Axi-cel	SOC
Modelled OS, median, months	[redacted]	[redacted]
ZUMA-7 OS, median (95% CI), months	Not reached ([redacted], NE)	[redacted] ([redacted] NE)
Key: CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; SOC, standard of care.		

In the ORCHARRD trial comparing ofatumumab (n=74) versus rituximab in combination with DHAP (n=83); O-DHAP vs. R-DHAP), no statistically significant difference was found between study arms for PFS or secondary survival endpoints of EFS and OS.[27] Median OS was 13.2 months versus 13.9 months with R-DHAP and O-DHAP, respectively. KM curves for modelled OS in the SoC arm alongside those observed with SoC in the ZUMA-7 trial and the ORCHARRD trial (SoC was rituximab

salvage chemotherapy) of ofatumumab in patients with relapsed or refractory LBCL are shown in Figure 28.

B.3.11. Interpretation and conclusions of economic evidence

In the base case, axi-cel was associated with incremental costs of [redacted], incremental LYs of [redacted] and an incremental QALY gain of [redacted]. This resulted in an ICER of £51,996 per QALY, which is just above the £50,000 willingness-to-pay threshold for end-of-life treatments. Clinical inputs for SOC OS as well as axi-cel up-front costs had the biggest impact on model outcomes.

Comparing the results from the previous axi-cel NICE submission (TA559)[52] for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies, this analysis estimated improved outcomes for patients receiving axi-cel in second line ([redacted] LYs and [redacted] QALYs versus [redacted] LYs and [redacted] QALYs, for second line and third line, respectively). As a result, this analysis highlights that delivering axi-cel earlier in the treatment pathway has the same cost implications to the National Health Service, whilst at the same time, providing better outcomes for patients and offering a greater proportion of patients the chance to achieve cure, as described in Section B.2.12.

One limitation of the model was the lack of HRQL data obtained from the ZUMA-7 trial for the post-event health state. Patients in the HRQL analysis set of ZUMA-7 were not mandated to complete patient reported outcome questionnaires after an EFS event, resulting in the data being both statistically and clinically uncertain. Data from the JULIET study was used as a substitute and was considered appropriate given it was conducted in the same population and for patients who had progressed after third-line treatment.

Scenario analysis using the ITT population, rather than the crossover adjusted curves, had a large influence on results, with the ICER increasing to £79,034. This is expected, as OS is higher for SOC in the ITT analysis, resulting in a smaller incremental QALY gain. Clinical experts described that the OS estimates from the ZUMA-7 trial may be over optimistic for the SOC arm, which may be driven by the fact that 56% of the patients in the SOC group received subsequent cellular immunotherapy off-protocol.[1] Clinical experts stated that the OS for the SOC arm

would be expected to lie between the observation from ORCHARRD and SCHOLAR-1, therefore, results from the crossover adjusted analysis are more applicable. In addition to this, clinicians agreed that the crossover adjusted analysis may still be conservative, as the modelled survival for the SOC arm with crossover adjustment still predicted optimistic outcomes for patients who will not receive subsequent cell therapy in third or later line settings. The scenario analysis where the SOC arm OS converged with EFS at 5 years was considered and showed that there was an increase in incremental QALY gains ([redacted] and [redacted] in the scenario analysis and base case analysis, respectively) and the ICER reduced to £49,792.

Reducing the time horizon had a large impact on results, which is expected given that the high upfront costs associated with axi-cel were applied without capturing the full lifetime benefits. Other scenario analyses did not deviate greatly from the base case, highlighting that the model results were robust to variations in key parameters and assumptions.

The cost-effectiveness analysis is highly generalisable to NHS England treatment setting. All costs informing the analysis were derived from UK sources. [redacted] indicating that the patient population in the ZUMA-7 trial is reflective of patients with r/r DLBCL in England.

Axi-cel is already reimbursed for the treatment of adult patients with r/r DLBCL and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy. Data from the ZUMA-1 trial showed that at four years, 44% of patients were still alive, supporting the emerging plateau in ZUMA-7 OS and the modelled estimates. It is possible that making CAR T available in earlier lines of therapy may result in more beneficial outcomes for patients. However, in recognition of the current uncertainty around the magnitude of benefit with axi-cel treatment in the second-line setting, it is acknowledged that axi-cel is likely to be a CDF candidate.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional clinical trial data

Appendix M: Real-world treatment patterns

Appendix N: Comparison of published studies

Appendix O: Survival Analysis

Appendix P: Summary of variables applied in the economic model

Appendix Q: ITT scenario analysis

Appendix R: Key feedback from experts

Appendix S: Report for crossover adjustment analysis

Appendix T: Report for patient reported outcomes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

Clarification questions

March 2022

File name	Version	Contains confidential information	Date
ID1684 axicel ERG clarification letter to PM for company response AICCIC v1.0	1.0	Yes	29th April 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

Identification and selection of relevant evidence

A1. Appendix D, Section D.1.1.5, page 15, Section D.1.2.5, page 30, and Section D.3, page 37. Please clarify the number of reviewers/assessors involved in the quality assessment of the studies identified by the SLR and the update and whether reviewers worked independently.

Two reviewers were involved in the quality assessment of the studies identified by the original and updated systematic literature review (SLR). The Quality assessment was conducted as part of the data extraction process. One reviewer performed the assessment and a second reviewer independently verified the assessment.

Baseline characteristics

A2. Document B, Section B.2.3.1, Table 6, page 34. Baseline characteristics reported in Table 6 include "Extranodal disease, n (%)". Please provide a breakdown of the number of participants according to the type of extranodal involvement, including the number of nodes.

Please find below a table for the extranodal involvement at baseline, which includes the number of participants according to the type of extranodal involvement and number of extranodal lesions.

Table 1: Extranodal involvement at baseline (FAS)

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

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

Adverse events

A3. Document B, Section 2.10.3, Table 11, page 61. The values in the row "Decreased platelet count" do not seem to be correct. Please check these values and amend them as needed.

Our apologies, there were typographical errors in Table 11 of Document B. A corrected Table 11 is provided below (**Table 2**), with the amended values bolded for clarity.

Table 2: Incidence of treatment-related TEAEs occurring in ≥ 10% of patients in either treatment arm, SAS

	Axi-cel (N = 170)		SOC (N = 168)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any treatment-related TEAE, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased neutrophil count	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Decreased platelet count	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]

	Axi-cel (N = 170)		SOC (N = 168)	
Preferred term	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]
Increased alanine aminotransferase	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Decreased lymphocyte count	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Hiccups	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinaemia	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; auto-SCT, autologous stem cell transplant; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; SOCT, standard of care therapy; TEAE, treatment-emergent adverse event.
Notes: For the axi-cel group, treatment-related TEAEs include TEAEs that are related to axi-cel. For the SOC group, treatment-related TEAEs include TEAEs that are related to immunochemotherapy, total body irradiation (given as part of conditioning for auto-SCT), high-dose therapy and auto-SCT. TEAEs include all AEs with an onset on or after the axi-cel infusion date in the axi-cel group or the first dose of immunochemotherapy in the SOC group. Multiple incidences of the same AE in one patient are counted once at the worst grade for each patient. Preferred terms are sorted in descending order of total frequency across both treatment arms. AEs are coded using MedDRA version 23.1 and graded per CTCAE version 4.03. Investigators were instructed to record fever separately from neutropenia if the fever was attributed to CRS.
Source: Table 35. ZUMA-7 CSR.[1]

Data synthesis

A4. PRIORITY. Document B, Appendix D, Table 2, Section D.1.1.4, page 12, Table 4, Section D.1.1.6, page 21, Table 6, Section D.1.2.4, page 28. Have you attempted (but not reported) a meta-analysis or network meta-analysis including ZUMA-7 and the randomised controlled trials identified in Appendix D? If so, please provide the full report of this analysis.

A meta-analysis or network meta-analysis have not been performed.

The RCTs identified in Appendix D were highly heterogenous in terms of participants, interventions and outcomes. A meta-analysis was therefore not performed as these factors are required to provide a meaningful outcome.[2]

A network meta-analysis is only required if technologies are being compared that have not been evaluated within a single RCT[3]. ZUMA-7 is an RCT, which provides head-to-head data for the relevant comparator to the decision problem being addressed, in the relevant population. As noted above, other identified RCTs were highly heterogeneous in terms of participants, interventions and outcomes. A network meta-analysis was therefore not performed, as it would not have provided additional information of value (to ZUMA-7).

Section B: Clarification on cost-effectiveness data

Clinical effectiveness parameters

B1. PRIORITY. Document B, Section B.3.3.3 and Section B.3.3.4, page 91-96. Mixture cure modelling assumes that a fraction of the modelled population will be 'statistically cured' after 5 years of event free. Those who are not 'statistically cured' experience EFS and OS risks based on extrapolation curves fitted to the full modelled cohort (including those who are cured and not cured). Please

- **Comment on the magnitude and direction of any biases that fitting extrapolation curves from the full cohort to the 'non-cured' fraction may cause.**

- **Clarify whether the extrapolation curves were validated with UK clinical experts and whether they were validated for the full cohort or the fraction of the cohort who are not long-term event-free / long-term survivors.**

- **Explore the impact of alternative methods (and scenario analyses) to account for more pessimistic outcomes (higher risks of not being event-free and higher risks of mortality) among the non-cured fraction.**

We appreciate the ERG's question and are happy to provide further detail on the methodology employed for extrapolation of survival in the economic model. Mixture survival models, as employed in this economic analysis, provide a way of modelling time to event in a variety of situations where a standard parametric function is inadequate to correctly describe the heterogeneity of data. They have been particularly utilised in cancer survival analysis, where the patient population can be represented as a mixture of two populations heterogenous for risk of dying: the patients that are bound to die of the disease, and the cured patients that do not present any excess mortality with respect to the general population.[4]

In practice, mixture cure models consider a population as a mixture of two groups: a proportion of patients who are considered cured and thus not at risk of experiencing the event of interest, with the remaining proportion being uncured, and that these subjects will eventually experience the event of interest and thus their survival function will tend toward zero.[5] Therefore, the overall survival curve is a weighted average of two curves, those of the cured patients, weighted by the cure fraction denoted as π, and uncured patients whose corresponding fraction is (1- π). Information of cure at the individual level is rarely available, and so in these models, as implemented with the economic model, we are concerned with population (or statistical) cure.[5]

The cured fraction π can either be an input to the model in the case when this value is estimated via external literature or other sources, or it can be generated by the statistical model based on the observed data. In the ZUMA-7 economic model, the cure fraction was generated by the clinical trial dataset from ZUMA-7 and not based on external estimates for the fraction of patients being cured which avoids any potential bias.

The survival curves for the ‘uncured’ populations can be found in the economic model under the ‘survival’ tab, represented by the lower dot-dash line in each respective arm, and the ‘statistically cured’ population as grey solid line (as shown below).

As illustrated above, the uncured proportion die much earlier than the cured proportion. Also note that ‘statistically cured’ population is subject to a standardized mortality ratio (SMR) multiplier to account for the impact of prior treatments, and disease-specific survival, and so die at a slightly higher rate than the general population.

Therefore, mixture cure modelling does not assume “a fraction of the modelled population will be ‘statistically cured’ after 5 years of event free.” It only assumes that two groups exist in the cohort: ‘statistically cured’ and ‘uncured’ and determines the proportion in each one of these groups, based on the survival distribution selected by the analyst. The statistical model is then able to generate a weighed survival curve based on these two groups, which we extrapolate to estimate long-term survival. Cure modelling greatest strength is its ability to quickly capture the plateau commonly observed in curative therapies and has been shown to accurately predict long term survival for axi-cel, as per ZUMA-1.[6]

However, whilst cure modelling is useful for survival extrapolation, it cannot determine which particular individuals in the dataset are deemed ‘statistically cured’ and ‘uncured’. Its purpose in this evaluation is to generate a realistic survival extrapolation. All extrapolations were validated by UK clinical experts during an external strategy meeting for the full cohort, and were deemed plausible.[7]

Long–term follow–up data from ZUMA-1 can be used to validate extrapolations, as extrapolations in the current model should lie above the ZUMA-1 data, given that

patients in ZUMA-7 are receiving CAR T as an earlier line of therapy and are therefore expected to have better long-term outcomes. Alternative extrapolations using mixture-cure models are shown in Figure 1 below. Both the log-normal and exponential models predict OS lower than the ZUMA-1 5-year data, and therefore are not considered plausible. The next most pessimistic model is the log-logistic mixture-cure model, which lies above the ZUMA-1 curve, and a scenario analysis provided in the original company submission showed that this had a minimal impact on the ICER (£53,075).

Figure 1: Overall survival mixture–cure model extrapolations for axi-cel

Key: KM: Kaplan–Meier; MCM, mixture-cure model.

Your clarification suggests a further partitioning of the ‘uncured’ population into those who are pre- and post-event. This would be complex as the purposed model structure would subsequently contain additional EFS and post-event ‘sub-states’ within the ‘cured’ and ‘uncured’ groups. Furthermore, it would require an estimation of the proportion of patients who remain event free in these states, and since the

model cannot determine exactly which patients those are, this would require additional assumptions.

Hence, for the purposes of economic evaluations additional assumption must be made to account for utilities and costs. The “5 years” relates to an additional conservative assumption we make that states that the proportion of the cohort who remain in the EFS state for longer than 5 years (and hence are likely to be cured) and have a quality of life akin to that of the general population and accrue no additional health care resource utilisation.

Like any other statistical model, mixture cure models have their limitations. For example, the mixture cure model assumes that there are two groups “cured” and “uncured” at the start which may not be appropriate in cases where cure can occur at any time during the follow up period.

B2. Document B, Section B.3.3.4.1, page 96-98. Please provide cost-effectiveness scenario analyses using alternative plausible adjustment methods for crossover (as reported in Figure 26), to further explore uncertainty surrounding the impact of the most appropriate cross-over adjustment methodology on the ICER.

Thank you for your question. You would like the company to use alternative crossover adjustment methods, subject to them being plausible, as per NICE TSD 16 guidance and those reported in Figure 26 of the main submission. In the base case we use the RPSTM model, with full recensoring, whilst maintaining the ITT p-value as per NICE TSD 16[8] and White et al. 2002.[9] We believe this is the most plausible model because:

- Most of the independently fitted models (when fitted to the generated KM curves) lie above the SOC ITT curve, which we heard from clinicians during an external strategy meeting in January 2022 is implausible[7]
- The HR approach produced more plausible results, as we heard from clinical feedback that it is likely that the resulting crossover adjusted curves would lie between the results from ORCHAARD (best case) and SCHOLAR-1 (worst case)[7]

- The alternative HR approaches (RPSFTM, no recensoring; RPSFTM, recensoring switchers only; IPCW, robust SE, wide intervals and IPCW, robust SE, 2-day intervals) do not produce plausible results as per the discussions with clinicians. As highlighted in Figure 2, Figure 3, Figure 4 and Figure 5 the alternative approaches result in the SOC overall survival curve lying above the ORCHARD overall survival curves.

Figure 2: OS estimates adjusted for crossover, using RPSFTM, no recensoring (HR = 0.604)

Key: Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care.
Note: ORCHARRD and SCHOLAR curves are included in this figure to contextualise model curves, but these studies do not provide data of direct relevance to the target population under appraisal.

Figure 3: OS estimates adjusted for crossover, using RPSFTM, recensoring switchers only (HR = 0.58)

Key: Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care.

Figure 4: OS estimates adjusted for crossover, using IPCW, robust SE, wide intervals (HR=0.695)

Key: Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care.

Figure 5: OS estimates adjusted for crossover, using IPCW, robust SE, 2-day intervals (HR=0.646)

Key: Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care.

As per the ERG request, Gilead have provided the cost-effectiveness results when using the alternative HRs (presented in Table 23 of the main submission) below.

As highlighted above, these alternative approaches are not plausible as clinical experts stated that the SOC overall survival curve should lie between the SCHOLAR-1 and ORCHARRD curves.

Table 3: Scenario results using alternative crossover adjustment

Alternative crossover approaches	ICER
RPSFTM, recensoring full analysis [redacted] used as company base case and most plausible model	[redacted]
RPSFTM, no recensoring [redacted]	[redacted]
RPSFTM, recensoring switchers only [redacted]	[redacted]
IPCW, robust SE, wide intervals [redacted]	[redacted]
IPCW, robust SE, 2-day intervals [redacted]	[redacted]
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RPSFTM, rank-preserving structural failure time	

As discussed during the clarification call, an updated analysis will be available during technical engagement where 4 additional events in the SOC arm will be included, and crossover adjustments will be re-estimated and re-assessed to determine the most plausible approach as per FDA request.

B3. Document B, Section B.3.3.3, Table 21, page 93 and Section B.3.3.4, Table 24, page 101. Please comment on the plausibility and face validity of the implied cure fractions for the base case EFS and OS extrapolations for both axi-cel and standard of care arms. For example, is cure post-EFS clinically plausible, and are the differences between treatments in terms of cure post-EFS realistic/achievable? Please provide details of any engagement with clinical expert opinion on this point.

Clinical experts were consulted during submission development to discuss the plausibility and face validity of the implied cure fractions for the base case EFS and OS extrapolations for both axi-cel and standard of care arms. As noted in the company submission, estimates for the standard of care arm were also compared with external datasets from the pre-CAR-T era as a further validity check, albeit with appropriate caution given the differences in the patient and study characteristics across datasets (see Table 25 of Section B.3.3.4.3).

In a world without CAR T-cell therapy available, clinical experts confirmed a minimal chance of remission with third- or later-line treatments.[7, 10, 11] They would typically expect DLBCL patients who relapse after current second-line care to follow a steep downward trajectory, with EFS and OS curves estimated to align by 5 years at the latest, perhaps even as early as by 1 year in the primary refractory or early relapse patient group.[7, 11] The small (<5%) cure post-EFS estimate for the standard of care arm in the base case model reflects this minimal chance of remission with further treatment and if anything is considered a conservative (optimistic) estimate, with the expected convergence of EFS and OS explored in a scenario analysis.

If axi-cel were made available at second-line, there may still be a chance of remission at third-line for some patients, as observed with current second-line care. The higher cure post-EFS estimate for the axi-cel arm (15%) in the base case model reflects this potential. As noted above, EFS and OS extrapolations were validated by clinical experts and there were no concerns on the differences in EFS and OS estimates shared. In the absence of an appropriate external dataset to conduct further validity checks of estimates for the axi-cel arm, scenarios that explore different OS extrapolations and thus different rates of cure post-EFS are provided in the company submission (see Table 53 of Section B.3.8.3). In recognition of the current uncertainty around the longer-term benefit with axi-cel treatment in the second-line setting, we acknowledge that axi-cel is likely to be a CDF candidate.

That said, with appropriate caveats around the differences in patient populations, trial designs and disease setting, we can look to ZUMA-1 to provide longer-term data for axi-cel in the treatment of R/R DLBCL and help contextualise the cure estimates for use of axi-cel in the second-line setting. Recently published 5-year data from ZUMA-1 report 5-year OS of 43% and exploratory EFS curves show a 5-year EFS of approximately 30% when axi-cel was used to treat patients in the third- or later-line setting.[12] Base case model estimates of cure fractions for axi-cel in the second-line setting are [redacted] for OS and [redacted] for EFS, representing an approximate [redacted] improvement in the overall cure rate between axi-cel use at second-line versus later-line that clinical experts previously thought was not ‘unreasonable'.[7] A similar magnitude of difference is also observed in the 2-year OS estimates between ZUMA-1 (51%) and ZUMA-7 (61%), and in the complete response rates (58% vs 65%,

respectively).[12-14] These data support an assumption of long-term survival benefit for a proportion of patients treated with axi-cel at second-line higher than that observed with axi-cel at later lines, that is, higher than 43%. The most pessimistic scenario applying this limit in the different OS extrapolations provided in the company submission is the application of the log-logistic MCM curve that has an implied cure fraction of [redacted]; as discussed in B1 and in the scenario analysis in the company submission, applying this curve increases the base case ICER by 2.1% to £53,075.

Quality of life and utilities

B4. PRIORITY. Document B, Section B.3.4.2, page 110; Section B.3.4.5, Table 32, page 116. Event-free survival utilities. The ERG notes that several different utility values are used in the economic model for the 'event-free survival' state (Base case analysis, Table 32, utility value = 0.785) or as scenario analyses 'on treatment' (pg. 110, 'event free' health state utility values = 0.772, 0.780 for soc and axi-cel respectively). For each of these utility values, please provide full details of how they were derived, specifically reporting:

- **How many participants and how many measurement time points contribute to each calculated EFS utility value? Specifically, were the utilities calculated as the average of all measurement time-points or was a different approach used?**
- **Please provide full details of the data underpinning the calculation, including mean, SD and n, utilities for each time point used in the derivation for each EFS state utility value?**
- **Please provide these data pooled across arms of the study and separately for each treatment arm.**

The rationale for partitioning the pre-event health states into off-treatment, on-treatment (axi-cel) and on-treatment (SOC) was to capture the adverse event associated with the treatments. As the PRO data suggests, patients in both arms experience impacts on their quality of life as a result of treatment, however, this is more enduring for SOC patients. Despite this analysis, the model base case analysis used the off-treatment event-free health state utility value in order to apply disutilities

associated with each specific adverse event separately, as this is the approach taken in previous NICE CAR T submissions.[15, 16] The scenario analysis uses the temporary lower health state (specific to treatment) multiplied by the average time on treatment to derive the weighted average decrement to QoL.

The sensitivity analysis reveals that using the on-treatment utilities is not a driver for cost-effectiveness, as these health states are transient relative to a patients expected life expectancy. However, that does not mean to say it is not important as a driver for treatment choice, since patient's value avoiding detrimental effects to their wellbeing from treatment, this has been shown in a discrete choice experiment conducted by Kite, embedded below.

We have conducted an additional analysis, as per your request where we pool across arms and event states. See below the MMRM outputs for utility estimates collapsed by event status regardless of treatment assignment.

Table 4: MMRM pooled utility estimates

Health state	**Estimate (95% CI)**
Pre-event	
Post-event	
Key: CI: confidence interval; MMRM, mixed-effect model with repeated measures.	

The results here suggest that post-event, a patient's QoL is marginally higher. This is counter intuitive and likely a result of significant selection bias and a very small sample size effecting the post-event utility analysis. More details on this is found in question B5.

In the document below, we share the full technical report for the post-hoc utility analysis of ZUMA-7 to derive the health state utilities. More information can be found in this document, including the number of observations underpinning the calculation

for the MMRM model (Table PH2.2.2) and the number of observations making up each health state (section 5.2).

B5. PRIORITY. Document B, Section B.3.4.5, Table 32, page 116. Post-event utilities. Post-event utilities. The ERG notes that it is unclear exactly how many respondents completed quality of life measurements post-event, with inconsistent reporting in different parts of the submission (Table 32: 'not administered', page 114: '<5% of the sample"). Please:

- **Clarify exactly how many participants completed each PRO QoL outcome measure post-event?**
- **Clarify why only a small proportion of post-event utility data are available? Was this in line with the statistical analysis plan (SAP)_for the study?**
- **Provide a copy of the final SAP for the QoL component of ZUMA-7.**
- **Provide descriptive statistics (mean, SD, N) for all QoL measures collected post-event, including mapped EQ-5D utilities for the pooled sample and separately by treatment arm.**
- **Provide a scenario analysis using the available data from ZUMA-7 in the cost-effectiveness model.**

The collection of post-event utilities was not mandated in the ZUMA-7 protocol and therefore only a small proportion of patients have available post-event utility data.

We acknowledge that there was an error in table 32, page 114 where we claim that "PRO questionnaires were not administered". They were in fact administered at some sites. The ZUMA-7 protocol states:

"All PROs were assessed at screening (within 14 days of randomization), start of chemotherapy (within 5 days of randomization for SOC arm and 5 days prior to axi-cel administration for the axi-cel arm), the date of axi-cel administration or the date of transplant, Day 50 (-7 to +21 days after randomisation), Day 100 (±14 days), Day

150 (± 14 days). In the long-term follow-up period beginning at month 9, PROs will be assessed every 3 months (± 28 days), until month 24."

After treatment, PRO questionnaires were administered at disease assessment visits, which were to occur for surviving patients until documented disease progression per central review or subsequent new lymphoma therapy. Notably, some sites continued to collect PROs after EFS events; but these comprised a minority of observations. As a result, the choice not to use ZUMA-7 post-event utilities in the cost-effectiveness analysis was based on the following reasons:

- Small sample size: As seen in Table 5 below, the post-event utility calculation was informed by [redacted] of the total number of PRO observations. In TA559, this was used as a rationale to avoid using these values[15]
- Potential selection bias: patients who are completing PRO questionnaires post-event are presenting patients and likely to be less severe since they are clearly able to coherently complete a questionnaire. Patients who are unable to complete the questionnaire are likely to be unwell or dead leaving only health participants in the sample post-event.
- The objective of the PRO analysis was to understand the effect of therapy over time on patient QoL, rather than the estimation of health state utility for purposes of economic evaluation. During the follow-up period PRO measures were collected at disease assessment visits, which were to only occur for surviving patients until disease progression per central review or new lymphoma therapy. Hence, collection of PRO data typically ceased post-event, and therefore is not representative of the entire health state period in the post-event state
- The event for the majority of the post-event utility data was progression, rather than new lymphoma therapy, which as we know from the PRO analysis has a transient decremental impact on QoL which would not be captured under the current analysis
- Post–event utilities should capture the entirety of the patient's quality of life, following the event until death. Utilizing the post-event utilities from the ZUMA-7 analysis would therefore overestimate patients QoL after an event since end of life disutilities are not captured.

Table 5: Frequency of EQ-5D-5L data for the post-event state

Treatment group	Time period	Visit	Active AE	Frequency	Percent
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]

Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Axi-cel	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]

SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
SOC	4: POST-EVENT	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; SOC, standard of care. **Notes:** the cumulative percentage of the post-event observations sums to [redacted]					

As per the request, an additional analysis of the utility estimates have been conducted, showing the pre- and post-event utilities by treatment, outlined in Table 6. The results from this analysis are implausible, with a higher utility in the post-event health state compared to the pre-event health state in the axi-cel arm, therefore these are not considered appropriate for modelling purposes.

Table 6: Utilities for the UK crosswalk for the pre- and post-progression states

Health state	**Utility (95% CI)**
Axi-cel	
Pre-event	[redacted]
Post-event	[redacted]
SOC	
Pre-event	[redacted]
Post-event	[redacted]
Key: CI, confidence interval; SOC, standard of care.	

As an alternative, we use utility data from the JULIET study in the base case, which is 0.710 and previously used in the NICE evaluation for Tisagenlecleucel (TA567).[16] The JULIET study was conducted in patients receiving Tisagenlecleucel in adult

relapsed or refractory DLBCL. The study collected SF-36 measures for patients enrolled in the trial and this data were mapped to derive EQ-5D utility scores based on UK preference weights, using the mapping algorithm reported by Rowen et al. 2009.[17] Alternatively, the ERG could consider using the ZUMA-1 derived pre-progression health state utility value of 0.72 (SE: 0.03) which can be considered post-event ZUMA-7 patients.[15]

Despite the issues with collecting post-event utilities described above, for completeness we present an additional scenario analysis using purely ZUMA-7 derived utility estimates. This was not conducted by treatment arm due to the implausible results outlined in Table 6.

Results for the scenario analysis using the ZUMA-7 post-event utility is in Table 7, and a scenario analysis using the ZUMA-1 pre-progression utility is in Table 8. The company base case is provided in Table 9 for comparison.

Table 7: Deterministic cost-effectiveness results (using ZUMA-7 post-event utility estimate of 0.779)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,678

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

Table 8: Deterministic cost-effectiveness results (using ZUMA-1 pre-progression utility estimate of 0.72)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,801
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care.							

Table 9: Deterministic cost-effectiveness results (company base case – JULIET utility estimate of 0.71)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,996
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care.							

Results show that despite a higher utility estimate being used, the ICER decreases in both cases, as most patients die after an event in the SOC arm, hence the accrual of post-event QALYs is much lower than in the axi-cel arm.

Further information can be found in Table 1 in the '*POST-HOC PATIENT-REPORTED OUTCOMES TO SUPPORT ECONOMIC MODELS'* document shared above. The table shows the mean, SD and N for the EQ-5D-5L index and VAS. This analysis was not conducted for the EORTC-QLQ-C30.

As requested, we provide a copy of the SAP for the QOL component for ZUMA-7.

[redacted]

We also provide the SAP for the post-hoc utility analyses to inform health-state utilities used in the economic model.

[redacted]

Resource use and costs

B6. PRIORITY. Document B, Section B.2.4.1, page 39 and Section B.3.5.2, page 121. Axi-cel acquisition costs. The ERG notes that although [redacted] of patients in the axi-cel group underwent leukapheresis, and had axi-cel successfully manufactured, treatment acquisition costs are only included in the model for the [redacted] who had an infusion. Please confirm that, in UK clinical practice, the NHS would only incur axi-cel treatment acquisition costs for patients who have received an infusion.

We can confirm that in UK clinical practice, the NHS only incurs axi-cel treatment acquisition costs for the patients that receive an infusion, therefore the method used in the model is reflective of clinical practice.

B7. Document B, Section B.2.4.1, page 39 and Section B.3.5.2, page 121. Axi-cel acquisition costs. The ERG notes that [redacted] patients were re-treated with axi-cel following progression. Whilst axi-cel re-treatment may be unlikely in UK clinical practice, the benefits of re-treatment are incurred on the OS curves in the economic model. The ERG, therefore, considers it reasonable to take into account the full costs of deriving those OS benefits in the estimation of cost-effectiveness. Please provide either:

- **An analysis appropriately adjusting the OS curve appropriately to remove the impact of re-treatment post-progression or**
- **An analysis where the re-treatment costs of axi-cel are included in the economic model.**

As per the ZUMA-7 protocol, patients in ZUMA-7 who achieved a PR or CR at the Study Day 50 disease assessment and subsequently experienced disease

progression were to have the option to receive a second course of lymphodepleting chemotherapy and axi-cel.

Censoring patients at the point of retreatment was considered as a potential approach to adjust overall survival for retreatment in the cost-effectiveness analysis; however this would have led to informative censoring and therefore was not considered appropriate. To avoid introducing potential biases, censoring in survival analysis should be non-informative; namely, participants who drop out of a study should do so due to reasons unrelated to the study.

It is acknowledged that including the retreated patients within the data is non-optimal, and while retreatment is not expected to occur in clinical practice (and is not requested for reimbursement in this submission), to align with the available clinical effectiveness data used to inform the model, cost-effectiveness results for axi-cel versus SOC when including axi-cel retreatment costs are presented in response to this question.

Of note, [redacted] which 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.

Of the [redacted] patients who were retreated with axi-cel, [redacted] required re-apheresis, [redacted] were retreated with a peripheral blood mononuclear cells (PBMCs) product (which refers to refers to axi-cel that was newly manufactured from cryopreserved PBMCs collected during the initial apheresis), and [redacted] were retreated with a ‘second bag’ (which refers to the cryopreserved second bag of axi-cel that was generated when the product was initially manufactured).

As described in Section B.3.5.2.1 of the company submission, the following treatment-related costs are considered within the axi-cel arm of the model:

- Leukapheresis
- Bridging therapy
- Conditioning chemotherapy
- Axi-cel drug acquisition costs

- Axi-cel infusion and monitoring hospitalisation costs

The level of retreatment costs considered in the model are dependent on the retreatment product received, as summarized in Table 10.

Table 10: Retreatment costs by product

Retreatment product	Retreatment costs considered
Re-apheresis (n = [redacted])	• Leukapheresis • Conditioning chemotherapy • Acquisition costs • Infusion and monitoring hospitalisation costs
PBMCs (n = [redacted])	• Conditioning chemotherapy • Acquisition costs • Infusion and monitoring hospitalisation costs
Second bag (n = [redacted])	• Conditioning chemotherapy • Infusion and monitoring hospitalisation costs
Key: PBMCs, peripheral blood mononuclear cells.	

As highlighted above, conditioning chemotherapy, axi-cel acquisition costs and infusion and monitoring hospitalisation costs were applied to an additional [redacted] of patients in the model. Table 11 summarizes the axi-cel treatment costs applied in the analysis, in the scenarios with and without retreatment.

Table 11: Axi-cel treatment costs by category

Retreatment product	Excluding retreatment	Including retreatment
Leukapheresis	[redacted]	[redacted]
Bridging therapy	[redacted]	[redacted]
Conditioning chemotherapy	[redacted]	[redacted]
Axi-cel acquisition	[redacted]	[redacted]
Infusion and monitoring hospitalization costs	[redacted]	[redacted]
Total	[redacted]	[redacted]

The deterministic cost-effectiveness results for including retreatment costs are presented in Table 12, with the company base case presented in Table 13. When compared with the company base case, the ICER for axi-cel versus SOC increases from £51,996 to £54,902, demonstrating that the retreatment has a relatively small impact on results.

Table 12: Deterministic cost-effectiveness results (including retreatment costs)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,902

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care

Table 13: Deterministic cost-effectiveness results (company base case)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,996

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

B8. Document B, Section B.3.5.5, page 136-137 and Appendix Q, page 211, Table 74. Subsequent treatment costs. The ERG notes that the company has consulted with clinical experts and adapted the distribution of post-progression treatments that would be used in clinical practice in NHS England to remove CAR-T therapy post-progression and to remove Nivolumab and Pembrolizumab. However, the OS curves have not been adjusted to account

for the different usage of subsequent treatments in UK clinical practice. Please:

- **Comment on the magnitude and direction of any bias this may cause, for both the base case and ITT cost-effectiveness analyses. What adjustments, if any, should be applied to the OS curves? Provide a scenario analysis applied to the base case (cross-over) where all subsequent treatment costs (except-axi-cel) are applied, as per those used in the ZUMA-7 trial**
- **Provide a scenario analysis applied to the ITT analysis (appendix Q) where all subsequent treatment costs are applied, as per those used in the ZUMA-7 trial**

The OS curves in the model have not been adjusted to account for the different usage of subsequent treatments in UK clinical practice. This was deemed appropriate as only a small number of patients receive Nivolumab and Pembrolizumab in the ZUMA-7 trial ([redacted] out of the [redacted] patients in the axi-cel arm and [redacted] out of the [redacted] patients in the SOC arm). Although it may be expected that not adjusting the OS curves could result in more favourable survival results, clinicians expect Nivolumab and Pembrolizumab are associated with relatively small survival benefits. This small survival benefit is expected to be balanced across both arms as a similar proportion receive Nivolumab and Pembrolizumab in each arm, therefore the magnitude of bias is expected to be small.

Results for the scenario analysis applied to the base case (crossover) where all subsequent treatment costs (except CAR T) are applied, as per those used in the ZUMA-7 trial is shown in Table 14 and the company base case in shown in Table 15.

Table 14: Deterministic cost-effectiveness results (including all subsequent treatment costs, except CAR T)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,099

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

Table 15: Deterministic cost-effectiveness results (company base case)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,996

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

Results for the scenario analysis applied to the ITT analysis where all subsequent treatment costs are applied, as per those used in the ZUMA-7 trial is shown in Table 16 and results from the original ITT analysis (with UK clinician estimates of subsequent treatment) are in Table 17. The ICER is lower when including subsequent treatment as per ZUMA-7, as a higher proportion of patients receive CAR T therapy in the SOC arm, driving higher costs in this arm.

Table 16: Deterministic cost-effectiveness results for ITT analysis (including all subsequent treatment costs)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,856
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care.							

Table 17: Deterministic cost-effectiveness results for ITT analysis (company ITT analysis)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£79,034
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care.							

B9. Document B, Section B.3.5.5, page 139. Please provide further details (study population, treatment line, setting etc) of the "previously published trial or observational evidence" sources used to derive the average number of treatment cycles for subsequent therapy costs, including how they were synthesised to provide the number of treatment cycles used in the model. Please also comment on the comparability of the populations from these studies to the ZUMA-7 trial population and the duration of subsequent therapy that might be expected in UK clinical practice.

The following text outlines how the number of cycles were determined for the different subsequent therapy options in the model.

For R-Chemo, an assumption of 3 cycles was used in the model. This was based on rounding up from the average of the four second-line regimens which were all

between 2 and 2.5 cycles per regimen in the model. The chemotherapy regimen guidelines from NHS trusts in England highlight that R-GDP, R-ESHAP and RICE should be administered for a maximum of 3 cycles, whilst R-DHAP should be administered for a maximum of 4.[18-22] Therefore using 3 cycles was considered appropriate.

For pola-BR, 6 cycles was based on the NHS Lymphoma chemotherapy protocol (version 1, November 2020).[23] This is deemed applicable as the protocol outlines that 6 cycles should be administered to patients with DLBCL who have relapsed or refractory disease, after previous chemotherapy, previous autologous or allogenic SCT or after previous CAR T therapy.

For R-Lenalidomide, a phase-II study in patients in elderly relapsed diffuse large B-cell lymphoma patients treated with lenalidomide plus rituximab was used to determine the number of cycles.[24] The paper reported that lenalidomide and rituximab was administered for four cycles, plus lenalidomide maintenance until disease progression or for 8 cycles. Only 7 out of 23 of the patients received the full maintenance therapy, therefore for simplicity, four cycles were applied in the model. Although this study was conducted in elderly DLBCL patients and may not be fully reflective of the ZUMA-7 population, increasing the number of cycles of R-Lenalidomide has a very small impact on the ICER.

Nivolumab and pembrolizumab were not used in the base case analysis, however the following information was used to inform the number of cycles for the scenario provided in question B8.

For nivolumab, a phase II study in patients with R/R DLBCL who are ineligible for or failed autologous transplantation was used to estimate the number of cycles.[25] Nivolumab was administered to patients every 2 weeks until disease progression. We estimated 2 cycles based on the study reporting a median of four doses (two doses per cycle) that were received by the cohort that failed autologous hematopoietic cell transplantation. Average age was slightly higher in the study compared to ZUMA-7 (62 versus 57), and the median prior lines of therapy was three.

There is limited data on pembrolizumab use in DLBCL, however, two studies were sourced to inform the number of cycles. The first study was a phase-II trial conducted in patients with DLBCL after auto-SCT.[26] Patients received pembrolizumab every 3 weeks for up to 8 cycles, however, only 62% completed all 8 cycles. The second study evaluated pembrolizumab in combination with R-CHOP in untreated patients with DLBCL.[27] Patients received up to 6 cycles, however, 26 out of 29 patients received all planned doses of pembrolizumab; two patients had 2 doses held, and one had 3 doses omitted. No data on the average number of cycles was available in both studies, therefore an assumption of 5 cycles was used in the model.

B10. Document B, Appendix Q, page 208-212. Given that the review of axi-cel on the CDF in England will be undertaken later this year, please provide a full set of scenario and probabilistic analyses for the ITT cost-effectiveness modelling in Appendix Q.

Given that the appraisal committee meeting for the review of axi-cel for the treatment of DLBCL after 2 or more systemic therapies on the CDF in England will be after this appraisal committee meeting for axi-cel in treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy, a full set of scenario and probabilistic analyses for the ITT population is not considered applicable. This analysis is considered out of scope and therefore the scenario analysis provided in Appendix Q is considered sufficient.

Section C: Textual clarification and additional points

Text clarifications

C1. Document B, Section B.3.4.2, page 110. Please review the text on page 110 for accuracy and correct as appropriate: "This resulted in an 'on-treatment' utility of 0.772 for the SOC arm, and for the axi-cel patients a lower utility of 0.780"

We can confirm this is a typo and that the text should read:

This resulted in an 'on-treatment' utility of 0.772 for the SOC arm, and for the axi-cel patients a higher utility of 0.780.

Abbreviations

C2. Document B. Please provide a list of abbreviations.

Abbreviation	Definition
1L	first-line
AAIPI	age-adjusted International Prognosis Index
ABC	activated B-cell
Admin	administration
AE	adverse event
AIC	Akaike information criterion
Allo-SCT	autologous stem cell transplant
Anth-bc	anthracycline based chemotherapy
AUC	area under the curve
auto-SCT	autologous stem cell transplant
ASCT	autologous stem cell transplant
BEAM	carmustine (BCNU), etoposide, ara-C, melphalan
BIC	Bayesian information criterion
BNF	British National Formulary
BR	bendamustine, rituximab
BSC	best supportive care
CAR	chimeric antigen receptor
CBV	cyclophosphamide, BCNU, etoposide
CC	complication and comorbidity
CEOP	cyclophosphamide, etoposide, vincristine, prednisolone
CEPP	cyclophosphamide, etoposide, procarbazine, prednisone
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHAP	dexamethasone, cytarabine and cisplatin
DLBCL	diffuse large B-cell lymphoma
DOR/DoR	duration of response
EBV+	Epstein-Barr virus-positive
ECG	electrocardiogram
ECHO	echocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
eMIT	electronic market information tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30
EPOCH	etoposide, vincristine, doxorubicin, bolus cyclophosphamide, prednisone
EQ-5D	EuroQol five dimensions
ESHAP	etoposide, methylprednisolone, high-dose cytarabine and cisplatin
FACT-G	Functional Assessment of Cancer Treatment-General
FACT-Lym	Functional Assessment of Cancer Treatment-Lymphoma
FAD	final appraisal determination
FAS	full analysis set
FL	follicular lymphoma
GBP	British pound sterling
GCB	germinal centre B-cell
G-CSF	granulocyte colony-stimulating factor
GDP	gemcitabine, dexamethasone and cisplatin
GEMOX	gemcitabine and oxaliplatin
GP	General practitioner
Haplo HCT	Haplo hematopoietic cell transplantation
HDT	high dose therapy
HGBL	high-grade B-cell lymphoma
HIV	Human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HR	hazard ratio
HRQL	health-related quality of life
HUI	health utilities index
ICE	ifosfamide, carboplatin and etoposide
ICER	incremental cost-effectiveness ratio
IFRT	involved field radiotherapy
iNHL,	indolent non-Hodgkin’s lymphoma
IPCW	inverse probability of censoring weights
IV	intravenous
IVE	ifosfamide, etoposide and epirubicin
IVIG	intravenous immunoglobulin
Liso-cel	lisocabtagene maraleucel
LPHD	lymphocyte predominant Hodgkin’s disease

Abbreviation	Definition
KM	Kaplan–Meier
LBCL	large B cell lymphoma
LDH	lactate dehydrogenase
LTR	Long terminal repeat
LYG	Life years gained
M	month
MEP	methotrexate, etoposide and cisplatin
MCM	Mixture cure model
mEFS	modified event-free survival
MIMS	Monthly Index of Medical Specialties
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines & Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MUD	matched unrelated donor
NA	not applicable
N/A	not applicable
NCT	National Clinical Trial
NE	non estimable
NEL	non-elective long-stay
NES	non-elective short stay
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
NR	not reached
NR	not reported
ORR	objective response rate
OS	overall survival
PET-CR	positron emission tomography-complete response
PD	progressive disease
PD	progressed disease
PF	progression free
PFS	progression-free survival
PMBCL	primary mediastinal large B-cell lymphoma
PO	orally
pola-BR	polatuzumab vedotin + bendamustine + rituximab R, rituximab

Abbreviation	Definition
PR	partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	patient reported outcomes
PSA	probabilistic sensitivity analysis
PSS	Personal and Social Services
PSSRU	Personal and Social Services Research Unit
QALY	quality-adjusted life year
QoL	quality of life
R	rituximab
R-Anth-bc	rituximab anthracycline based chemotherapy
R-CEPP	rituximab, cyclophosphamide, etoposide, procarbazine and prednisone
R-CEOP	rituximab, cyclophosphamide, etoposide, vincristine, prednisone
R-CHOP	rituximab with cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone
R-DA-EPOCH	rituximab dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin
R-DexaBEAM	dexamethasone, carmustine, etoposide, cytarabine, and melphalan
RCT	randomised controlled trial
R-DHAP	rituximab + dexamethasone, high-dose cytarabine and cisplatin
R-DHAX	rituximab, dexamethasone, oxaliplatin, high-dose cytarabine
R-ESHAP	rituximab + etoposide, methylprednisolone, cytarabine, cisplatin
R-GDP	rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin
R-GEM-L	rituximab, methylprednisolone, gemcitabine, lenalidomide
R-GemOx	rituximab, gemcitabine, oxaliplatin
R-GEM-P	rituximab, methylprednisolone, gemcitabine, cisplatin
R-ICE	rituximab + ifosfamide, carboplatin and etoposide
R-MICE	moderately intensive rituximab, cyclophosphamide, etoposide
R-MINE	rituximab, mesna, ifosfamide, mitoxantrone, etoposide
RPSFT	rank-preserving structural failure time
RPSFTM	rank preserving structural failure time model
RT	radiotherapy
r/r	relapsed or refractory
sAAIPI	second-line age-adjusted International Prognostic Index
SAE	serious adverse event
SAS	safety analysis set
scFv	single-chain variable region fragment

Abbreviation	Definition
SCT	stem cell transplant
SD	standard deviation
SE	standard error
SF-36	Short Form Health Survey-36
SF-6D	Medical Outcomes Study Short-Form 6 dimension
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	standard of care
SOCT	standard of care therapy
TA	technology appraisal
TBI	total body irradiation
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TFL	transformed follicular lymphoma
TLPL	transformed lymphoplasmacytic lymphoma
TMZL	transformed marginal zone lymphoma
TNLPHL	transformed nodular lymphocyte-predominant Hodgkin lymphoma.
TTNT	time to next treatment
UK	United Kingdom
VAS	Visual analogue scale
WTP	Willingness to pay
Z-BEAM	ibritumomab tiuxetan (Zevalin®) BEAM

References

C3. If possible, please send the reference package as a RIS file.

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References

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Anthony Nolan
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). 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. The responses in our submission relate specifically to the impact of relapsed or refractory Diffuse Large B-Cell Lymphoma for people who require, or who have received, a stem cell transplant. 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, Patient organisation submission Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684] 3 of 11 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 manufacturer(s) of the technology and/or comparator	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)

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	- For ongoing work related to helping patients during the pandemic grant received (£15,000) 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?	Our submission is based on feedback received from people personally affected by relapsed or refractory diffuse large B-cell lymphoma, including patients and their carers. This information was gathered through an online survey of patients and their families, 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. The survey was also circulated to patient and ambassador networks by Blood Cancer UK. We have also consulted with clinical experts to understand more about the experiences of patients and the range of current standard of care treatment options for transplant recipients.
Living with the condition	
6. What is it like to live with the condition? What do carers	**Receiving a diagnosis of diffuse Large B-cell lymphoma**

experience when caring for someone with the condition?	• Patients diagnosed with diffuse Large B-cell lymphoma (DLBCL) described experiencing generalised symptoms that they had not thought were indicative of cancer. These included swelling, stomach pains, indigestion-like feelings and weight loss, which took some time to diagnose. One patient described visiting their GP 4 to 5 times over a 6-month period before they eventually received their diagnosis. **Experiencing relapsed or refractory diffuse large B-cell lymphoma** • Patients described feeling shocked and heartbroken when they heard their cancer had relapsed. One patient described the 'paralysing fear' they experienced when returning to hospital for a check-up, only to find out that the disease had come back. They discussed the difficulty of their treatment and the fear of having to go through 'gruelling' chemotherapy again. • Another spoke about feeling knocked back by their relapse, after believing they had made real progress through extremely difficult treatment cycles, they described feeling 'back at square one' in their treatment journey. **Impact on daily life** • Intravenous treatments for the conditioning regimen and post-transplant recovery mean that patients are often required to spend significant periods of time in hospital, as an in-patient. It was commented that this can often impact people's ability to lead a normal life, including working and socialising. • Patients told us that living with a relapsed or refractory disease 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. o 'I was unable to socialise for years' said one patient. Another commented 'I was in and out of hospital constantly. I felt that I added so much disruption to my family's lives'. **Mental health and wellbeing impact** • Patients spoke about their treatment journey taking several years, but many admitted that the mental health impact has been even longer-term, outlasting their physical recovery. Despite trying to remain positive many reflected on feeling extremely down during points of their treatment. • 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.

	• Body image was raised, with people commenting on the impact of swellings and weight changes. One patient told us, “when I started to lose my hair, that was when I thought I was going to die’. • Disease relapse was also highlighted as having a significant impact on mental health, with patients commenting that it felt like a ‘setback’, adding to the uncertainty of recovery and the impact on their friends and family. **Experience of Carers** • One carer we spoke to reflected on the huge amount of strain that caring for someone with relapsed 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. • 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’. • Concerns about infection post-stem cell transplant are particularly worrying for carers. Carers describe feelings of anxiety and fear regarding the potential of spreading infection to their loved ones at a time when their immune systems were at their most vulnerable.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Patient experience of current standard of care treatments and side effects** • The patients that we spoke to had experience with a range of treatments currently available on the NHS. They reflected on the need to take multiple drugs over a prolonged period, which often required remaining in hospital for extended stays. • Salvage high-dose chemotherapy followed by autologous stem cell transplantation is the standard of care and is effective for approximately two-thirds of all patients undergoing this treatment as a 2nd-line therapy. • The high-dose conditioning regimen 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 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'. • The hope for many, is that if any new drugs are more effective or better tolerated than existing, aggressive treatments, this could have a positive impact on patients. • R-CHOP (CHOP chemotherapy with the drug rituximab) o After a DLBCL relapse, one patient had to have further treatment of chemotherapy and a stem cell transplant. After their pre-transplant chemotherapy, they 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) o Another patient had this regimen following their first disease relapse. They 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) o 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.
8. Is there an unmet need for patients with this condition?	• Approximately one- third of DLBCL patients experience relapsed or refractory disease and this remains a major cause of morbidity and mortality. There is a large unmet need for additional treatment options for patients with relapsed DLBCL. **Conditioning regimen** • Salvage high-dose chemotherapy followed by autologous stem cell transplantation is the standard of care for chemosensitive relapses in DLBCL. Various salvage regimens are available, such as LEAM and BEAM conditioning, but the quest for an optimal regimen continues. • A substantial proportion of patients are not eligible for high-dose chemotherapy followed by autologous stem cell transplant (ASCT). This may result from advanced age or comorbidities; because they are refractory to second-line treatment; or because they express a desire not to undergo the treatment. **The need for new treatments**

	• Ineligible patients have distinctly lower survival rates (Feugier et al, 2005; Thieblemont & Coiffier, 2007), and treatment options comprise of conventional chemotherapy, enrolment in phase I or II clinical trials, radiotherapy in localised lesions, rituximab therapy and optimal supportive care. • New therapies are needed for patients with DLBCL that is resistant to standard therapies. Indeed, unresponsiveness to standard chemotherapy and relapse after ASCT are indicators of an especially poor prognosis. • From personal experience, patients 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. References: • Feugier, P., et al., (2005). Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J. Clin. Oncol, 23(18), 4117–4126. https://doi.org/10.1200/JCO.2005.09.131 • Thieblemont, C., & Coiffier, B. (2007). Lymphoma in older patients. J. Clin. Oncol., 25(14), 1916–1923. https://doi.org/10.1200/JCO.2006.10.5957
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	**Improved outcomes** • Patients and clinical representatives spoke about the potential for better response rates longer term, with a key potential benefit being improved survival outcomes and progression free survival. • Patients told us that if CAR-T therapies provide a smaller toxicity and side-effect profile this would be an improvement from their experience of existing treatments. • Data suggests there is a defined benefit above the standard of care for certain populations with improved survival outcomes and progression free survival, and this may serve as a viable alternative for those unlikely to tolerate high-dose chemotherapy. • Locke et al. investigating ZUMA-7 trial analysis found 2-year overall survival stood at 61% for the CAR-T arm, compared to 52% in the standard-care arm. • In the BELINDA trial, Bishop et al. compared tisagenlecleucel (162 patients) with ASCT (160 patients) but

	observed no substantial differences in the frequency of complete response or in event-free survival. References: • Locke, Miklos, Jacobson et al., (2022), Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma, N Engl J Med 2022;386:640-54. • Bishop, Dickinson, Purtill et al., (2021), Second-Line Tisagenlecleucel or Standard Care in Aggressive BCell Lymphoma, N Engl J Med 2022;386:629-39.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	• Patients and carers did not voice any specific concerns about the disadvantages of this treatment; however, they did raise queries about potential side effects, noting the importance of quality of survival. • Clinical experts consulted as part of this work raised uncertainty around the long-term risks and outcomes of CAR-T therapies. Further, they raised that it is possible that this is technology may only benefit a relatively small number of patients. • CAR-T therapies are not being considered as a replacement therapy to the existing standard of care, but rather an alternative for appropriate patients. Identifying eligibility will be determined by good clinical judgment and a careful history and physical examination of the most important aspects of a patient following their last treatment. How these assessments are made, and protocols adopted may create deviations around the manufacturers' directions.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• Patients with refractory DLBCL have poor overall survival rates, and this is especially true for older patients and those with comorbidities. • Patients with severe medical or psychiatric illness, active central nervous system involvement, or HIV seropositivity can be considered ineligible for autologous transplantation. • Patients with chemorefractory, relapsed disease, including acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and NHL could benefit more from accessing CD19 CAR-T therapies.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	• We have not identified any equality issues

Other issues	
13. Are there any other issues that you would like the committee to consider?	• The cost of current standard of care treatments is well understood, but the introduction of new CAR-T as a 2 nd line treatment is less well defined. Given the comparable outcomes to salvage, pathway tariff costings should be understood. • Agreement will also be required on what will be considered after a poor CAR-T result. If an allograft is not appropriate, clarification is needed on how 2 nd line CAR-T will affect later treatment decision making. • Guidance is required on the protocols to determine refractory or relapsed eligibility for CAR-T treatment, this will avoid significant divergence across clinical practice. The clinical community should be consulted on the development of this harmonisation process.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- The current standard of care for relapsed or refractory DLBCL can significantly improve the outcomes of up to two-thirds of patients.
- Patients experience a range of serious physical and mental challenges as a result of relapsed or refractory DLBCL.
- Relapsed or refractory DLBCL has a significant impact on the quality of life of both carers and patients.
- Alternative treatment options are needed for treating relapsed or refractory DLBCL, but overall improvement in outcomes still requires attention.
- Patients and clinical representatives 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

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

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- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Blood Cancer UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Blood Cancer UK is the UK's leading blood cancer research charity. We fund world-class research and provide information, support, and advocacy to anyone affected by the different types of blood cancer – from leukaemia, lymphoma, and myeloma to the rarest blood cancers that affect just a small group of people. We also provide education and training to healthcare professionals including nurses, caring for people with blood cancer. Blood Cancer UK has ~100 employees and is funded primarily through donations and legacies.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	We received ~£100k from Kite/Gilead for Covid-19 vaccine research.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Blood cancer UK has close relationships and maintains regular contact with the haemato-oncology patient and clinical community. We maintain regular contact with them through our Healthcare Professional Advisory Panel (HPAP), Nurses Working Group (NWG), our patient ambassador network etc. We additionally maintain relationships with many other blood cancer specialists – from research nurses to academic researchers – through our Information and Support, Research, and Policy, Campaigns and Engagement teams. We discussed Axicabtagene ciloleucel (Axi-cel) with our patient community including several who received Axi-cel as a 3L treatment for relapsed/refractory DLBCL. We reached patients with experience of the technology through our social media channels, newsletters and through our clinical networks. In particular, we spoke to 8 patients and 2 carers. Through these conversations, we received a wide breadth of experiences of people from relatively diverse backgrounds (including 2 patients from an ethnic minority background) of different ages, geographies and experience of Axi-cel's side effects. Some patients experienced very little side effects while two patients were admitted to ICU following treatment and stated they'd still recommend Axi-cel as it gave them their life back with better quality. We also gathered views of some of our clinical community, in particular, a Consultant Haematologist based at a major London teaching hospital and a research nurse based in Birmingham.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	DLBCL is an aggressive disease and is the most common form of non-Hodgkin lymphoma with over 5,000 new diagnoses each year in the UK. Although it can develop at any age, it's more common in older people, typically over the age of 60. The most common symptoms are swollen lymph nodes usually in the neck, armpit or groin. Patients may also experience chest or abdominal pain, bone pain, coughing or breathlessness. DLBCL can also cause B symptoms such as unexplained fever, drenching night sweats and unexplained weight loss. There is a heavy burden borne by patients and carers who experience refractory / relapse disease in both managing symptoms of disease combined with the toxicity of treatment. Around 10-15% of people with DLBCL have refractory disease, meaning the cancer doesn't respond to treatment. A further 20-30% of patients will relapse, usually in the first 2-5 years. At this stage, people have already suffered from the impact of going through chemotherapy for many months, often alongside steroids, experiencing side effects like infections, fatigue, nausea and vomiting, diarrhoea, nerve damage, hair loss, mouth sores and insomnia. Carers play a critical role in patients' disease and treatment journey and caring for someone with DLBCL is often very challenging and burdensome. Carers are fundamental to a patient's day to day wellbeing, helping with everything from transportation, managing appointments to their nutritional needs. A carer we spoke to revealed that due to and during his wife's journey with DLBCL, his mental health declined 'quite significantly' that he's had to start counselling and is still on antidepressants, as watching his wife decline has had a 'lasting impact' on him. As burden of treatments mount, carer's needs and quality of life should also be prioritised.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Both the disease itself and its treatments can significantly affect quality of life. Experiences of treatments vary. Although patients are grateful for the therapy options, treatments for DLBCL can be aggressive, burdensome and demanding with regards to logistics and health-related quality of life. It subsequently can have significant and extensive impacts on patients' mental health and day-to-day life. Most commonly used initial treatment is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). For transplant- eligible patients who have chemotherapy-sensitive disease, salvage chemotherapy with autologous stem cell transplant (ASCT) is also an option. However, the patients who fail R-CHOP (refractory / relapsed disease) have poorer outcomes. The chemo-resistant subset is a population who view the current treatment landscape as suboptimal or somewhat futile as there's limited treatment options that offer a long-term remission for this cohort. For these patients, the key areas of concern with regards to current treatments include insufficient response, fear of relapse, side effects and the necessity for repeated treatment cycles which one patient described as being a "constant confrontation with mortality." A patient who underwent stem cell transplantation described it was the "lowest point of my life, I was completely washed out… it took two to five months to feel I was recovering." Another patient described that during her second line chemotherapy treatment, she decided she could not continue with "chemo wrecking my body without getting rid of the cancer…it had huge impacts on my mental health."
8. Is there an unmet need for patients with this condition?	Yes, there is a significant unmet need in the relapsed / refractory DLBCL setting for effective, ideally curative treatments, or at minimum for treatments with less side effects than current options which can also provide durable remissions, where traditional chemotherapy has failed. A Consultant Haematologist we spoke to stated that "patients diagnosed with DLBCL reaching second line treatment face a significant challenge: having an intense treatment that fails in up to 75% of cases. This is three out of four transplant-eligible patients in second line are subjected to a futile treatment… Because of this, some patients see 2L treatment like a toll they need to pay to get to CAR-T cell therapy." In addition to

	the physical challenges and impact, side effects from intense rounds of chemotherapy combined with the possibility of treatment failure has a significant emotional burden on patients and carers.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	There is excitement in both the clinical and patient community re. Axi-cel's potential movement to the 2L context. Both communities have identified that the transition will mean the opportunity for earlier use of a potentially curative treatment where more DLBCL patients can have an earlier chance at a cure. One consultant haematologist told us "apart from avoiding futile treatment, having the most effective treatment in 2L rather than in 3L for high risk patients only makes sense: it spares chemotherapy toxicity and healthcare costs in high-risk patients (i.e. patients unlikely to respond to standard 2L treatment) and allows a more effective CAR T cell treatment." A nurse also told us that Axi-cel is a "lot gentler than having a transplant." This was mirrored in our conversations with patients. One patient described "CAR-T was a lot easier to handle than the unsuccessful stem cell transplant" they underwent. Another patient expressed "the chemotherapies I had in earlier lines of treatment felt as if it were attacking me as well as the cancer, whereas CAR-T was just attacking the cancer in a better, controlled way…. I would have been grateful if I had it at second line." Another patient described Axi-cel as "totally simple, easy and painless" at the time. Although he later experienced flu-like symptoms and had to be admitted to ICU for a few days, he recovered "fairly quick and was absolutely fine" two weeks later. He expressed that "previous lines of chemotherapy made me feel like a chronic case of being unwell and a reminder of general illness, whereas CAR-T experience was an acute, short burst of side effects." The patient added that "with chemo, I was in a constant haze, and it took a while to come back to my life each time…with CAR-T, I was able to mentally pick up my life quicker because I didn't ever leave it…. I became less conditioned to being vulnerable." This was mirrored through another patient who stated that the benefits of CAR-T outweigh any inconvenience.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Like with all treatments, patients can be anxious about the potential, serious side effects. This was highlighted in our conversations with DLBCL patients who had been treated with Axi-cel. One patient said "I was worried about the side effects, but I had a great team looking after me who explained everything beforehand…. I felt reassured and knew this was a great chance regardless." A carer told us that "it was emotionally challenging when she [his wife] was put in an induced coma after CAR-T…it was quite stressful at the time but now looking back I think she'd say it was worth it because the treatment handed her back to us and I'll forever be grateful." Another drawback highlighted by patients is the requirement to stay close to the hospital even after treatment. This can bring logistical and practical challenges for some patients, especially if they do not have the support of carers. However, the requirement to stay within close proximity to the hospital also provides reassurance to patients. Many of the patients we spoke to describe the disadvantages, side effects or inconveniences caused by receiving Axi-cel are far outweighed by the benefits it provides.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	A consultant haematologist highlighted to us the importance of identifying the right subset of patients (i.e those unlikely to respond to chemotherapy and likely to respond to Axi-cel and that by identifying the right subset of patients (who have high-risk genetic lesions, patients who are refractory to chemotherapy, patients who are not transplant eligible), we will only spare futile treatments and reduce healthcare costs.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As CAR-T is restricted to only commissioned CAR-T centres, it could cause 'short-lived' geographical inequality. It could pose challenges for the patients who live further from centres and cannot afford, for financial or logistical reasons, to travel longer distances. However, this issue should become less significant as the number of CAR-T centres increase in the UK.
Other issues	
13. Are there any other issues that you would like the committee to consider?	-
Key messages	
15. In up to 5 bullet points, please summarise the key messages of your submission: • Diffuse Large B-Cell Lymphoma is a curative disease. However, a significant proportion of patients will fail to respond to first line therapy or will relapse after an initial response. This population lives with the challenges associated with the disease itself combined with the side effects from treatment as well as the psychological impacts of ineffective treatments. This has significant effects on the quality of life of both patients and carers.	

- Current treatment options do not offer a cure or produce durable remissions for all patients with DLBCL. This demonstrates a significant need for effective therapies earlier in the disease course. Patients with R/R DLBCL frequently have to cope with constant fatigue, fear of relapse and anxiety about side effects of treatment.
- With regards to treatments, the most important aspects to patients are its curative potential and its ability to improve quality of life.
- Offering Axi-cel to appropriate patients earlier in the treatment course could provide improved access, offer more patients an opportunity of a cure and better quality of life as a result.
- Although complex, Axi-cel spares appropriate patients from undergoing futile treatments and associated side effects and gives them the opportunity to return to relative normality quicker with regards to fewer hospital appointments in the long run and their health-related and general quality of life.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- 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 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Lymphoma Action
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12	Gilead - £1,000 for Lymphoma Management

months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
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?	We sent a survey to our network of patients and carers asking about their experience of current treatment and their response to this new technology, with particular emphasis on quality of life. We received two responses from patients with a relevant diagnosis, which we have used as the basis of this submission. We have also included information based on our prior experience with patients with this condition.
Living with the condition	
6. What is it like to live with the condition? What do carers	DLBCL is an aggressive lymphoma. Patients have said it is *"difficult"* to live with DLBCL. Most people with DLBCL first notice rapidly-enlarging lumps, often in the neck, armpit or groin but they can be in the chest or abdomen. Symptoms can vary depending on where the lymphoma is growing. DLBCL in the stomach

experience when caring for someone with the condition?	or bowel can cause abdominal discomfort or pain, diarrhoea or bleeding and DLBCL in the chest can cause a cough or breathlessness. Around 1 in 3 people with DLBCL experience fevers, night sweats and unexplained weight loss. Fatigue, loss of appetite and severe itching are also common. DLBCL is treated with the aim of cure. However, up to 50% of patients are refractory to treatment or relapse after initial treatment. The prognosis for patients with relapsed or refractory DLBCL is poor, with median survival less than a year. During treatment, patients often spend many weeks in hospital, isolated from family and friends. One patient commented, *"Life was completely on hold".* Side effects of intensive chemotherapy, such as sickness, diarrhoea, hair loss and neutropenia can be extremely debilitating, affecting many aspects of life. One patient reported the side effects they had experienced as: "*Fatigue, constipation, weakness, lack of sleep, sore mouth, sore gums, loss of appetite, change of taste, and loss of hair*." Another said "*I had to be nursed … I couldn't stand up, I had to use a walker."* It can take months or even years after treatment to recover. Patients report taking a year or more off work to recover from intensive chemotherapy regimens and stem cell transplants. Many experience financial worries. One patient said: "*We are both mainly retired so our finances were not greatly affected, and apart from domestic concerns for our grown up kids we live fairly normal lives."* Some side effects, especially fatigue and peripheral neuropathy, can last for many years and have a significant impact on quality of life. Younger patients may experience fertility issues or early menopause. The psychological impact of the diagnosis is enormous. Patients report experiencing insomnia, anxiety and a 'constant fear of dying'. Spending many weeks in hospital can have a detrimental effect on the patient and the family as a whole. Even after successful treatment, the relief of getting back into some kind of normal life is marred by the anxiety of relapse. One patient said*: "I lived in fear of recurrence, especially as I continued to have discomfort in the neck and some abdominal symptoms."* Late effects of treatment are also a psychological and physical challenge. People with DLBCL can be very ill and caring for someone with DLBCL can be emotionally challenging and time-consuming. One patient said: *"I think my wife was quite badly affected by my initial diagnosis … Me too probably, but the relatively good percentage overall survival, even 'cure' in my type helped us tackle the problem."* Some carers take significant amounts of time off work to transport their loved one to-

	and-from hospital, care for dependants, collect medications and visit hospital. It can be very difficult for carers to understand what their loved one is experiencing. They often feel helpless, anxious and scared.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most people with DLBCL are treated with chemo-immunotherapy, sometimes followed by radiotherapy. High-dose chemotherapy regimens might be used. For relapsed or refractory DLBCL, salvage chemotherapy followed by stem cell transplant is the most common treatment option. Treatment is very intense and some people are not able to tolerate it. Patients feel their "*quality of life is affected"* with current treatment. One patient said: "*Current treatments do work but are very invasive."* People who experience a subsequent relapse may be eligible to have CAR T-cell therapy. Again, this is a very intensive treatment that can cause serious side effects. Additionally, patients have to remain stable for long enough to receive the treatment. The long-term durability and late effects of CAR T-cell therapy are as yet unknown. Most patients experience significant side effects and many go on to develop late effects. Treatment has a long-lasting impact on physical and mental wellbeing. Most patients felt it took many years to recover from their treatment. However, patients are unanimously grateful that treatment has given them another chance. One patient said: "*I was concerned that the treatments would be very tough … Thankfully apart from one acute infection scare and modest side effects my experience was very acceptable."*
8. Is there an unmet need for patients with this condition?	There is an unmet need for patients who have not benefitted from available treatments. CAR T-cell therapy offers hope when other treatments have failed; it is potentially life-saving. One patient said: *"In most respects I have made a good recovery, bearing in mind I still have a slight chance of relapse, so my interests in second line therapies and potentially more successful first line treatments both for myself and others remains high."*

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	CAR T-cell therapy offers hope when other treatments have failed; it is potentially life-saving. One patient said *"Targeted treatment sounds better, simpler and more effective."* Another said: *"I think that despite the difficulties and, I assume, cost, the increased chances of long remission/cure of disease is very important. I believe this therapy is a springboard for a range of potentially very effective new therapies where costs ought to moderate over time … I appreciate that currently the treatment needs to be managed in a Cancer Centre or large Teaching Hospital, and that for some people travel might be an issue, but I believe that the need for hospital in-patient status is getting less and less as more is learned about prediction and management of major problems."*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	CAR T-cell therapy can cause life-threatening side effects. One patient who had CAR T-cell therapy for DLBCL said "*I felt unwell and slowly my energies seemed to drain away day-by-day … My hand tended to shake as days went by, I noticed how my fine motor control had diminished … I did feel unwell, at times, very unwell."* Around 1 in 5 people who have CAR T-cell therapy need treatment on an intensive care unit. CAR T-cell therapy is only given in hospitals that have the facilities and staff to treat side effects effectively. Patients need to stay close to the hospital or in hospital for long periods of time after treatment so they can be monitored. This can be isolating and it puts a strain on patients and their families.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	One patient wrote: *"various scientific studies make clear which groups are likely to benefit most from better overall or progression free survival. These include age, prior fitness, other diseases, capacity and capability of the delivering team/hospital etc.*
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No equality considerations.

Other issues	
13. Are there any other issues that you would like the committee to consider?	None

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • Prognosis for people with relapsed or refractory DLBCL is extremely poor and any new treatment offers a potential lifeline. • Current treatments for relapsed or refractory DLBCL are very intensive, requiring long stays in hospital away from the support of family and friends and incurring serious side effects and late effects. • People with relapsed or refractory DLBCL often take many months to recover from treatment and need significant time off work. The psychological, social and economic impact of this is considerable.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

Thank you for agreeing to give us your organisation's 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- 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 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologists

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ **X** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Cure is the main aim of treatment though chances of achieving a cure vary substantially depending on age of the patient, transplant eligibility and other disease characteristics.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Durable complete remission as assessed by PET-CT scan.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Outcomes for patients with relapsed DLBCL are sub-optimal. Length of 1st remission has a major bearing on their outcomes with 2nd line therapy. Patients relapsing >12 months after RCHOP have an estimated 2 year OS of around 60% and PFS of around 45-50%. But patients relapsing within 12 months of RCHOP chemotherapy have very poor outcomes with current treatment. The chances of 2 year OS are around 35% and PFS is <20% even in transplant eligible patients who are fit for intensive chemotherapy based approaches. Outcomes for older or non-transplant eligible patients are treated with non-curative treatment approaches and their outcomes are even worse with expected 2 year overall survival of <20%.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients who are fit and transplant eligible (typically <70 years of age) are treated with a curative intent with 2-3 cycles of intensive salvage chemotherapy (with regimens such as R-GDP, R-ICE, R-DHAP, R-IVE, R-ESHAP) followed by consolidation with high dose chemotherapy (with BEAM or LEAM) and autologous stem cell transplant if they have chemo-sensitive disease. Patients who are less fit and/ or transplant ineligible are treated with a non-curative intent with less intensive chemotherapy regimens (such as R-Gem-Ox or Polatuzumab-bendamustine-rituximab). Elderly or frail patients are offered palliative approaches which may include low dose oral chemotherapy based regimens.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCSH guidelines 2016. NICE guideline 2016.
• Is the pathway of care well defined? Does it	For transplant eligible patients, the treatment pathway is as described above and fairly standard. There is variability in approach to treatment for non-transplant eligible patients with use of a wide variety of

vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	chemotherapy regimens of varying intensity. In the last year polatuzumab-bendamustine-rituximab regimen has emerged as an important treatment option for these patients.
• What impact would the technology have on the current pathway of care?	CAR T therapy in 2nd line treatment of DLBCL represents a major shift which will transform the current treatment pathway. Zuma 7 trial only included patients who had primary refractory disease or those who relapsed within 12 months of 1st line therapy. Patients relapsing >12 months after 1st line therapy were not included. Availability of CAR T therapy in 2nd line treatment for DLCBL patients relapsing within 12 months of RCHOP is expected to improve their outcomes significantly. For transplant eligible patients, treatment with axicel resulted in a 2 year EFS and PFS of 41% and 46% in the Zuma 7 trial compared to only 16% and 27% in the SOC arm. Zuma 7 trial enrolled only transplant eligible patients as the control arm was intensive chemo and transplant. However current UK experience is that some non-transplant eligible patients may still be eligible for CAR T therapy. CAR T therapy in 2nd line setting may offer even greater benefit to non-transplant eligible but CAR T fit patients who are currently treated with non-curative intent.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No. 2nd line chemotherapy is currently delivered in BCSH level 2 centres and autologous stem cell transplants are performed in all level 3 centres. CAR T therapy is currently only delivered in a limited number of commissioned CAR T centres which is soon to expand to include most allogeneic stem transplant centres.
• How does healthcare resource use differ between the technology and current care?	CAR T therapy is a form of ATMP which comes with specific commissioning, regulatory and governance requirements. Delivering this treatment needs a heavy investment in trained and qualified staff including advanced supportive mechanisms. However, much of this investment is already in place in the NHS within the currently commissioned CAR T centres and the centres soon to be commissioned.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	CAR T therapy will only be delivered in the tertiary care setting in commissioned CAR T centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Delivery of CAR T therapy needs heavy investment in trained and qualified staff including advanced supportive mechanisms from allied specialties such as ICU, neurology, etc. However, much of this investment is already in place in the NHS within the currently commissioned CAR T centres and the centres soon to be commissioned.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. For transplant eligible patients, treatment with axicel resulted in a 2 year EFS and PFS of 41% and 46% in the phase 3 Zuma 7 trial compared to only 16% and 27% in the SOC arm. ORR and CR in axicel arm were 83% and 65% and in the SOC arm were 50% and 32% respectively. There was a trend to improved OS for the axicel arm. Patient related outcomes were also better in the axicel arm in this trial.
• Do you expect the technology to increase length of life more than current care?	Yes, As above. Axicel is likely to confer a significant PFS benefit for patients relapsing within 12 months of RCHOP.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Patient related outcomes in the Zuma 7 trial showed better QoL measures for patients in the axicel arm especially in the initial few months following treatment but the measures seem to converge at later time points.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Zuma 7 only enrolled patients who relapsed within 12 months of RCHOP chemotherapy. Patients relapsing >12 months after RCHOP historically have better outcomes with SOC chemotherapy and transplant and therefore it is uncertain if CAR T therapy will confer better outcomes for them.
The use of the technology	
13. 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 therapy can only be delivered in selected tertiary centres which have all the necessary facilities including highly trained and qualified staff for managing the complex patient pathway. Transplant eligible patients are currently treated in autograft centres and will need to be treated in commissioned CAR T centres in future. There is need for enhanced monitoring, ICU and neurological facilities on site for safe delivery of CAR T therapy. These already exist in current CAR T centres. There may be a need for patients to travel some distance from their home for this treatment and a requirement to stay within an hour of the CAR T centre for 4 weeks post infusion which may present difficulties for some patients.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not applicable. CAR T therapy is a one time, single infusion treatment, so stop/ start rules don't apply.
15. 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.
16. 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	Yes. CAR T therapy is a revolutionary treatment which has produced impressive results in previously untreatable cancers. It represents a major innovation in cancer immunotherapy and in our ability to treat cancers without resorting to intensive chemotherapy or stem cell transplants. It is currently commissioned in 3rd line treatment setting.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	YES. It is already currently commissioned in 3rd line treatment setting.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. For transplant ineligible patients it offers the chance of improved survival and potential cure without added toxicity of high dose chemotherapy and stem cell transplant.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most critical side effects such as CRS or neurotoxiciy are seen within days after the infusion of CAR T cells. Most patients recover fully from these. A proportion of patients will have persistent low blood counts needing blood and platelet support for many months. A minority of patients may have recurrent infections and need immunoglobulin replacement therapy. Covid infection may confer high mortality.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	YES. Zuma 7 is a phase 3 randomised trial with a design which reflects current treatment pathway in the UK.

• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Response rates (ORR and CR), and survival (EFS, PFS and OS). They were all measured in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	With current follow up there is a trend to improved OS. Need longer follow up to see how this curve develops. However, important to note OS curve is influenced by 56% of patients failing 2nd line therapy in the SOC arm receiving commercial CAR T therapy in the 3rd line.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	High mortality with Covid-19 infection in patients post CAR T therapy. New treatments such as monoclonal antibodies and antivirals may prove useful in these patients who often lack the ability to mount an antibody response to vaccination.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance 649?	Tafasitamab + lenalidomide in relapsed/ refractory DLBCL for non-transplant eligible patients has shown promising results in patients who are not primary refractory.
21. How do data on real-world experience compare with the trial data?	No RWE for 2nd line CAR T therapy but RWE from 3rd line application of axicel therapy has shown results comparable to the Zuma 1 study. The performance of SOC arm in this study is as would be expected for patients relapsing within 12 months of RCHOP and similar to what is reported from previous trials in this setting (ORCHARRD and CORAL studies).
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Currently there is a lot variation in the geographical spread of CAR T centres with 3 in London and only 1 for the entire South West of England located in Bristol. However this is expected to be less of an issue with more centre being commissioned in future.
22b. Consider whether these issues are different from issues with current care and why.	Yes. Currently the number of CAR T centres is much less when compared to the number of level 2 or level 3 autograft centres.

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • CAR T therapy is an innovative form of advanced cellular immunotherapy which has revolutionised treatment of DLBCL in 3rd line setting. • Outcomes for patients with DLBCL who have primary refractory disease or relapse within 12 months of RCHOP are very poor with current SOC treatment. • Axicel CAR T therapy confers a significant improvement in response rates, EFS and PFS for these patients compared to SOC. • There is a trend to improved OS with axicel compared to SOC but longer follow up required. • CAR T therapy has well defined but manageable toxicity profile and needs to be delivered in specialist commissioned CAR T centres.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS England CAR-T tariff

Information provided to NICE as of 17 October 2022

Summary

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

Description

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

Methods:

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

25th October 2022

Celia Mayers
Project Manager, Technology Appraisals & HST
+44 (0) 161 413 4116

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

Dear Celia,

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

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

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

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

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

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

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

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

The information provided by NHS England does not:

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

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

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

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

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

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

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

Please contact me if you have any further queries.

Yours sincerely

A. G. Lundie

Gordon Lundie

Executive Director, Market Access and Reimbursement

Schedule

True cost of treatment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evidence

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

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

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

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

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

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

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

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

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

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

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

    b. **Variation**

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

    For example:

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

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

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

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

Costs included that may not be relevant

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

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

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

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

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

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

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

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

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

Technical query

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

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Appendix A – ID3980

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

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

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

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

Notes: [redacted] PAS applied

Appendix B – ID1684

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

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

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

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

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

Appendix C – ID1685

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

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

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

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

Notes: [redacted] PAS applied

Appendix D – ID1494

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

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

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

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

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

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

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

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

Produced by Aberdeen HTA Group

Authors

Dwayne Boyers[1]
Moira Cruickshank[2]
Neil Scott[3]
Elisabet Jacobsen[1]
Sachin Kumar[3]
Mari Imamura[2]
Paul Manson[2]
Gavin Preston[4]
Miriam Brazzelli[2]

1 Health Economics Research Unit, University of Aberdeen, UK
2 Health Services Research Unit, University of Aberdeen, UK
3 Medical Statistics Team, Institute of Applied Health Sciences, University of Aberdeen, UK
4 NHS Grampian, Aberdeen, UK

Correspondence to Miriam Brazzelli
Health Services Research Unit, University of Aberdeen
3rd Floor, Health Sciences Building, Foresterhill
Aberdeen, AB25 2ZD
m.brazzelli@abdn.ac.uk

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Rider on responsibility for report

The view 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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Aberdeen HTA Group, 2022.

Contribution of authors

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

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List of abbreviations

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

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

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

1. Executive Summary

1. Executive summary

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

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

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

1.1 Overview of the ERG's key issues

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

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

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

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

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

Table 1 Summary of key issues

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

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

1.2 Overview of key model outcomes

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

Overall, the technology is modelled to affect QALYs by:

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

Overall, the technology is modelled to affect costs by:

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

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

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

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

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

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

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

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

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

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

Issue 1 Axi-cel retreatment costs

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

Issue 2A Long-term extrapolation of clinical effectiveness data

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

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

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

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

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

1.7 Summary of ERG's preferred assumptions and resulting ICER

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

Cost parameters:

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

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

Clinical parameters:

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

Utility parameters:

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

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

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

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

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

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

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

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

2.2 Background

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

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

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

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

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

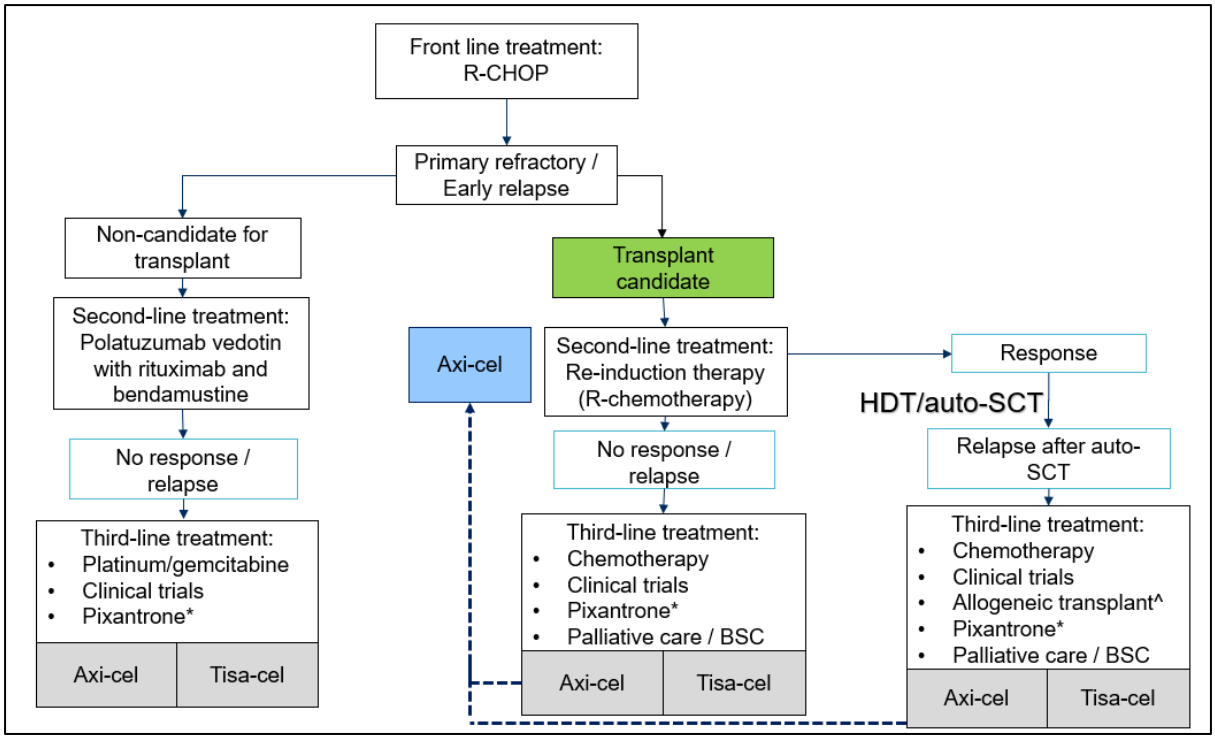

Figure 1 Clinical pathway of care for DLBCL and proposed axi-cel positioning [reproduced from Document B, Figure 4 of the CS]

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

2.3 Critique of company's definition of decision problem

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

Table 3 Summary of the company's decision problem

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

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

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

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

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

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

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

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

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

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

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

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

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

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

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

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

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

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

3.2.1 Included studies

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

<table>
<tr><td>Study</td><td colspan="5">ZUMA-7</td></tr>
<tr><td>Study design</td><td colspan="5">ZUMA-7 is an ongoing Phase III, randomised, open-label study evaluating the efficacy of axi-cel compared with SOC treatment.</td></tr>
<tr><td>Population</td><td colspan="5">Adults with primary refractory (no CR to frontline therapy) or early relapse (CR followed by relapse within 12 months of frontline therapy) DLBCL after one systemic therapy who are intended for transplant.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Axi-cel</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Re-induction therapy with HDT plus auto-SCT consolidation in responders</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">ZUMA-7 presents the pivotal, regulatory, clinical evidence in support of axi-cel in r/r DLBCL</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• EFS
• OS
• PFS
• Response rate
• Adverse effects of treatment
• HRQL</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Duration of response
• Time to next treatment
• Clinically significant changes in safety laboratory test values, including antibodies to axi-cel</td></tr>
<tr><td colspan="6">Key: auto-SCT, autologous stem cell transplant; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HDT, high dose therapy; HRQL, health-related quality of life; OS, overall survival; PFS, progression-free survival; r/r, relapsed or refractory; SOC, standard of care.
Notes: Bolded outcomes are those used in the economic modelling.</td></tr>
</table>

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

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

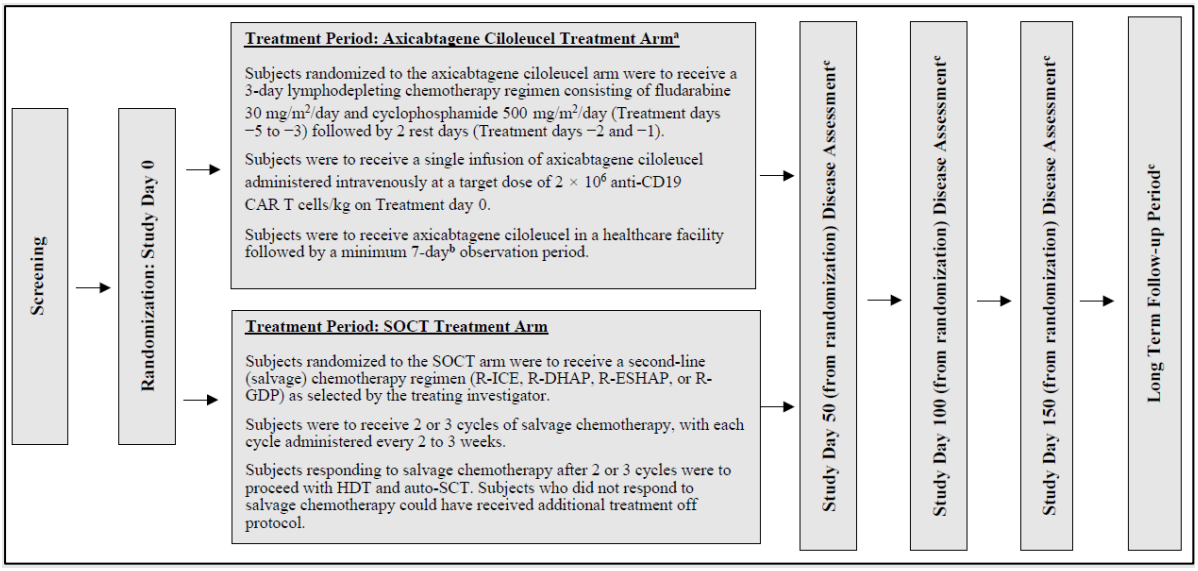

Figure 2 Study scheme for ZUMA-7 [reproduced from Figure 5, Document B of the CS]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.2.2 Primary and secondary efficacy endpoints

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

Primary endpoint: ZUMA-7

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

Table 9 Summary of EFS outcomes

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

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

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

[redacted].

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

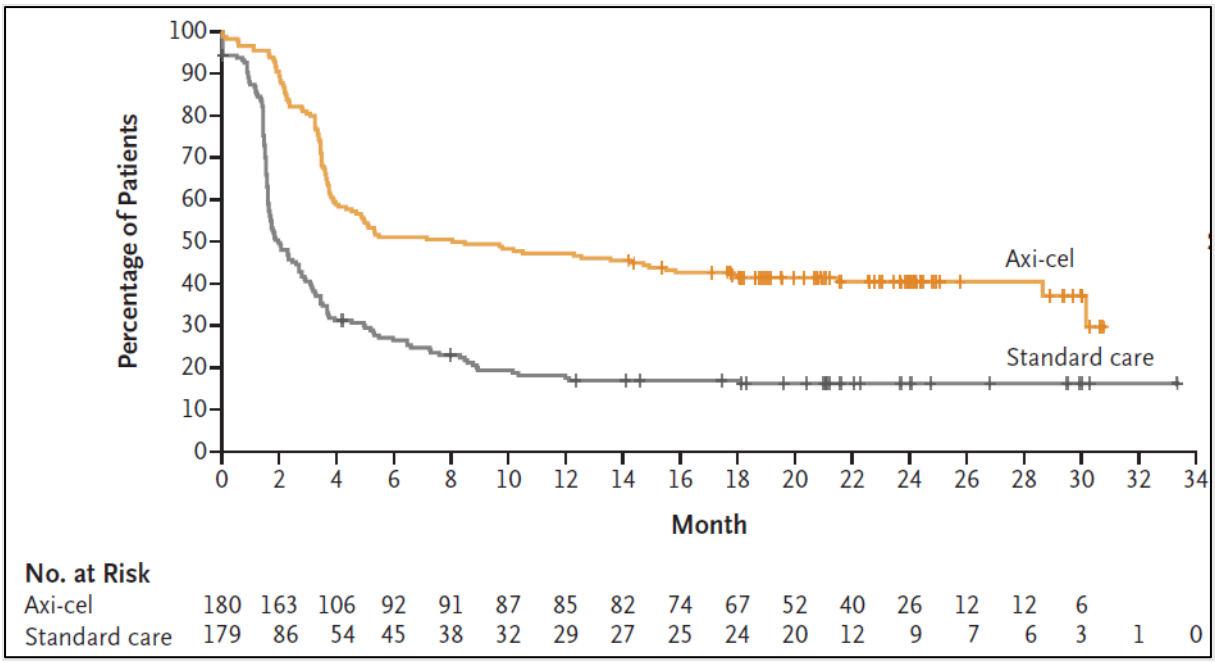

Figure 3 Kaplan-Meier plot for EFS as per central assessment, FAS [reproduced from Figure 6, Document B of the CS]

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

Secondary endpoints: ZUMA-7

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

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

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

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

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

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

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

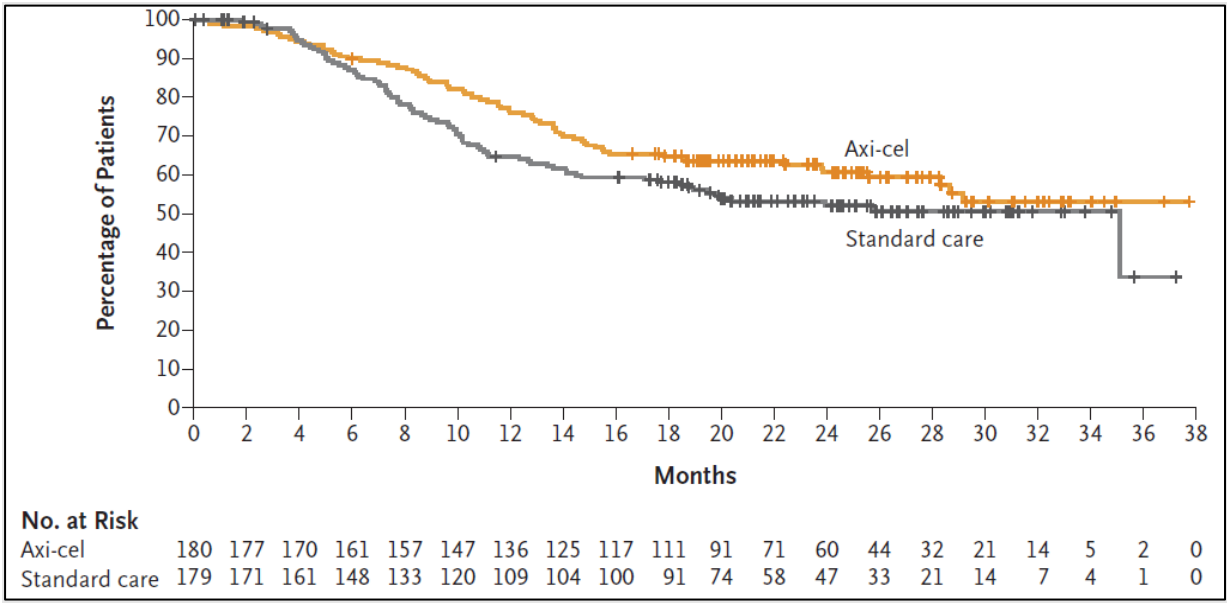

Figure 4 Kaplan–Meier plot for OS, FAS [reproduced from Figure 7, Document B of the CS]

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

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

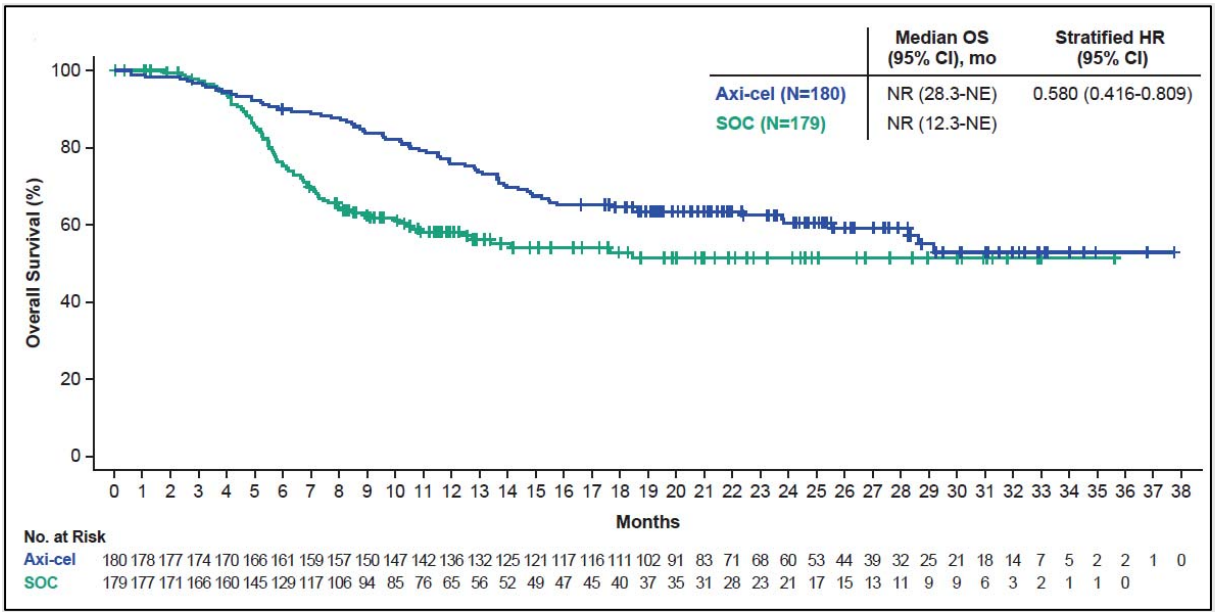

Figure 5 Kaplan–Meier plot of OS – sensitivity analysis using RPSFT model, FAS [reproduced from Figure 8, Document B of the CS]

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

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

Table 11 Summary of additional secondary outcomes reported in the CS

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

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

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

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

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

3.2.3 Adverse events

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

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

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

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

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

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

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

Adverse events of special interest

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.5 Additional work on clinical effectiveness undertaken by the ERG

None.

3.6 Conclusions of the clinical effectiveness section

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

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

4 COST EFFECTIVENESS

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

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

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

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

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

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

4.2.1 NICE reference case checklist

Table 14 NICE reference case checklist

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

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

4.2.2 Model structure

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

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

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

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

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

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

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

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

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

4.2.3 Population

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

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

4.2.4 Interventions and comparators

Intervention – axi-cel

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

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

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

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

Comparator – standard of care (SOC)

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

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

4.2.5 Perspective, time horizon and discounting

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

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

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

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

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

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

4.2.6 Treatment effectiveness and extrapolation

Clinical parameters used in the economic model.

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

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

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

Event-free survival

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

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

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

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

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

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

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

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

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

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

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

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

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

Overall survival

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

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

Mixture cure modelling

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

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

Axi-cel OS

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

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

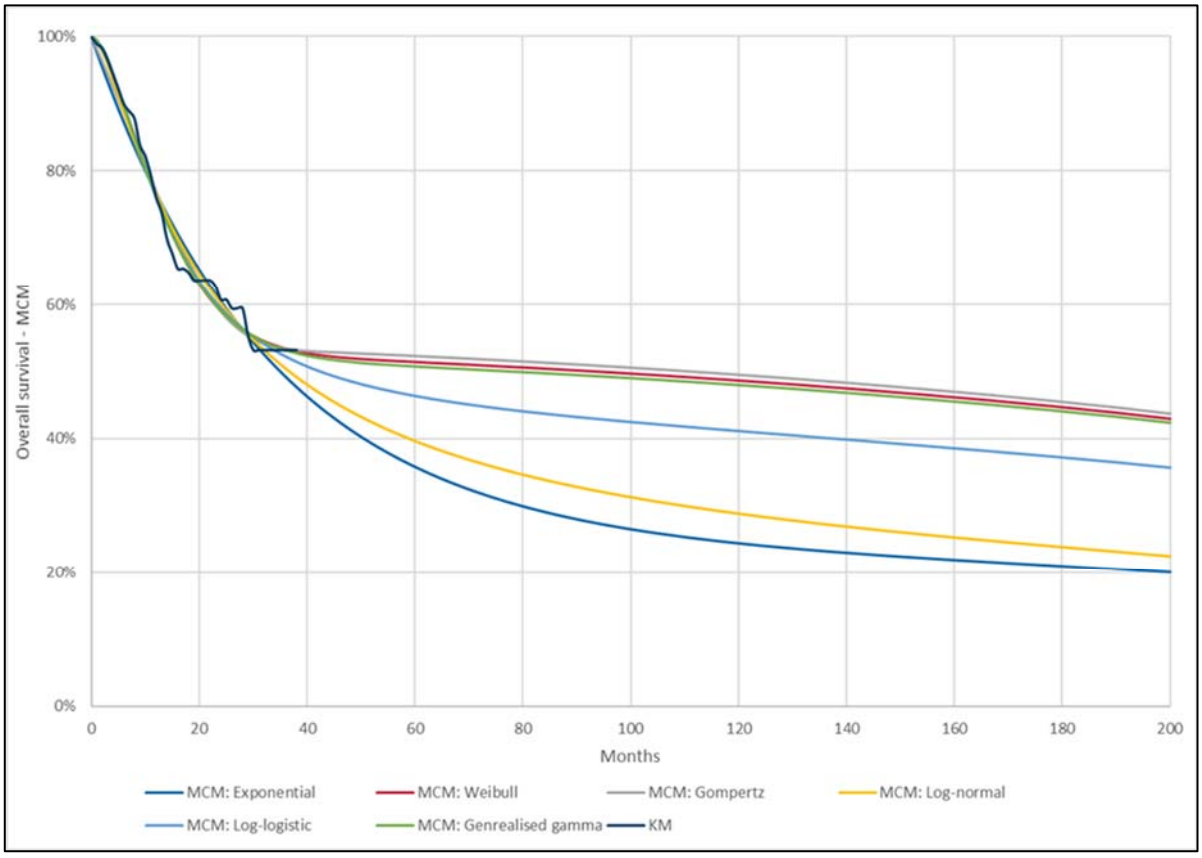

Figure 9 Axi-cel, alternative mixture cure models [re-produced from Figure 27, Document B of the CS]

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

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

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

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

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

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

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

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

TTNT

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

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

4.2.7 Health related quality of life

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

Event free utilities

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

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

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

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

Post-event utilities

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

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

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

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

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

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

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

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

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

Adverse event disutilities

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

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

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

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

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

4.2.8 Resources and costs

Axi-cel treatment acquisition and administration costs

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

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

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

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

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

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

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

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

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

SOC treatment acquisition and administration costs

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

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

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

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

Table 17 ERG and company preferred SOC costing assumptions

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

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

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

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

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

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

Health state resource use and monitoring costs:

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

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

Adverse event costs:

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

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

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

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

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

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

Subsequent (post-event) treatment costs:

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

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

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

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

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

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

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

5 COST-EFFECTIVENESS RESULTS

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

5.1 Company's cost-effectiveness results

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

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

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

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

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

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

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

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

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

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

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

5.2 Company's sensitivity analyses

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

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

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

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

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

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

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

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

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

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

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

5.3 Model validation and face validity check

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

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

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

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

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

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

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

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

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 ERG's preferred assumptions

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

Cost parameters:

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

Clinical parameters:

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

Utility parameters:

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

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

Table 24 ERG's preferred model assumptions

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

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

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

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

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

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

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

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

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

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

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

6.4 Conclusions of the cost-effectiveness section

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

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

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

7 End of life

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

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

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

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

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

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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 relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

'*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 9 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 '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Data availability

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report – pages xvii, 31 and 32 Suggested that a new / additional data cut will be provided / available shortly	Please could you amend the phrase from "a new data cut" to "a new analysis post-FDA review" and the phrase "an updated analysis using data from an additional data cut" to "an updated analysis post-FDA review"	The new data available are updated time to event analyses requested by the FDA and subsequently provided to the EMA that revise censoring of four patients in the SOC arm. These patients were initially censored as 'lost to follow up' but were subsequently confirmed to have died during the study period.	The suggested re-phrasing has been implemented for clarity.

Issue 2 ITT scenario analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report – pages xix, 49, 77, 99 The ERG report suggests there is uncertainty around the requirement for a cross-over analysis due to the ongoing CDF review on the use of axi-cel at third-line plus and that the appropriateness of using a cross-over vs ITT analysis depends on the outcome of	Please could you reword to acknowledge the uncertainty is due to the choice of cross-over model but that the cross-over analysis is aligned to NICE's position statement on CDF treatments.	The current wording in these instances suggest there is debate over whether cross-over analysis is needed, but as acknowledged in other references to the cross-over analysis within the ERG report, this is aligned to NICE's position statement on CDF treatments. NICE further confirmed at	This is not a factual inaccuracy. The ERG has stated throughout the report, that the company's approach is in line with NICE's positioning statement on CDF treatments. However, the ERG also considers it important to make the committee aware of the upcoming CDF review and the potential implications this might have for the

<table>
<tr><td>the upcoming CDF review</td><td></td><td>scoping through clarification that the ITT analysis is considered out of scope of this appraisal.</td><td>cost-effectiveness of axi-cel in the current appraisal.

We have reviewed the wording of the quoted text to ensure clarity.</td></tr>
<tr><td>ERG report - Page xix
The ERG report states that “The use of a cross-over analysis instead of ITT analysis and the choice of cross-over method have implications for the OS projection for the SOC arm of the model. Scenario analyses show these changes can lead to substantial increases in the ICERs.</td><td>Please could you amend the sentence to read:
Scenario analyses show these changes can substantially impact the ICER, with alternative cross-over models shown to increase the ICER and ITT analysis shown to decrease the ICER (when subsequent CAR T treatment costs are also updated).</td><td>The current sentence suggests that the ITT analysis substantially increases the ICER, which is not the case when subsequent CAR T treatment costs are also updated, as per the preferred approach to considering a world where CAR-T therapies are available for third-line treatment. In this more appropriate ITT analysis, the ICER <u>decreases</u> from the base case estimate.</td><td>This is not a factual inaccuracy. The text was referring to the choice of cross-over model. This has now been clarified.</td></tr>
<tr><td>ERG report – Page 75
ITT scenario analyses presentation as per the original company submission included in Table 20 alongside additional scenarios and difference between the two not immediately obvious from table alone</td><td>Please could you update the ITT scenario analyses presentation as per the original company submission to the following:
<table><tr><td>OS: ITT analysis
Subsequent Tx: Clinical expert opinion</td><td>OS: Crossover adjusted
Subsequent Tx: Clinical expert opinion</td></tr></table></td><td>This would better allow the ‘naïve’ reader to understand the original vs updated ITT scenario analyses.</td><td>We have updated the description in the table as suggested and clarified the inclusion/exclusion of 3rd line CAR-T therapies.</td></tr>
</table>

Issue 3 Modelling errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG model – costs sheet and ERG report – page 64 The report states that for the updated auto-SCT costs in the ERG preferred unit cost is £16,668 inflated to 2020/21 values, however, the model applies £10,405.97	Please amend the model by fixing the inflation calculation error to ensure the correct cost is being applied	Correction of inflation calculation	The ERG thanks the company for highlighting this formula error, which has a minor impact on the ICER. This has now been corrected and relevant analyses updated accordingly.

Issue 4 Misinterpretation of results

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report – page 46 The report states that the generalised gamma distribution for OS results in the highest life years gained out of the different mixture cure models available	Please could you make the following amendment: Different models lead to substantial variability in expected LYGs, ranging from [redacted] (worst case, likely implausible: exponential) to [redacted] (likely optimistic: gompertz). The company base case (generalised gamma) leads to [redacted].	The wording in the report suggests that the company base case selected the most optimistic model, however, the gompertz and Weibull models resulted in higher life years gained.	We have revised the sentence to improve clarity and note that the generalised gamma is optimistic among the clinically plausible extrapolations.

Issue 5 Costs used for auto-SCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report – page xv, xx, xxii, 35, 64, 82, 91, 93	Gilead believe the original cost used in the company submission for auto-SCT, obtained from NG52, is the appropriate	The costs were obtained from NG52 as the NHS reference costs cover the cost of the initial	This is not a factual inaccuracy. There was insufficient justification in

The report and ERG model uses SA26A to cost auto-SCT, which is lower than the cost used in the company submission and underestimates the total cost of auto-SCT.	cost. Please could the ERG reconsider this amendment.	procedure and no follow-up costs. As mentioned in NG52, a clinician involved in the development of the clinical guideline had indicated that the NHS reference costs underestimated total costs associated with auto-SCT, see the text below: *"The cost of the autologous and allogeneic transplantation procedure was estimated to be £34,000 and £82,000, respectively based upon the tariff utilised by the transplanting haematologist on the guideline committee. It should be noted that alternative values of £16,359 and £36,288 were available from NHS Reference costs but they were thought to be considerable underestimates of the true cost and so were not used in the base case* *analysis."* The company submission used the lower estimate suggested in NG52 in order to be conservative, and in addition, this is closer aligned with the cost used in TA567, where a cost of £28,398.07 was applied	the company submission to support the decision to use NG52 costs. Further, the text from NG52 is vague and does not describe why the NHS reference costs are inappropriate. It is unclear what tariffs the guideline committee member was referring to and, therefore, it was not possible for the ERG to validate the NG52 costs.

		and accepted.	

Issue 6 Retreatment costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report - Page xv, xvii, xx, 55, 58, 59, 82, 91 The ERG report states that retreatment costs should be included due to modelled benefits in the axi-cel arm.	Gilead believe that the retreatment costs should not be included in the base case model.	As mentioned in the clarification responses, [redacted] which 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. Given that a small proportion ([redacted]) receive retreatment, it is unlikely to have a substantial impact on the efficacy being modelled.	This is not a factual inaccuracy, and the ERG maintains its position.

Issue 7 AE reporting errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response

ERG report – page 27 Table 12 1. The percentage for Grade ≥3 serious TEAE for the SOC group is incorrect 2. The percentage of Grade ≥3 diarrhoea for the axi-cel group is incorrect 3. The percentage of any grade decreased platelet count for the axi-cel group is incorrect	1. Please could you amend the percentage value for Grade ≥3 serious TEAE for the SOC group (column 4) from "67 (40.0)" to "67 (39.9)" 2. Please could you amend the percentage value for Grade ≥3 diarrhoea for the axi-cel group (column 2) from "2 (1.1)" to "2 (1.2)" 3. Please could you amend the percentage value for any grade decreased platelet count for the axi-cel group from "7 (4.0)" to "7 (4.1)"	The amendment will correct the percentages for the TEAEs in ZUMA-7	Text amended as suggested.
ERG report – page 28 The percentage for Grade ≥3 serious TEAE for the SOC group is incorrect (this is related to point 1 above)	Please could you amend the sentence (the change has been underlined) to read: "Serious TEAEs occurred in 50.0% of participants in the axi-cel arm and 45.8% of the SOC arm, of which 42.4% and <u>39.9</u>%, respectively, were of Grade 3 or higher."	The amendment will correct the percentage for Grade ≥3 serious TEAE for the SOC group in ZUMA-7	Text amended as suggested.
ERG report – page 29 The percentage for aphasia in the SOC group is incorrect	Please could you amend the sentence (the change has been underlined) to read: "The most commonly reported neurological events were tremor (25.9% and <1%, respectively), confusional state (23.5% and 2.4%, respectively), aphasia (21.2% and <u>0.0</u>%, respectively) and encephalopathy (17.1% and 1.2%, respectively)."	The amendment will correct the percentage for aphasia in the SOC group in ZUMA-7	Text amended as suggested.
ERG report – page 28 The sentence which states the	Please could you change the sentence from:	The amendment will correct the ordering of the most commonly	The sentence has been amended as follows:

most commonly reported treatment-related TEAEs in the axi-cel group is missing pyrexia	"The most commonly-reported treatment-related TEAEs in the axi-cel arm were hypotension ([redacted]%), headache ([redacted]%), sinus tachycardia ([redacted]%) and fatigue ([redacted]%)." To "The most commonly-reported treatment-related TEAEs in the axi-cel arm were pyrexia ([redacted]%), hypotension ([redacted]%), headache ([redacted]%), sinus tachycardia ([redacted]%) and fatigue ([redacted]%)."	reported treatment-related TEAEs in the axi-cel group	"The most commonly-reported treatment-related TEAEs in the axi-cel arm were pyrexia ([redacted]%), hypotension ([redacted]%), headache ([redacted]%), sinus tachycardia ([redacted]%) and fatigue ([redacted]%)." The value for pyrexia has been specified as [redacted]% in accordance with rounding (i.e., from [redacted])

Issue 8 Terminology errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report – page xiv, xvi, xix, xxi, 35, 36, 38, 40, 45, 47, 48, 49, 51, 52, 53, 65, 70, 76, 77, 80, 84, 86, 92, 99, 100 CAR-T treatment line is described as 3rd line	Please could you amend to read "3rd line plus" or "third line plus"	The amendment clarifies that some patients receive CAR-T at later lines in ZUMA-1	Text revised as suggested in all instances (referring to ZUMA-1 or to the upcoming CDF review of TA559).
ERG report – page xix It is stated that 56% of patients were expected to receive axi-cel but ZUMA-7 included other CAR-T options	Please could you amend the sentence (the change has been underlined) to read: [redacted] were expected to receive <u>a subsequent cellular therapy.</u>	The amendment clarifies that some SOC patients in ZUMA-7 went on to receive a different subsequent cellular therapy to axi-cel	Text revised as suggested.

ERG report – page xxii Table 2 The heading of the ICER column is described as change from company base case	Please could you amend the column 4 heading to "ICER"	The amendment clarifies that the ICER values presented are absolute values	We have revised the table to include both the absolute ICER and the change from the company base case.
ERG report - Page 34, Table 14 The ERG report incorrectly states that post-event utilities are applied for 5 years	Please could you amend the sentence (the change has been underlined) to read: The company instead use SF-36 data, mapped to EQ-5D from the JULIET study for post-event utilities <u>for the duration of the model</u>.	The amendment will align with how the model applies the post-event utilities	Text revised as suggested.
ERG report - Page 34, Table 14 The ERG report incorrectly states that pre-event utilities from ZUMA-1 were available, also 3rd line does not indicate that patients received further lines of therapies in ZUMA-1	Please could you amend the sentence (the change has been underlined) to read: The ERG considers <u>pre-progression</u> EQ-5D utilities from the ZUMA-1 study (<u>3rd line plus</u> treatment) to be a more appropriate source for post-event utilities that maintains consistency with the NICE reference case.	The amendment will align with the utilities that are available from the ZUMA-1 trial	Text revised as suggested.
ERG report - Page 35, Table 14 The ERG report incorrectly states that after five years post-event the general population utilities are applied	Please could you amend the sentence (the change has been underlined) to read: Aligns with the reference case, up until five years <u>pre-event</u>, where general population utility is assumed <u>beyond this point</u>.	The amendment will align with how the model applies utilities, post-event utilities are applied for the entire duration, whereas patients remaining in the event-free state have general population utilities applied after 5 years.	Text revised as suggested
ERG report – page 40 The report states that the validity of mixture cure modelling was supported by	Please could you amend the sentence (the change has been underlined) to read: The ERG's clinical expert supports the validity of the assumption of cure, and the	The amendment will align with the data that was used to validate the model, as 5-year follow-up data from ZUMA-1 was	Text revised as suggested.

using 4-year follow-up data from the ZUMA-1 trial	ERG is satisfied that the validity of mixture cure modelling in r/r/ DLBCL is supported using 5-year follow up data from the ZUMA-1 study (for 3rd line treatment).	available	
ERG report – page 45 The report states that axi-cel 3rd line plus treatment showed [redacted]% of patients to be alive after 4 years, but 5 year data is available	Please could you amend the sentence (the change has been underlined) to read: As described for EFS, the ERG agrees that mixture cure modelling is clinically appropriate and that the prospect of cure is supported by 5-year follow up from the ZUMA-1 study, where axi-cel as a 3rd line plus treatment showed [redacted]% of patients to be alive after 5 years.	The amendment will align with the data that was used to validate the model, as 5-year follow-up data from ZUMA-1 was available.	Text revised as suggested.
ERG report – page 50 The utility data from ZUMA-7 is described as pre-progression	Please could you amend the sentence (the change has been underlined) to read: "The ERG is satisfied that the use of pre-event utility data from the ZUMA-7 study is the most appropriate source for modelling event-free utility."	The amendment clarifies that utility data from ZUMA-7 is pre-event data	Text revised as suggested.
ERG report – page 52 The report states that data from the ZUMA-1 trial for pre- and post-event states were used in a scenario analysis	Please could you amend the sentence (the change has been underlined) to read: The ERG also considers the company's scenario analysis using ZUMA-1 data, from third line plus disease for both pre-progression and post-progression to be questionable because patients have more advanced disease and lower QoL would be expected.	The amendment will align with the health states from the ZUMA-1 trial for which utilities were used in a scenario analysis (pre-progression and post-progression).	Text revised to improve clarity.
ERG report – page 52 The report states that data	Please could you amend the sentence (the change has been underlined) to read:	The amendment will align with the correct health state for which	Text revised to improve clarity.

from the ZUMA-1 trial for the pre-event state is used, but it is pre-progression.	The company's suggestion, provided during clarification (B6), that using ZUMA-1 utilities for the pre-progression state (0.72), applied to the post-event state for the current assessment would be a reasonable approach.	the utility value from the ZUMA-1 trial is available from (pre-progression).	
ERG report – page 67 The report states that post-progression therapies from ZUMA-7 are used in the model, rather than post-event	Please could you amend the sentence (the change has been underlined) to read: The company report a distribution of different post-event therapies as per the ZUMA-7 study and as per advice sought from UK clinical experts in Tables 47 and 48 respectively.	The amendment will align with the approach used in the model, where post-event subsequent therapies are used	Text revised as suggested. Additional similar typos have been identified and corrected throughout the report.
ERG report – page 75, table 20 The scenario analysis where SOC EFS is using the Weibull MCM does not specify it is a MCM	Please could you amend the wording to "SOC EFS = Weibull (MCM)"	The amendment clarifies that the Weibull MCM was used in the scenario analysis	Text revised as suggested.
ERG report – page 97 Table 25 The description of the OS ITT analysis is not clear	Please could you amend the scenario 1 analysis heading to "OS ITT analysis (efficacy only)"	The amendment clarifies the scenario is based on efficacy only	Not a factual inaccuracy as the text states "OS"; however, we have amended the text as requested to ensure clarity.

Issue 9 Cross-referencing errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report – page 26 The page reference for	Please could you amend the sentence (the change has been underlined) to read:	The amendment will align the page numbering with that in the	Text amended as suggested.

Appendix T is incorrect	"The full report of the patient-reported outcomes is available as an embedded document within Appendix T (Document B, p.217) of the CS."	Company Submission	
ERG report – page 27 The table reference for the TEAEs is incorrect	Please could you amend the sentence (the change has been underlined) to read: "The company presents details of TEAEs and treatment-related TEAEs in Table 9 , Table 10 and Table 11, Document B of the CS, respectively and a summary is presented in Table 12 below, including TEAEs and treatment-related TEAEs occurring in at least 30% of participants in either arm of ZUMA-7."	The amendment will align the table numbering with that in the Company Submission	Text amended as suggested.
ERG report – page 29 The adverse events of special interest section reference for the Company Submission is incorrect	Please could you amend the sentence (the change has been underlined) to read: "Section B.2.10.4, Document B of the CS presents adverse events of special interest, consisting of neurological events, cytokine release syndrome (CRS), cytopenia events, infections and hypogammaglobulinaemia."	The amendment will align the section numbering with that in the Company Submission	Text amended as suggested.

Issue 10 Missing sources

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
ERG report - Page xiv The ERG report states that costs and utilities are derived from ZUMA-7, TA559, UK clinical experts and literature, but fails to mention TA567.	Please could you amend the sentence (the change has been underlined) to read: Costs and utilities are derived from ZUMA-7, TA559, TA567, UK clinical experts and literature.	The amendment will align with the sources that are currently used in the model.	Text amended as suggested.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

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.

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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 **Tuesday 19 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	Eleonora Lovato
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

Key issue	Does this response contain new evidence, data or analyses?	Response
Axicabtagene ciloleucel retreatment costs	Yes	While we do not believe patients in the UK will be retreated with axicabtagene ciloleucel (axi-cel) in clinical practice, as shown in the current real-world data ([redacted]), we do acknowledge the base case modelling approach of removing costs of retreatment without adjusting for any potential effect of retreatment is not ideal. [redacted] in ZUMA-7 received axi-cel retreatment ([redacted]). Of there-treated patients, [redacted] had a confirmed response to axi-cel retreatment but most were of short duration ([redacted]) with only one retreated patient having an ongoing response of [redacted] at the time of primary analysis (data cut-off 18 March 2021). The impact of keeping these patients in the base case efficacy analyses is therefore expected to be minimal, and if anything, biased against axi-cel given these patients are not 'good responders' in the majority. An informative censoring approach which would be needed to adjust efficacy analyses is expected to introduce more bias. In response to ERG clarification questions, Kite has provided a scenario analysis that includes axi-cel retreatment cost. When compared with the company base case, the ICER for axi-cel versus SOC increases by <£3,000, demonstrating that the retreatment costs have a relatively small impact on results. The conclusions remain the same following the model updates with post-FDA updated analyses (company

base case ICER: £51,155 vs scenario including re-treatment costs: £54,007), as summarized in the tables below.

Considering the modest effect of retreatment observed in ZUMA-7 and the known lack of retreatment in the UK, Kite retain their position that base case analyses excluding costs of retreatment while not adjusting for retreatment effect are not ideal but are more reflective of expected outcomes and costs in UK clinical practice, and that the inclusion of retreatment costs represents a conservative yet unrealistic costing scenario.

Deterministic cost-effectiveness results (company base case, post-FDA analysis)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,155

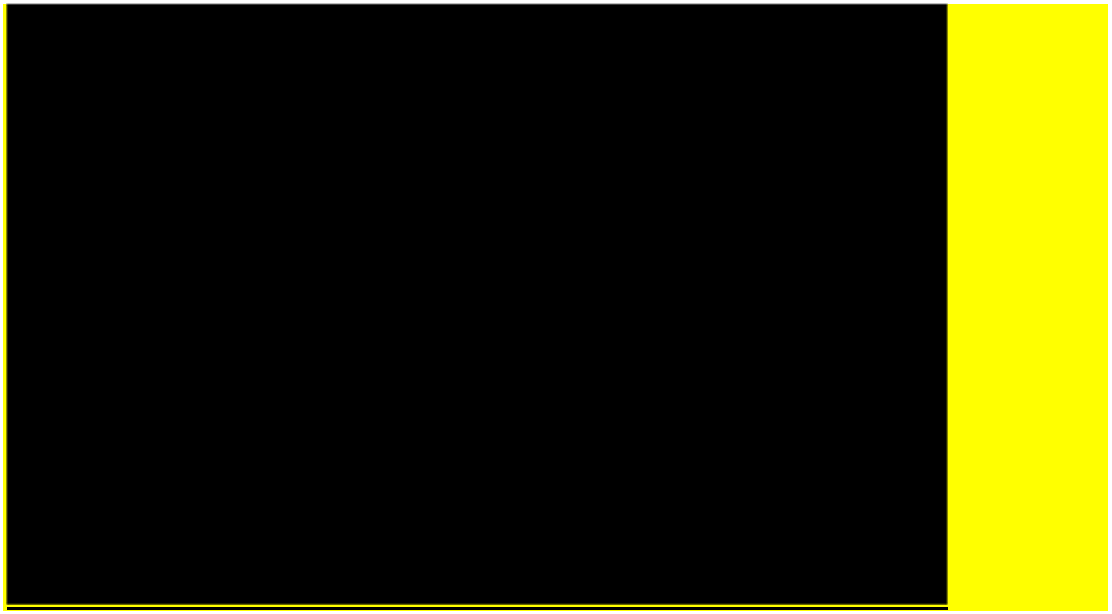
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

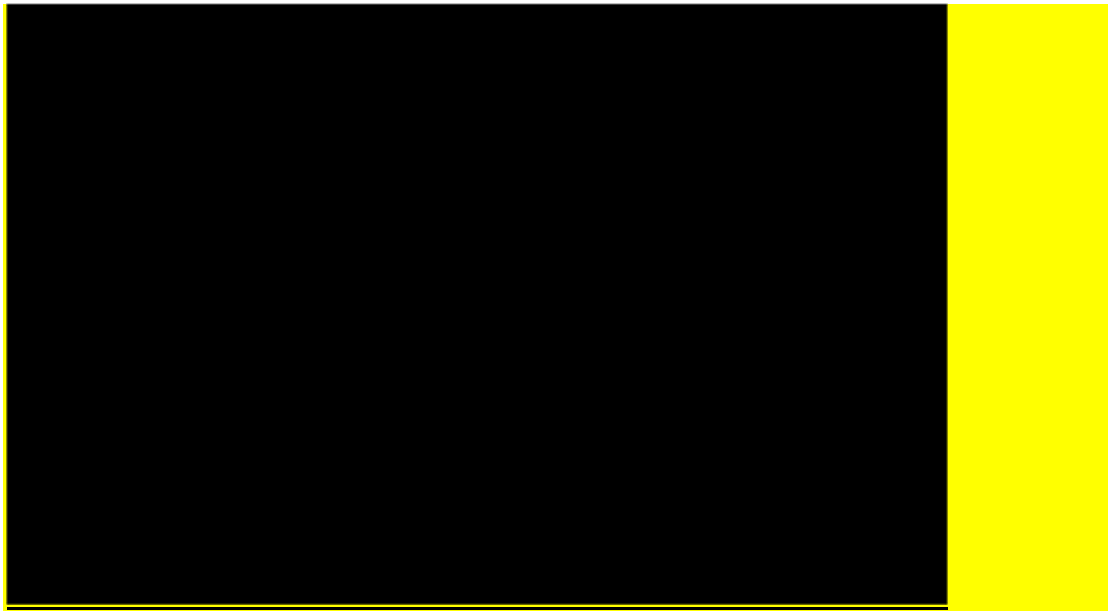
<table>
<tr><td></td><td></td><td>
Deterministic cost-effectiveness results (including retreatment costs, post-FDA analysis)
<table>
<tr><td rowspan="2">Technologies</td><td colspan="3">Total</td><td colspan="3">Incremental</td><td rowspan="2">ICER (£/QALY)</td></tr>
<tr><td>Costs (£)</td><td>LYG</td><td>QALYs</td><td>Costs (£)</td><td>LYG</td><td>QALYs</td></tr>
<tr><td>SOC</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Axi-cel</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£54,007</td></tr>
<tr><td colspan="8">Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SOC, standard of care</td></tr>
</table>
</td></tr>
<tr><td>Long-term extrapolation of clinical effectiveness data</td><td>Yes</td><td>
Kite agrees that the potential long-term benefits of axi-cel in this setting is an unavoidable area of uncertainty and is one of the main reasons we think axi-cel is a likely candidate for interim funding through the cancer drugs fund (CDF).
In the absence of longer-term follow-up data from ZUMA-7 at this time, the company have looked to model the most plausible longer-term outcomes using data that are available in similar settings, supported by clinical expert opinion.
Long-term data providing at least 5 years of follow-up are available for R/R DLBCL patients treated at 3L+ with axi-cel in ZUMA-1. After ≥5 years of follow-up, the 5-year OS rate was 42.6% (95% confidence interval [CI]: 32.8, 51.9) among 3L+ patients treated with axi-cel.[1] Only one death and one progressive disease event was observed since the 4-year data cut. Exploratory analysis further showed that among patents with (n=62) and without (n=39) an event-free survival (EFS) event by Month 24, 5-year OS rates were 11.3% (95% CI: 5.0, 20.5) and 92.3% (95% CI: 78.0, 97.5), respectively.
With appropriate caveats around naïve comparisons, outcomes from ZUMA-1 can reasonably be expected to fall below those predicted for ZUMA-7 given the later disease setting (63% of patients were treated in the 4L+ setting) and thus poorer prognosis of the ZUMA-1 population compared with the ZUMA-7 population (see
</td></tr>
</table>

		Appendix A for a summary of baseline characteristics). Indeed, in naïve comparison of observed data, we see an approximate 10% improvement in 2-year overall survival (OS) (61% vs 50%) and in the complete response rates (58% vs 65%) between axi-cel arms of ZUMA-7 and ZUMA-1.[1, 2] The company model base case predicts a 53% cure fraction for axi-cel in the second-line (2L) setting, aligning to this 10% improvement when compared to the observed 5-year OS in ZUMA-1 of 43%.[1] The ERG model base case predicts a 46% cure fraction for axi-cel in the 2L setting, representing a 3% improvement when compared to the observed 5-year OS in ZUMA-1. As part of the original evidence submission, clinical experts were asked to comment on the validity of the modelled survival benefit for axi-cel in the 2L setting, considering data available in the 3L+ setting. Generally, the experts noted that you would expect survival to be considerably higher in the ZUMA-7 trial versus ZUMA-1, given the differences between the patients, and when asked to comment on the magnitude of difference, stated that a 10% estimated improvement was not 'unreasonable'.[3] Some of the key clinical differences between patients receiving 2L vs 3L+ treatment highlighted by clinicians included: • Decreased tumour burden, lower lactate dehydrogenase (LDH) levels and fewer comorbidities • Absence of long-term morbidity, mortality and quality of life impacts of autologous stem-cell transplant (auto-SCT) • Increased 'window of opportunity' to respond to definitive treatment considering the high likelihood of progressive disease with re-induction chemotherapy • In addition, a recent exploratory analyses of tumour characteristics showed that markers of T-cell function and trafficking (gene expression signatures IS15 and IS21) were generally higher in ZUMA-7 patients than in ZUMA-1 patients, reflecting a more favourable immune contexture for axi-cel to induce response.[4]

		While the company therefore acknowledge that the ERG model base case is described as a more conservative estimate of the potential longer-term benefit for axi-cel in the 2L setting, we would argue that it is in fact pessimistic and misaligned with clinical expectations and plausibility in the context of external data. In addition, the ERG's main consideration for selection of the axi-cel OS extrapolation was based on the goodness of fit statistics as determined by the AIC/BIC. The AIC/BIC statistics only evaluate goodness of fit of the model in question compared to the observed data. Relative to the modelled time horizon (50 years), the observed data only extends (on average) to the first 24 months in both arms. The MCM extrapolations showed variation in the long-term survival extrapolations and cure fractions, however all had similar AIC/BIC scores. As a result, when deciding which extrapolation was most suitable, the aim was to strike a balance between choosing the best fitting model where possible (based on goodness of fit data), whilst maintaining clinical credibility, with reference to the SOC arm and other external datasets, such as ZUMA-1, as explained above.
Crossover adjustment method for overall survival in the standard of care arm of the model	Yes	As part of the original submission and clarification responses, Gilead/Kite has explored different crossover adjustment methods as per NICE TSD 16 and White et al. 2002. The crossover adjustment analysis was updated following post-FDA updated analyses. In the base case Gilead/Kite uses the RPSTM model, with full recensoring. We believe this is the most plausible model because: • We heard from clinical experts during an external strategy meeting in January 2022 that the expected OS trend among DLBCL patients eligible for 2L treatments is likely to be between the observation from ORCHARRD (best case, these patients were not as severe as ZUMA-7 patients) and SCHOLAR-1 (worst case, as this was in the 3L+ setting). • HR approach using the RPSTM model, with full recensoring (company base case) predicts the expected OS curve which aligns the clinical expectation and satisfied the criteria set out in the TSD 16 • The alternative HR approaches (RPSFTM, no recensoring; RPSFTM, recensoring switchers only; IPCW, robust SE, wide intervals and IPCW, robust SE, 2-day intervals) do not produce plausible results as per the discussions with clinicians.

		• As highlighted in Figure 3 to Figure 7 below the alternative approaches result in the SOC overall survival curve lying above the ORCHARD overall survival curves. **Company base case: Overall survival estimates adjusted for crossover (post-FDA analysis), using RPSFTM, recensoring full analysis (HR = 0.416)**  **Key:** Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care. **Note:** ORCHARRD and SCHOLAR curves are included in this figure to contextualise model curves, but these studies do not provide data of direct relevance to the target population under appraisal.

		Overall survival estimates adjusted for crossover (post-FDA analysis), using RPSFTM, no recensoring (HR = 0.577)  **Key:** Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care. **Note:** ORCHARRD and SCHOLAR curves are included in this figure to contextualise model curves, but these studies do not provide data of direct relevance to the target population under appraisal.

		Overall survival estimates adjusted for crossover (post-FDA analysis), using RPSFTM, recensoring switchers only (HR = 0.575)  **Key:** Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care. **Note:** ORCHARRD and SCHOLAR curves are included in this figure to contextualise model curves, but these studies do not provide data of direct relevance to the target population under appraisal.

		Overall survival estimates adjusted for crossover (post-FDA analysis), using IPCW, robust SE, wide intervals (HR=0.618)  **Key:** Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care. **Note:** ORCHARRD and SCHOLAR curves are included in this figure to contextualise model curves, but these studies do not provide data of direct relevance to the target population under appraisal.

		Overall survival estimates adjusted for crossover (post-FDA analysis), using IPCW, robust SE, 2-day intervals (HR=0.574)  **Key:** Axi-cel, Axicabtagene ciloleucel; OS, overall survival; SOC, standard of care. **Note:** ORCHARRD and SCHOLAR curves are included in this figure to contextualise model curves, but these studies do not provide data of direct relevance to the target population under appraisal.

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: Auto-SCT costs	Section 4.2.8	No	Gilead/Kite believes that the ERG preferred costs for auto-SCT underestimates the true cost incurred by the NHS. As mentioned in NG52, the true costs of autologous and allogenic transplant were considered to be much higher than that reported in the NHS reference costs. Also, TA567 used a total cost of £28,398.07, as they included follow-up costs reported by the UK Stem Cell Strategy Oversight Committee (2004). This was supported by the appraisal committee and therefore the cost suggested by the ERG does not align with previous submissions in DLBCL. Recent research into the analysis of hospital activity and costs following stem cell transplant in England showed that in 2015/16 the total costs of autologous transplant for adults was £16,629 for the transplant hospital stay.[5] This does not include the costs of follow-up, which the report highlights that following transplant spell discharge, patients continue to incur high costs until 365 days post-discharge. Gilead/Kite

			believes that the NHS reference costs only account for the cost associated with the initial hospital stay and does not capture any follow-up costs which might include critical care stay, A&E visits and any outpatient appointments. In addition, Wang et al. 2016 published a UK based study looking at the treatment cost and life expectancy of DLBCL. The study followed patients newly diagnosed with DLBCL in the UK's population-based Haematological Malignancy Research Network from 2007 to 2013. The study showed that the cost of auto-SCT was estimated to be £42,000.[6] Gilead/Kite believes that the value used in the original submission may be conservative (£34,000), as this was the lower estimate suggested by NG52 and is lower than the value used in the Wang et al. 2016 study.[6]
Additional issue 2: Axi-cel as an end-of-life therapy	Section 7	Yes	Primary refractory or early relapse DLBCL patients intended for transplant have a poor prognosis with current second-line care, and in the absence of CAR T-cell therapy, these patients are not expected to survive beyond 2 years. Indeed, in this poor risk patient cohort, clinical experts suggested patients who relapse after current second-line care would follow a steep downward trajectory with EFS and OS curves estimated to align as early as by 1 year, and that patients would typically survive around 12 to 18 months. In addition to data provided in the original submission, new data following post-FDA updated analyses further support axi-cel as an end-of-life therapy in this population, demonstrating a [redacted] 2-year survival rate with second-line care in adjusted

			survival analyses from the ZUMA-7 SOC arm vs a 61% 2-year survival rate with axi-cel.[2] The use of 2-year survival rate data to inform end-of-life criteria is more appropriate in a setting where a small proportion of patients may survive for a long time as this can result in marked differences in median vs mean survival estimates. Precedence for this was set in previous technology appraisals of CAR T-cell therapies where this phenomenon is observed including TA567.

Summary of changes to the company's cost-effectiveness estimate(s)

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 (reported in submission); axi-cel versus current standard of care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £51,996
Updated company base case with post-FDA data update; axi-cel versus current standard of care			ICER change from base case (original submission): -£842
Issue 1: Axicabtagene ciloleucel retreatment costs	Excluded axicabtagene ciloleucel retreatment acquisition costs	Company maintained its position in excluding axicabtagene ciloleucel retreatment acquisition costs, however, company has provided a scenario analysis to include axi-cel retreatment costs in the response above	ICER: £54,006 ICER change from base case (original submission): +£2,010
Issue 2: Long-term extrapolation of clinical effectiveness data	• Applied Generalised Gamma mixed cure model for long-term OS extrapolation in axi-cel arm • ERG preferred base case is to apply Log-logistic mixed cure model for OS extrapolation in axi-cel arm	Company maintained its position in selecting Generalised Gamma mixed for axi-cel arm cure model as base case, however, company has provided a scenario analysis to apply Log-logistic mixed cure model for axi-cel OS (ERG preferred base case)	ICER: £52,144 ICER change from base case (original submission): +£148

Issue 3: Crossover adjustment method for overall survival in the standard of care arm of the model	• Applied RPSFTM, recensoring full analysis cross-over approach for HR • The selected approach is the same as ERG's preference in the cross-over analysis.	• Cross-over analysis are updated following post-FDA data update and revised HRs are applied	ICER: £51,154 ICER change from base case (original submission): -£842
Issue 4: Auto-SCT costs	• Applied auto-SCT cost of £37,735.95 (inflated from £34,000 from NICE NG52) • ERG preferred base case using auto-SCT cost of £17,181.37 (inflated from 2019/2020 HRG tariff elective SA26A £16,668)	Company maintained its position in applying auto-SCT cost reference from NICE NG52 as base case, however, company has provided a scenario analysis to apply auto-SCT cost based on HRG tariff (ERG preferred base case)	ICER: £52,881 ICER change from base case: +£885
ERG base case (reported in ERG report); axi-cel versus current standard of care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £58,205
ERG base case with post-FDA data update; axi-cel versus current standard of care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £57,172
Company base case following technical engagement; axi-cel versus current standard of care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £51,154
Key: ERG, Evidence Review Group; OS, overall survival.			

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis (PSA) was performed around the revised company base case to simultaneously take into account the uncertainty associated with parameter values. One thousand simulations were run, this was justified by the flattening of the PSA convergence. The revised PSA cost-effectiveness plane is presented in Figure 1 showing that all of the iterations fell in the north-east quadrant.

The average incremental costs over the simulated results were [redacted], and the average incremental QALYs were [redacted], giving a probabilistic ICER of £52,384. This is similar to the revised company base case deterministic analysis with incremental costs and incremental QALYs of [redacted] and [redacted], respectively, and ICER of £51,154. The cost-effectiveness acceptability curve is presented in Figure 2 showing that at a willingness-to-pay threshold of £50,000, the probability of axi-cel being more cost-effective compared to SOC is [redacted].

Revised one-way sensitivity analysis (OWSA) results (Figure 3) were consistent with the original submission. As shown in the tornado diagram, the three most influential parameters on the model results were the percentage of patients receiving axi-cel, the number of cycles of Pola-BR received in the 3L SoC arm, and the mean patient age (years).

Scenario analyses around the revised base case are presented in Table 5. Results were generally consistent with the original scenario analysis presented in the submission. The scenario analysis that resulted in the biggest deviation from base case results was when the model adopted a shorter time horizon (10 years) as well as the ITT analysis, where OS for the SOC arm was not crossover adjusted. Overall, the sensitivity and scenario analyses explored indicate that under a range of assumptions and across different parameters, the estimated cost-effectiveness of axi-cel is close to the decision-making threshold for end-of-life medicines.

Figure 1: Revised PSA scatter plot at £50,000 threshold (with PAS)

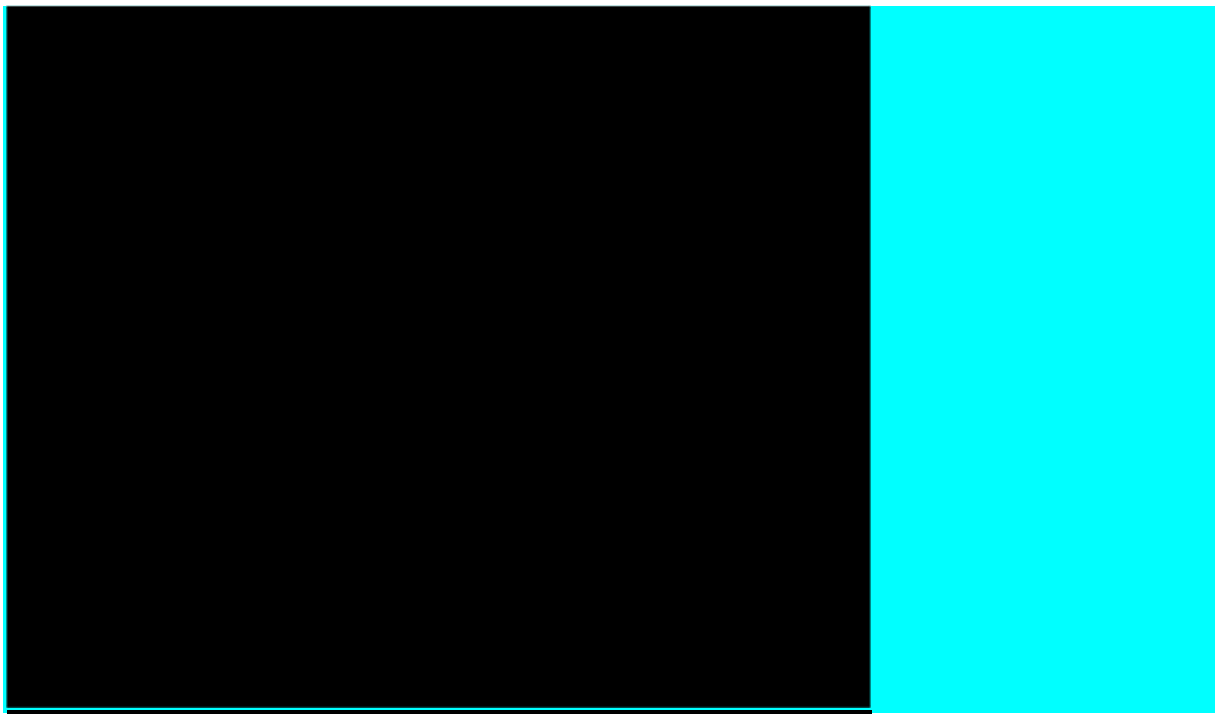


Figure 2: Revised cost-effectiveness acceptability curve (with PAS)

Figure 3: Revised one-way sensitivity analysis, Tornado diagram (with PAS)

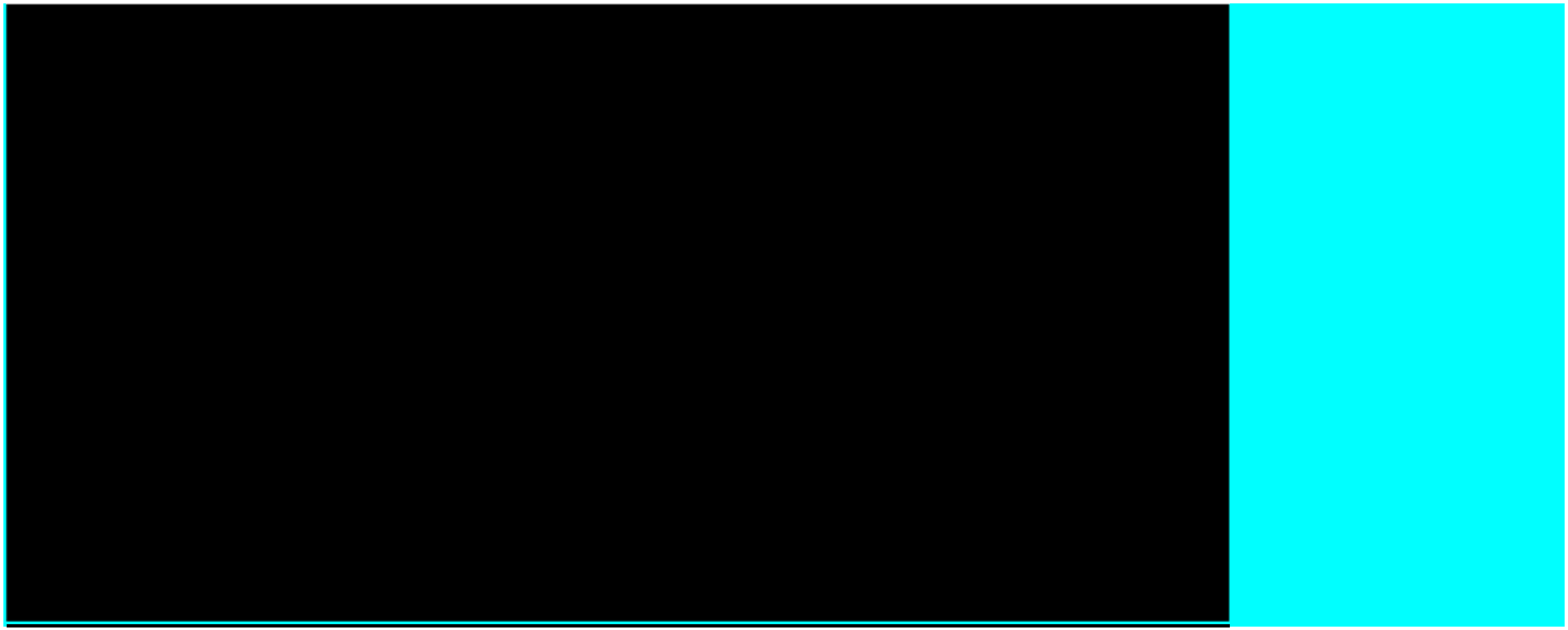


Table 5: Revised scenario analysis (with PAS)

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
Base case	-	[redacted]	[redacted]	**£51,154**	**-**
Time horizon = 10 years	50 years	[redacted]	[redacted]	£109,041	113.2%
Time horizon = 20 years		[redacted]	[redacted]	£65,082	27.2%
Discount rates = 1.5%	3.5%	[redacted]	[redacted]	£40,015	-21.8%
Axi-cel OS = Weibull (MCM)	Generalised gamma (MCM)	[redacted]	[redacted]	£51,051	-0.2%
Axi-cel OS = Log-logistic (MCM)		[redacted]	[redacted]	£52,144	1.9%
Axi-cel EFS = Generalised gamma (MCM)	Log-logistic (MCM)	[redacted]	[redacted]	£50,871	-0.6%
SOC EFS = Weibull	Exponential (MCM)	[redacted]	[redacted]	£51,169	0.0%
SOC OS convergence with EFS at 5 years applied	No convergence applied	[redacted]	[redacted]	£49,416	-3.4%
Utility values based on literature (ZUMA-1)	Based on ZUMA-7 and JULIET study	[redacted]	[redacted]	£53,291	4.2%
No AE disutilities applied and on-treatment specific utilities applied	AE disutilities included and no on-treatment specific utility applied	[redacted]	[redacted]	£51,131	0.0%

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change from base case ICER
Cure time point = 2 years	5 years	[redacted]	[redacted]	£49,940	-2.4%
Cure time point = 7 years		[redacted]	[redacted]	£51,702	1.1%
Use of ZUMA-7 estimates for SOC distribution	UK clinical expert estimates	[redacted]	[redacted]	£51,111	-0.1%
ITT analysis (assuming CAR T is routinely funded by NHS) and use of clinician estimates of subsequent treatment	Crossover adjusted (assuming CAR T is not routinely funded by NHS)	[redacted]	[redacted]	£72,025	40.8%
ITT analysis (assuming CAR T is routinely funded by NHS) and use of ZUMA-7 estimates of subsequent treatment	Crossover adjusted (assuming CAR T is not routinely funded by NHS)	[redacted]	[redacted]	£40,145	-21.52%
Include axi-cel retreatment acquisition cost	Excluded axi-cel retreatment costs	[redacted]	[redacted]	£54,006	5.6%
Applied ERG's preferred auto-SCT cost source (£17,181.37; inflated from 2019/2020 HRG tariff elective SA26A £16,668)	Auto-SCT cost of £37,735.95 (inflated from £34,000 from NICE NG52)	[redacted]	[redacted]	£52,881	3.4%

Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality adjusted life year.

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2. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. *N Engl J Med*. 2021.
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4. Locke FL, Chou J, Vardhanabhuti S, et al. Association of pretreatment (preTx) tumor characteristics and clinical outcomes following second-line (2L) axicabtagene ciloleucel (axi-cel) versus standard of care (SOC) in patients (pts) with relapsed/refractory (R/R) large B-cell lymphoma (LBCL). ASCO Annual Meeting. Chicago, IL, USA. 3 - 7 June 2022. 7565.
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6. Wang H-I, Smith A, Aas E, et al. Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort. *Eur J Health Econ*. 2017; 18(2):255-67.
7. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *New England Journal of Medicine*. 2017; 377(26):2531-44.
8. Kite Pharma Inc. KYE-C19-101 (ZUMA-1). (Clinical Study Report) 2017.

Appendix A

Characteristic, n (%)	ZUMA-7 axi-cel (N = 180)	ZUMA-1 axi-cel (N = 81)
Age		
Median, years (range)	58 (21–80)	58 (25–76)
≥ 65, n (%)	51 (28)	17 (22)
Male, n (%)	110 (61)	50 (65)
ECOG 1[a], n (%)	85 (47)	49 (64)
Disease stage III/IV, n (%)	139 (77)	67 (87)
Prior therapy lines, n (%)		
1	180 (100)	[redacted]
2	0	
3	0	
4	0	
5	0	
>5	0	
Refractory status, n (%)		
Primary refractory	133 (74)	2 (3)
Refractory to second-line or subsequent therapy	N/A	59 (77)
Prior autologous stem-cell transplant, n (%)	0	[redacted]

Key: DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group.

Source: Locke et al. 2021[2]; Neepalu et al. 2017[7]; ZUMA-1 CSR[8]

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

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 section 1. 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.

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 **Tuesday 19 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.

Part 1: Treating relapsed or refractory diffuse large B-cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew McMillan
2. Name of organisation	Nottingham University Hospitals NHS Trust / also Chair of National Car T cell Clinical Panel (NCCP) NHS England
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐x A specialist in the treatment of people with relapsed or refractory diffuse large B-cell lymphoma? ☐ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or the 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)	☐x 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.	Nil

8. What is the main aim of treatment for relapsed or refractory diffuse large B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Curative therapy
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)	Long term remission
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Yes
11. How is relapsed or refractory diffuse large B-cell lymphoma 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?	Already well described in available submissions., specifically re second line chemo and ASCT. BCSH guidelines Pathways well defined Current technology would have a major effect on pathways of care.

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? • 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)	Proposal will effectively move CAR T cell therapy from 3rd to 2nd line replacing second line chemo and ACST Clinical setting can only be NSE approved CAR T cell approved centres (currently 10 but projected to encompass all current UK Allogeneic transplant centres in the next 12-24 months.) Significant infrastructure requirements will be needed to support CAR T cell expansion
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?	To be determined To be determined
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Elderly , less fit possibly Also potentially those with very rapidly progressive disease

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)	Probably , more difficult Geographical equity of access by expanding CAR T cell centres will be essential
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Clear definition of eligibility will be essential
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? • 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	No
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

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?	Significant need for Intensive Care support in around 20% of patients
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?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	No RW experience in second line

23. 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 this condition and this treatment? 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. 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.	Issues are : Possible geographic inequity Possible Age biased case selection in the referral pathway needs to be carefully monitored

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

Issue 1: Axicabtagene ciloleucel retreatment costs	My view is that re treatment is unlikely to be either clinically effective or cost effective. I would favour it not being included in the analysis
Issue 2a: Long-term extrapolation of clinical effectiveness data	This is a really important question as there is likely to be long term immunodeficiency (B lineage) even in the cured group . This is of even greater importance in the post pandemic world and may be potentially associated with mortality as well as morbidity. SOC care patients post Auto SCT may also be affected but are likely to get faster and more complete recovery. The lack of longer term post CART data with respect to this is a concern.

Issue 2b: Crossover adjustment for overall survival in the standard of care arm of the model	I believe this is the most significant question in this assessment. Firstly I believe we have to assume that 3rd line CAR T will be approved in the current CDF review in order to make an appropriate judgement on the second line CAR T appraisal. This means that, if this second line appraisal is not approved and subsequently 3rd line CAR T is withdrawn then it would be essential that this appraisal should be revisited. However , on the assumption that CAR T 3rd line continues to be available then I would argue that the OS outcome in ZUMA 7 should be the primary focus of this Technology Appraisal. When 3rd line CAR T is available I would argue that the PFS and EFS endpoints in ZUMA 7 are not applicable (emphasised by the high rate of trial cross over in the trial) as the question we need to answer is whether second line CAR T is superior to second line current standard of care PLUS the currently commissioned third line CAR T . The finding of a superior EFS and PFS in ZUMA 7 was entirely predictable and , to my view, is not an argument for approval as it does not and could not include the very significant benefit attaching to third line CAR T therapy. Cost analysis will no doubt allow assessment of the financial saving of curing the (relatively small) group of patients for whom current second line SOC treatment is successful, as though small in number the very large cost differences with respect to this versus CAR T means that it will be financially important. This also means the the question of the RPSFTM analysis in the document can be set aside as all the focus should be on the unmanipulated OS outcome. Unlike some situations ,we should certainly be taking account of any benefit from non trial crossover to CAR T and not making any attempt to discount its effect from the analysis. One of my key criticisms of ZUMA 7 is the fact that crossover was NOT allowed with in the protocol as it was for the similar BELINDA and TRANSFORM studies with (Tisa cel and Lisa Cil respectively). Quality of life however is also important though as if OS is equivalent the necessity patients

	to fail second line SOC treatment before accessing CAR T may be detrimental to QOL . The outcome of existing second line SOC treatment given third line after second line CAR T is unknown.

Are there any important issues that have been missed in ERG report?	I think it is important to take account of various unsatisfactory aspects of the trial design of ZUMA 7 Firstly no chemotherapy bridging was allowed. This is the same issue as was discussed with ZUMA 1 ,which also did not allow chemo bridging, but we know that the majority of third line CAR T patients in England do require chemo bridging. It is likely that the exclusion of bridging will have a 'cherry picking ' effect which could exaggerate the efficacy of CAR T. Secondly, as mentioned above, the choice of EFS as the primary end point was unsatisfactory for assessing the outcome in the context of third line CAR T being available. Only OS or possibly 'time to second progression ' would be appropriate. Thirdly , the exclusion of on-protocol crossover to CAR T is unhelpful as , though Crossover did occur , it is likely to have been delayed or even prevented by this decision. This may contribute to a greater difference between the intervention and the SOC arms. None of these criticisms apply to the similar BELINDA and TRANSFORM studies. Lastly , I am not clear whether NICE wish to assess all second line patients (as in the scope) even though the ZUMA 7 study was carried out only in 'Transplant eligible " patients.

Part 3: Key messages

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

1. Focus should be on ZUMA 7 OS outcome not EFS
2. The problems of ZUMA7 trial design should be carefully assessed as it is the only data being reviewed (esp Endpoints, Bridging and no crossover)
3. Patient group ? -all second line or only if 'Transplant eligible.'
4. Critical need to be able to assume that Third line CAR T remains available
5. RPSFTM analysis unlikely to be helpful

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.

□ x **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

Clinical expert statement and technical engagement response form

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

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 section 1. 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.

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 **Tuesday 19 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.

Part 1: Treating relapsed or refractory diffuse large B-cell lymphoma 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 Sridhar Chaganti
2. Name of organisation	Royal College of Pathologists and British Society of Haematology
3. Job title or position	Consultant Haematologist
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 relapsed or refractory diffuse large B-cell lymphoma? ☒ A specialist in the clinical evidence base for relapsed or refractory diffuse large B-cell lymphoma or the 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.	None

8. What is the main aim of treatment for relapsed or refractory diffuse large B-cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Cure is the main aim of treatment though chances of achieving a cure vary substantially depending on age of the patient, transplant eligibility and other disease characteristics.
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)	Durable complete remission as assessed by PET-CT scan.
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory diffuse large B-cell lymphoma?	Outcomes for patients with relapsed DLBCL are sub-optimal. Length of 1st remission has a major bearing on their outcomes with 2nd line therapy. Patients relapsing >12 months after RCHOP have an estimated 2 year OS of around 60% and PFS of around 45-50%. But patients relapsing within 12 months of RCHOP chemotherapy have very poor outcomes with current treatment. The chances of 2 year OS are around 35% and PFS is <20% even in transplant eligible patients who are fit for intensive chemotherapy based approaches. Outcomes for older or non-transplant eligible patients are treated with non-curative treatment approaches and their outcomes are even worse with expected 2 year overall survival of <20%.
11. How is relapsed or refractory diffuse large B-cell lymphoma 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?	Patients who are fit and transplant eligible (typically <70 years of age) are treated with a curative intent with 2-3 cycles of intensive salvage chemotherapy (with regimens such as R-GDP, R-ICE, R-DHAP, R-IVE, R-ESHAP) followed by consolidation with high dose chemotherapy (with BEAM or LEAM) and autologous stem cell transplant if they have chemo-sensitive disease. Patients who are less fit and/ or transplant ineligible are treated with a non-curative intent with less intensive chemotherapy regimens (such as R-Gem-Ox or Polatuzumab-bendamustine-rituximab). Elderly or frail patients are offered palliative approaches which may include low dose oral chemotherapy based regimens. • BCSH guidelines 2016. NICE guideline 2016. • For transplant eligible patients, the treatment pathway is as described above and fairly standard. There is variability in approach to treatment for non-

	transplant eligible patients with use of a wide variety of chemotherapy regimens of varying intensity. In the last year polatuzumab-bendamustine-rituximab regimen has emerged as an important treatment option for these patients. • CAR T therapy in 2nd line treatment of DLBCL represents a major shift which will transform the current treatment pathway. Zuma 7 trial only included patients who had primary refractory disease or those who relapsed within 12 months of 1st line therapy. Patients relapsing >12 months after 1st line therapy were not included. Availability of CAR T therapy in 2nd line treatment for DLCBL patients relapsing within 12 months of RCHOP is expected to improve their outcomes significantly. For transplant eligible patients, treatment with axicel resulted in a 2 year EFS and PFS of 41% and 46% in the Zuma 7 trial compared to only 16% and 27% in the SOC arm. Zuma 7 trial enrolled only transplant eligible patients as the control arm was intensive chemo and transplant. However current UK experience is that some non-transplant eligible patients may still be eligible for CAR T therapy. CAR T therapy in 2nd line setting may offer even greater benefit to non-transplant eligible but CAR T fit patients who are currently treated with non-curative intent.
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? • 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)	No. 2nd line chemotherapy is currently delivered in BCSH level 2 centres and autologous stem cell transplants are performed in all level 3 centres. CAR T therapy is currently only delivered in a limited number of commissioned CAR T centres which is soon to expand to include most allogeneic stem transplant centres. • CAR T therapy is a form of ATMP which comes with specific commissioning, regulatory and governance requirements. Delivering this treatment needs a heavy investment in trained and qualified staff including advanced supportive mechanisms. However, much of this investment is already in place in the NHS within the currently commissioned CAR T centres and the centres soon to be commissioned.

	• CAR T therapy will only be delivered in the tertiary care setting in commissioned CAR T centres. • Delivery of CAR T therapy needs heavy investment in trained and qualified staff including advanced supportive mechanisms from allied specialties such as ICU, neurology, etc. However, much of this investment is already in place in the NHS within the currently commissioned CAR T centres and the centres soon to be commissioned.
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 transplant eligible patients, treatment with axicel resulted in a 2 year EFS and PFS of 41% and 46% in the phase 3 Zuma 7 trial compared to only 16% and 27% in the SOC arm. ORR and CR in axicel arm were 83% and 65% and in the SOC arm were 50% and 32% respectively. There was a trend to improved OS for the axicel arm. Patient related outcomes were also better in the axicel arm in this trial. • Yes, As above. Axicel is likely to confer a significant PFS benefit for patients relapsing within 12 months of RCHOP. There is a trend to OS benefit but longer follow up is required for this data to mature. • Yes. Patient related outcomes in the Zuma 7 trial showed better QoL measures for patients in the axicel arm especially in the initial few months following treatment but the measures seem to converge at later time points.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Zuma 7 only enrolled patients who had primary refractory disease or relapsed within 12 months of RCHOP chemotherapy. Patients relapsing >12 months after RCHOP historically have better outcomes with SOC chemotherapy and transplant and therefore it is uncertain if CAR T therapy will confer better outcomes for them.
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	CAR T therapy can only be delivered in selected tertiary centres which have all the necessary facilities including highly trained and qualified staff for managing the complex patient pathway. Transplant eligible patients are currently treated in autograft centres and will need to be treated in commissioned CAR T centres in future.

acceptability or ease of use or additional tests or monitoring needed)	There is need for enhanced monitoring, ICU and neurological facilities on site for safe delivery of CAR T therapy. These already exist in current CAR T centres. There may be a need for patients to travel some distance from their home for this treatment and a requirement to stay within an hour of the CAR T centre for 4 weeks post infusion which may present difficulties for some patients.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not applicable. CAR T therapy is a one time, single infusion treatment, so stop/ start rules don't apply.
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? • 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	No.
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 therapy is a revolutionary treatment which has produced impressive results in previously untreatable cancers. It represents a major innovation in cancer immunotherapy and in our ability to treat cancers without resorting to intensive chemotherapy or stem cell transplants. It is currently commissioned in 3rd line treatment setting. • YES. Intensive chemotherapy followed by autologous stem cell transplant consolidation for patients with chemo-sensitive disease was established as standard of care for relapsed DLBCL in 1995 based on a small randomised study. With addition of rituximab to 1st line chemotherapy a high proportion of patients have chemorefractory disease at relapse. This is the 1st phase 3 randomised study since 1995 to show improved outcomes for relapsed/refractory DLBCL with a new treatment compared to current SOC. CAR T therapy is already currently commissioned in 3rd line treatment setting.

	• Yes. For transplant ineligible patients it offers the chance of improved survival and potential cure without added toxicity of high dose chemotherapy and stem cell transplant.
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?	Most critical side effects such as CRS or neurotoxiciy are seen within days after the infusion of CAR T cells. Most patients recover fully from these. A proportion of patients will have persistent low blood counts needing blood and platelet support for many months. A minority of patients may have recurrent infections and need immunoglobulin replacement therapy. Covid infection may confer high mortality.
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?	YES. Zuma 7 is a phase 3 randomised trial with a design which reflects current treatment pathway in the UK. NA • Response rates (ORR and CR), and survival (EFS, PFS and OS). They were all measured in the trial. • With current follow up there is a trend to improved OS. Need longer follow up to see how this curve develops. However, important to note OS curve is influenced by 56% of patients failing 2nd line therapy in the SOC arm receiving commercial CAR T therapy in the 3rd line. • High mortality with Covid-19 infection in patients post CAR T therapy. New treatments such as monoclonal antibodies and antivirals may prove useful in these patients who often lack the ability to mount an antibody response to vaccination.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	No RWE for 2nd line CAR T therapy but RWE from 3rd line application of axicel therapy has shown results comparable to the Zuma 1 study. The performance of SOC arm in this study is as would be expected for patients relapsing within 12 months of RCHOP and similar to what is reported from previous trials in this setting (ORCHARRD and CORAL studies).

23. 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 this condition and this treatment? 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. 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.	Currently there is a lot variation in the geographical spread of CAR T centres with 3 in London and only 1 for the entire South West of England located in Bristol. However this is expected to be less of an issue with more centre being commissioned in future. Yes. Currently the number of CAR T centres is much less when compared to the number of level 2 or level 3 autograft centres.

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

Issue 1: Axicabtagene ciloleucel retreatment costs	Retreatment costs should not be an issue as I do not see a role for retreatment with axicel. I am not aware that retreatment was routinely permitted in the Zuma 7 trial. There is hardly any data to support retreatment with axicel for patients failing prior axicel therapy. I do not see this can be justified outside of a clinical trial context.
Issue 2a: Long-term extrapolation of clinical effectiveness data	Though follow up on Zuma 7 trial is currently limited, there is >5 year follow up data from the Zuma 1 trial which is reassuring with very few if any events in patients who are alive and progression free 18-24 months post CAR T infusion. From a clinical point of view it would be reasonable to expect the Zuma 7 patient cohort to have similar pattern of efficacy.
Issue 2b: Crossover adjustment for overall survival in the standard of care arm of the model	Crossover adjustment is complex statistics. OS in the SOC arm of Zuma 7 is far better than would be predicted from previous clinical trials in the same setting. Patients receiving CAR T therapy in the 3rd line setting is an important factor contributing to this OS curve. Even though cross over was not allowed in the study, 56% of patients failing 2nd line therapy in the SOC arm of Zuma 7 trial, went on to receive CAR T

	therapy in 3rd line. If 3rd line CAR T therapy were not available their OS would be expected to be much worse and there may be a justification for adjustment for crossover.
Are there any important issues that have been missed in ERG report?	Zuma 7 trial allowed steroids for bridging but chemotherapy bridging was not allowed. The other 2 randomised trials in the same setting (BELINDA and TRANSFORM) allowed chemo bridging. There is a possibility that absence of option to bridge with chemotherapy may have led to investigators electing not to recruit patients with rapidly progressive disease into the Zuma 7 trial. However, I see this as a minor criticism. The strict selection criteria for all of these trials and the screening timelines would mean the recruited patient population is selective irrespective of whether chemo bridging was allowed or not. Zuma 7 trial did not allow crossover in the study from the SOC arm to CAR T arm. The other 2 randomised trials in the same setting (BELINDA and TRANSFORM) allowed crossover for patients failing treatment on the SOC arm. Whilst this could a minor criticism of the Zuma 7 trial, I do not see it having any bearing on outcomes. As seen from the trial data, despite a lack of crossover, a significant 56% of patients failing 2nd line SOC therapy did go on to receive CAR T therapy in 3rd line. The main benefit of allowing crossover is that it might encourage patients to participate in the trial especially in parts of the world where CAR T therapy is not routinely available outside of clinical trial context.

Part 3: Key messages

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

1. CAR T therapy is an innovative form of advanced cellular immunotherapy which has revolutionised treatment of DLBCL in 3rd line setting.

2. Outcomes for patients with DLBCL who have primary refractory disease or relapse within 12 months of RCHOP are very poor with current SOC treatment.

3. Axicel CAR T therapy confers a significant improvement in response rates, EFS and PFS for these patients compared to SOC.
4. There is a trend to improved OS with axicel compared to SOC but longer follow up required.

5. CAR T therapy has well defined but manageable toxicity profile and needs to be delivered in specialist commissioned CAR T centres.

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.

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NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

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 relapsed or refractory diffuse large B-cell lymphoma or caring for a patient with relapsed or refractory diffuse large B-cell lymphoma. 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.

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 **Tuesday 19 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

Part 1: Living with this condition or caring for a patient with relapsed or refractory diffuse large B-cell lymphoma

Table 1 About you, relapsed or refractory diffuse large B-cell lymphoma, current treatments and equality

1. Your name	Robert Cross
2. Are you (please tick all that apply)	☐ A patient with relapsed or refractory diffuse large B-cell lymphoma? ☒ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with relapsed or refractory diffuse large B-cell lymphoma? ☐ 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 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 relapsed or refractory diffuse large B-cell lymphoma?	After the shock of being diagnosed with follicular lymphoma in September 2020 there is the constant stress and anxiety of being seriously ill and not knowing about the longer-term outcome of the illness. I experienced anxiety about how my life might negatively change especially towards my family (wife plus two teenage daughters) and how it may affect my work. I underwent chemotherapy which in itself was stressful especially when initially being warned about all the possible side effects. I also had a number of biopsies which were unpleasant. On the positive side my oncologist used terminology like 'controllable' and 'treatable' which helped me stay positive. Also, I experienced very few side effects from the chemotherapy and I was able to live my life largely unaffected. As my immunity was compromised, I spent most of my time in isolation but with my family. Luckily, I was able to work from home. There was an initial clearance of the follicular lymphoma, but once the residual lump was found and unsuccessfully treated with current treatments this led to more stress and anxiety.
If you are a carer (for someone with relapsed or refractory diffuse large B-cell lymphoma) please share your experience of caring for them	**The following is from [redacted] (wife and main carer for Robert Cross):** Realising that the follicular lymphoma had transformed was stressful as prior to this we had been informed the illness was manageable. Now transformed, it felt as if it was a serious illness and negative thoughts to the potential of losing him were a real possibility. Until that point Rob and I were positive about his prognosis and it wasn't until CAR-T that Rob was physically and mentally negatively affected.

	The list of possible side effects are huge, with potential long-term, physical and cognitive impairment. In addition, there was also a possibility that the CAR-T treatment might actually cause death. The thought of Rob losing his physical and or cognitive functionality was very daunting and we found ourselves having conversations about quality of life and defining his requests. For Rob, not being able to fully function was a horrific prospect. Even though we knew we didn't really have options, CAR-T was pretty much the only way to go, the side effects of CAR-T felt like a gamble. We all experienced increased anxiety as Rob's treatment took place during COVID19 and visitors were not allowed in hospital. This is exemplified during phone calls when Rob became very upset and agitated. This was also demonstrated when seeing him post treatment, he had lost muscle tone and a great deal of weight (approximately two stone). His debilitated physical condition together with his loss of cognitive functioning was a huge shock. This was evident again when our daughters (14 and 17) saw him after almost six weeks. I understand we were very lucky that Rob's previous treatments had not outwardly compromised his physical and cognitive functioning, however the number of weeks without face-to-face contact exacerbated the debilitating effects that CAR-T created. Since CAR-T compromises immunity, I do wonder even without COVID19, whether we would have been allowed face to face contact. Please note, due to lack of familial contact, I believe Rob was detrimentally affected and our daughters were placed in unnecessary emotional turmoil. I found being provided with statistics on percentage survival rates over 5 years unhelpful. I would have preferred not to have known this.
7a. What do you think of the current treatments and care available for relapsed or refractory diffuse large B-cell lymphoma on the NHS?	My initial chemotherapy worked well in that there was an initial clearance of the follicular lymphoma, however there was a remnant node which was unsuccessfully treated with E-SHAP and R-CHOP. So, I believe that the treatments can and do

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	work but sometimes they do not, it feels a bit like a lottery. Also, I was fortunate not to experience too many side effects from the chemotherapy. I also had issues with cannulas because my veins were often difficult to locate which meant I was always anxious prior to chemotherapy sessions. My view on the current chemotherapy treatments is mixed because initially my follicular lymphoma was cleared but the remnant node remained. So, whilst some patients would have seen a full recovery from this treatment, I did not. Also, I know that many patients experience far worse side effects than I did, so again, everyone responds differently to the treatment.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory diffuse large B-cell lymphoma (for example, how axicabtagene ciloleucel is given or taken, side effects of treatment, and any others) please describe these	The disadvantages include the many side effects that are well documented. In my case I experienced very few of these. I occasionally vomited and had mild hair loss. There is also the inconvenience of having the chemotherapy infused in many sessions, with each session taking many hours. In my experience I found the canulation stressful due to my veins being difficult to locate. As the treatment compromises the red blood cell count, I also had to receive a number of blood transfusions which again take up time and is inconvenient.
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**	The main advantage is that I am now 6 months into complete metabolic remission and the residual lump continues to reduce in size. This treatment has worked when current NHS treatments have failed. My quality of life has been restored and now live a full life again with my family and at work. The initial infusion was very quick compared to chemotherapy. The treatment has worked. The treatment is quicker than having multiple sessions of chemotherapy.

treatment that you have described in question 8? If so, please describe these	
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	The risks are the well-documented side effects especially with CRS and ICANS. There is also the uncertainty as whether the treatment will work. After the infusion on 28th February 2022 I suffered the following side effects: • CRS grade 1 – spiked temperature • Bacterial infection • CRS grade 2 - persistently hypotensive • Regularly reviewed by ITU team but remained on ward • AKI and hypotension treated with IV fluids • New c. diff colonisation with severe diarrhoea • Bilateral subconjunctival haemorrhage - transfused blood and platelets • 5th March 2022: Grade 1 ICANS. Prophylaxis. Low ICE score. • 9th March 2022: Grade 2 ICANS. Regular reviews by OCU team • Discharged 16th March to local hospital flat and later allowed home During my treatment I was often confused and irritable. I lost 2 stone in weight. During my recovery I was constantly tired and very frail having lost weight and muscle mass. Apart from the physical and mental side effects there is also the effect it had on family and work. Initially I was reliant on my wife staying at the hospital flat to look after me. My daughters remained at home where a relative looked after them. I was away from work for several months. My immunity system was severely compromised so I lived in isolation and there were occasions when my family caught COVID so we had to isolate from each other within our home.

	However, during the past six months I have continued to recover and received my vaccinations leading me to live a normal life. My blood counts have continued to improve.
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 view is that everyone should be entitled to have this treatment if required. However, bearing in mind the potential side effects, if a patient were to undergo this treatment who has other underlying health issues, the course of treatment and recovery may be more challenging.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory diffuse large B-cell lymphoma 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 Find more general information about the Equality Act and equalities issues here.	No. Everyone should be given the opportunity to receive this treatment. This treatment cannot be dependant on whether a patient can get childcare. This criteria has huge socioeconomic limitations.

13. Are there any other issues that you would like the committee to consider?	No, but I would like to reinforce my point that this treatment worked for me when current NHS treatments have failed. The positive effect it has had on me and my family is incredible.

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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

Issue 1: Axicabtagene ciloleucel retreatment costs	Cannot comment.
Issue 2a: Long-term extrapolation of clinical effectiveness data	Cannot comment.
Issue 2b: Crossover adjustment for overall survival in the standard of care arm of the model	Cannot comment
Are there any important issues that	Cannot comment.

have been missed in ERG report?	

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Part 3: Key messages

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

- Axicabtagene ciloleucel retreatment has worked for me whereas current NHS treatment have not worked.
- The side effects from the treatment can be very harsh but they are relatively short-term
- My health and the quality of life of my family and myself has returned to pre-diagnosis levels.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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Patient expert statement and technical engagement response form

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

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 relapsed or refractory diffuse large B-cell lymphoma or caring for a patient with relapsed or refractory diffuse large B-cell lymphoma. 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.

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 **Tuesday 19 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.

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Part 1: Living with this condition or caring for a patient with relapsed or refractory diffuse large B-cell lymphoma

Table 1 About you, relapsed or refractory diffuse large B-cell lymphoma, current treatments and equality

1. Your name	Rebecca Hallam
2. Are you (please tick all that apply)	☐ A patient with relapsed or refractory diffuse large B-cell lymphoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or refractory diffuse large B-cell lymphoma? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): A senior nurse caring for patients with DLBCL and those undergoing CAR T therapy
3. Name of your nominating organisation	
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 relapsed or refractory diffuse large B-cell lymphoma? **If you are a carer (for someone with relapsed or refractory diffuse large B-cell lymphoma) please share your experience of caring for them**	I have nursed patients with haematological cancers including DLBCL for 20 years and seen the developments in treatments over this time – the introduction of monoclonal antibodies, the introduction of different conditioning regimens for autografts and the development of CAR T cells. New treatments always offer hope and life extending therapy to patients with relapsed / refractory DLBCL
7a. What do you think of the current treatments and care available for relapsed or refractory diffuse large B-cell lymphoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Treatment options and success decreases for patients with relapsed / refractory DLBCL with each successive episode of disease progression. We counsel patients that their chance of remission / cure diminishes with every relapse and subsequent line of therapy. Treatment options vary dramatically depending upon the patient's disease status, age, fitness, and comorbidities.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory diffuse large B-cell lymphoma (for example, how axicabtagene ciloleucel is given or taken, side effects of treatment, and any others) please describe these	Initial treatment for relapsed / refractory DLBCL involves usually outpatient chemotherapy but the side effects of this should not be underestimated. Patients may be able to stay at home but they are at increased risk of prolonged neutropenia, mucositis and excessive fatigue. Conditioning for an autograft is also very substantial chemotherapy doses with significant side effects (neutropenia. fatigue, mucositis, alopecia, nausea and vomiting). An autograft involves approximately 14 days as an inpatient and then a 2-3 month recovery period

	CAR T cell therapy may hold less physical side effects but only a limited number of centres in the UK provide this therapy and the impact of being away from home, often a significant distance from home, can be too much of a barrier for patients to pursue this therapy. Side effects from the lymphodepletion for CAR T cells are not as severe as conventional chemotherapy but the ICANs / CRS side effects for the CAR T cells can be significant and warrant a stay in the ICU. CRS can also be fatal. The impact of an ICU stay on the patient and their family both physically and psychologically can be significant.
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**	a+b) CAR T cell therapy offers an additional line of therapy to patients unable to proceed with an autograft and thus offers the hope of a long term cure in patients with relapsed / refractory disease. c) It is an option for patients who have no other treatment options due to disease aggression and co-morbidities.
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	The current provision of centres that can provide this therapy – CAR T cell therapy requires patients to attend one of 12 centres nationally and stay near that hospital for a minimum of 30 days. They need a care giver with them at all times once discharged form hospital for the first 30 days from cell infusion. For some patients being far away from home for a prolonged period is not possible, it limits the chances of continuing work / education. It does mean that if a patient is admitted to the ITU then care givers often have little support around them – they may be far

	from home, with a treating team they do not know well. This can be extremely difficult and impacts upon the patient.
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	Patients who are unable to proceed with an autograft for health reasons (poor lung function , poor cardiac function but with a performance status of 2 or less) or patients with refractory / progressive disease who are never able to proceed to auto cell collection or cell return can benefit significantly from CAR T cell therapy.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory diffuse large B-cell lymphoma 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 Find more general information about the Equality Act and equalities issues here.	As documented above, more centres need to offer this therapy for patients nationwide to be able access the treatment.
13. Are there any other issues that you would like the committee to consider?	

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

Issue 1: Axicabtagene ciloleucel retreatment costs	
Issue 2a: Long-term extrapolation of clinical effectiveness data	
Issue 2b: Crossover adjustment for overall survival in the standard of care arm of the model	
Are there any important issues that	

have been missed in ERG report?	

Part 3: Key messages

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

- CAR T cell therapy is a life prolonging treatment option for patients who have no other treatment avenues due to disease aggression and co-morbidities.
- More centres need to provide this therapy across the UK for patients to ensure equity in access.
- 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.

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Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

ERG critique of the company's response to Technical Engagement

Produced by Aberdeen HTA Group

Authors Dwayne Boyers

Health Economics Research Unit, University of Aberdeen, UK

***C*orrespondence to** Dwayne Boyers (Senior Research Fellow)
University of Aberdeen, Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: d.boyers@abdn.ac.uk

Date completed: **06 October 2022**

Contains: [redacted]

Version: **2**

Overview

This report provides the ERG's brief commentary and critique of the company's (Kite, a Gilead company) submitted response to technical engagement and in advance of the first AC meeting for this appraisal. The commentary/critique provided below should be read in conjunction with the company's submitted response to technical engagement. The commentary provides the ERG's brief critique of A) the company's updated "post-FDA" analyses; B) the company's responses to each of the three key issues for technical engagement; and C) two further issues of disagreement between company and ERG base case analyses. A confidential appendix to this report describes the impact of revised company and ERG analyses following technical engagement, applying confidential price discounts for subsequent treatments used in the economic model.

Updated analyses post-technical engagement

The company provided a revised economic model and updated set of base case analyses during technical engagement. This "post-FDA" analysis involved the company updating overall survival (OS) curves for the comparator (standard care) arm of the model to account for [redacted] participants, originally thought lost to follow up in the ZUMA-7 study, who were subsequently identified as having died during the study follow up period.

The ERG requested access to the company's revised economic model to generate the post-FDA analyses and are satisfied that all analyses are fully integrated within the economic model and a full range of deterministic and probabilistic analyses applied to the company's new base case.

The ERG has reviewed the company's revised analyses and is satisfied that it is appropriate to remove the [redacted] participants who died from the standard care OS curves. As with the company's original submission, the analysis uses cross-over adjustment, specifically a rank preserving structural failure time (RPSFT) model in the base case analysis. The hazard ratios prior to and after the updated post-FDA analyses for a range of cross-over models considered by the company are illustrated in Table 1 for information.

Table 1. Comparison of original and post-FDA cross-over analysis hazard ratios

Modelling approach	***Original submission***	***Post-FDA analysis***
RPSFT, full re-censoring	[redacted]	[redacted]
No re-censoring	[redacted]	[redacted]
Re-censoring switchers only	[redacted]	[redacted]
IPCW, robust SE, wide intervals	[redacted]	[redacted]
IPCW, robust SE, 2-day intervals	[redacted]	[redacted]

Overall, the ERG is satisfied that the company's updated post-FDA analysis is appropriate and that the decision to retain a RPSFT model with full re-censoring for the base case analysis is appropriate. Additionally, the impact on the ICER is small, with the revision leading to a small reduction in both the company and ERG preferred ICERs. The company's preferred base case ICER reduces from £51,996 to £51,154, and the ERG preferred base case ICER from £58,205 to £57,172.

Issue 1: Axi-cel re-treatment costs

In the ZUMA-7 study, [redacted] patients ([redacted]) in the axi-cel arm received re-treatment with axi-cel. The company preferred approach is to remove the re-treatment costs from the model because re-treatment is unlikely in UK clinical practice. The company response to TE provides further clarification that, among those re-treated with axi-cel, [redacted] had a confirmed response of short duration, and [redacted] had a sustained response. The company also quote real-world data which shows that [redacted].

The ERG agrees with the company's position that axi-cel re-treatment is highly unlikely in UK clinical practice and this has been confirmed with the ERG's clinical expert. However, the ERG's concern that including the benefits of treatment whilst excluding the costs may lead to a bias in favour of axi-cel remains and is acknowledged by the company. The ERG notes the company's data on response among those re-treated with axi-cel, but there are several remaining uncertainties. It is unclear how the company are defining response, and it is unclear whether the remaining [redacted] patients responded, presumably they were non-response. Given that it appears that there may be some benefit for a small proportion of re-treated patients, though that benefit is difficult to quantify, the concern that the company's base case approach introduces bias remains. Whilst acknowledging that re-treatment is unlikely in UK clinical practice, the ERG retains its preference to include the re-treatment costs in the model to reduce the potential for bias and to ensure consistency between the modelled costs and benefits.

Issue 2: long-term extrapolation of clinical effectiveness data

The company and ERG both acknowledge substantial uncertainty surrounding long-term extrapolations. The company prefer to use a generalised gamma mixture cure model (MCM) to model axi-cel OS, whereas the ERG prefer to use a log-logistic MCM. The company has provided further clarification to justify their approach, by comparing model projections with at least five years follow up data from the ZUMA-1 study, where axi-cel is used for R/R DLBCL patients at third line plus, where outcomes would be expected to be poorer than the positioning for this assessment at second line.

The ERG has reviewed the additional information provided by the company. The ERG agrees it is appropriate to compare OS data between ZUMA-7 and ZUMA-1, and that it is reasonable (with the caveats of a naïve comparison) for the ZUMA-7 modelled OS curve to lie above the ZUMA-1 long-term data. Both the company and ERG preferred analyses meet this criterion.

The magnitude by which the OS profile of second line patients treated with axi-cel should exceed those at third line plus is less clear. The company quotes clinical expert opinion stating that 2nd line axi-cel treated patients could expect a 10% benefit in OS over 3rd line plus. However, it is unclear from the company's documentation whether clinical experts were reported an absolute (aligned with company approach) or relative (aligned with ERG approach) 10% higher expected OS.

Whilst comparison with the ZUMA-1 data is helpful in terms of assessing clinical plausibility, these comparisons should be interpreted cautiously. It is not entirely correct to make a direct comparison between modelled cure fractions and OS data, and the ERG consider it more appropriate to compare the modelled projections under company and ERG preferred base cases with the data from ZUMA-1.

The ERG would like to clarify that goodness of fit (AIC / BIC) was only one consideration in our approach to selecting a preferred extrapolation curve. The ERG relied primarily on clinical expert opinion that both the generalised gamma and log-logistic curves could be considered equally clinically plausible. The ERG agrees that there are only small differences between the statistical fit of the curves to the data but note that the log-logistic has a slightly better fit. The ERG then considered the magnitude of uncertainty and considered a conservative preference for the log-logistic curve to be more appropriate. The ERG acknowledges that both curves are clinically valid. These are finely balanced judgement calls and only longer-term data will provide greater certainty about the most appropriate long-term extrapolation curves to use for axi-cel OS.

For the reasons stated above, the ERG retains its preference to use the log-logistic curve to model axi-cel OS but acknowledges that both have merits. To help the committee reach a

decision on the most appropriate axi-cel OS curve, the company and ERG preferred approaches are compared in Table 2 below.

Table 2. Comparison of company and ERG preferred axi-cel OS extrapolations

	Company preferred approach	***ERG preferred approach***	***Axi-cel data from ZUMA-1 (3L +) for comparison***
MCM used	Generalised gamma	Log-logistic	--
Modelled cure fraction	[redacted]	[redacted]	--
AIC	702.1	700.00	--
BIC	714.9	709.6	--
Modelled median OS	[redacted]	[redacted]	NR[A]
Mean Life years gained (discounted)	[redacted]	[redacted]	--
2-year OS	[redacted]	[redacted]	--
5-year OS	[redacted]	[redacted]	42.6% (5-yr OS rate)
10-year OS	[redacted]	[redacted]	NR

[A] *Not reported by the company, potentially median OS was not yet reached in ZUMA 1 at the quoted follow up time point. Further clarification from the company would be beneficial for comparison purposes.*

Issue 3: Crossover adjustment method for OS in the standard of care arm of the model

The company has provided a full set of graphical illustrations, updated to account for the post-FDA analysis, to show the clinical validity of different cross-over adjustment approaches compared with projections from the ORCHARD and SCHOLAR-1 studies. The base case analysis uses a RPSFT model with full re-censoring to derive the HR of mortality for the standard of care arm compared to axi-cel. The company's justifications are detailed in their response to technical engagement.

ERG has reviewed the company's updated analyses (see section 1 above) and are satisfied that the RPSFT model with full re-censoring remains the most appropriate cross—over model

for the standard of care arm. The ERG and company base case analyses therefore remain in agreement. Despite this agreement on the base case approach, it remains important to consider the potential magnitude of uncertainty surrounding different analysis approaches. As noted in the ERG report, the use of axi-cel as a third line plus treatment on the CDF will shortly be due for review by NICE. The decision of that review, if considered for the current assessment could lead to important implications for the ICER. If a positive recommendation for axi-cel at 3L plus was integrated into the current assessment, this would substantially reduce uncertainty, negating the need for a complex cross-over analysis. The ERG would like to re-iterate that if this were the case, a further review of the most appropriate modelling approach, including an assessment of the most appropriate extrapolation curve for standard of care OS would be required.

Other issues for consideration

There remain two additional areas of disagreement between the company and ERG base case analyses around auto-sct costs and end-of-life consideration. Furthermore, the ERG has become aware of a tariff price paid by NHS England for CAR-T therapy, which could have important implications for the ICER. These issues are addressed in turn below:

End of life

The company claim that axi-cel is a treatment that meets NICE's end-of-life criteria, demonstrating a [redacted] 2-year survival rate for standard of care, compared with a [redacted] 2-year survival rate for axi-cel.

As noted in the ERG report, axi-cel clearly meets the criteria for being a life extending treatment, but there is greater uncertainty regarding whether patients treated with standard of care could normally expect to have a life expectancy of less than 2-years. The median life expectancy for the standard care arm of the model (where CAR-T therapies are assumed unavailable as third line treatment), using data from the post-FDA analysis is just [redacted] for both the company and ERG preferred analyses with cross over adjustment, increasing to approximately [redacted] when cross-over adjustment is removed. Mean life year gains for the standard of care arm, with cross-over adjustment are [redacted] (undiscounted: [redacted]) for the company preferred base case analysis, decreasing to [redacted] (undiscounted: [redacted]). ERG mean life year gains are lower that company preferred LYGs

because the HR from the cross-over analysis is applied to an extrapolation with a lower axi-cel cure fraction for OS, compared with the company preferred base case. For scenarios where CAR-T therapy would be available at 3L plus, the mean LYGs for the standard of care arm would be substantially higher. Based on the model predictions, the ERG is satisfied that axi-cel meets the life extending criteria. However, a judgement call is required as to whether the median or the mean are the most appropriate statistic to consider for standard of care life expectancy. The decision should also be informed by a consideration of whether CAR-T therapies would be available to patients at future lines of treatment.

SCT costs:

The company note that the ERG preferred approach does not align with previous NICE assessments of DLBCL, specifically TA567 where higher costs for auto-SCT were included.

The ERG's original concern was that the NG52 tariff applied in the company's economic model was not transparent. The company has not provided a sufficient justification for the ERG to change its position in this regard. The company quotes studies that report higher costs than the quoted tariff and higher than the reference costs used by the ERG. However, the company does not appear to have made an argument to use these data in their analyses or provided a scenario analysis demonstrating the impact on the ICER. The ERG would prefer a detailed, documented costing approach that clearly describes the resource use inputs, in a manner similar to that used for axi-cel costing, over a tariff payment from NG52 that lacks transparency and is several years old. At the very least, if applying tariff prices, an attempt should be made to identify the current value of the corresponding auto-sct and allo-sct tariffs for 2021 / 2022.

CAR-T tariff

Following the recent publication of the ACD for axi-cel for treating relapsed or refractory follicular lymphoma, it has come to the ERG's attention that a specific tariff (£96,016) is paid for CAR-T delivery in people aged 19 years and older. The ERG's understanding is that this tariff covers costs from the point a patient is identified as requiring CAR-T therapy, until 100 days after infusion, but that this tariff does not include CAR-T treatment acquisition costs, associated chemotherapy and bridging therapy costs, high-cost drug tariffs or intensive care admission. The ERG considers a scenario analysis where the tariff is applied to the axi-

cel arm of the model, according to the assumptions outlined in Table 3. Should further information become apparent with regards to resource use included /excluded from the tariff, this scenario may require updating in future.

Table 3. Resources assumed to be included / excluded from the CAR-T tariff

CAR-T tariff includes	**CAR-T tariff excludes**
Axi-cel treatment administration (including for any re-treatment) & hospital stay	Axi-cel treatment acquisition costs
Leukapheresis	Subsequent treatments
Chemo administration costs	Chemo drug costs
Bridging therapy with Chemotherapy (administration costs)	Bridging therapy with Chemotherapy (drug costs)
Non-ICU AE management (based on the assumption that all AEs happen prior to day 100)	ICU management of AEs (regardless of time point)
IVIG treatment up to day 100	IVIg treatment beyond day 100

Application of the above tariff considerably increases the ICER for axi-cel. The magnitude of increase may depend, in part, on whether CAR-T therapies were included as a third line treatment, as well as the approach taken to cost other high-cost procedures, including auto-sct and allo-sct. Whilst the ERG is satisfied that the tariff is an accurate reflection of the payment received by hospitals for delivering CAR-T care, the ERG raises some concerns about its use in the current assessment that could generate biases in the estimation of the most appropriate ICER.

The first concern is that a tariff price for axi-cel may not accurately reflect the opportunity cost of care delivery, particularly if the treatment becomes established standard of care, with economies of scale developing over time. It is likely that any bias associated with applying a price as opposed to a cost would favour standard of care in this scenario.

The second concern is that it is inconsistent to apply a tariff price to axi-cel, but a cost to treatments in the comparator arm (auto and allo-sct). To mitigate any biases, the ERG would prefer to see two scenario analyses that maintain consistency of approach for costing

modelled treatments in the intervention and control arms. One scenario should apply a tariff price for axi-cel, auto-SCT and allo-SCT. This tariff would include the quoted £96,016 for axi-cel but should also include recent (2021/22) tariff prices for auto and allo-SCT as opposed to inflated values from NG52. A second scenario should then apply a resource-based costing approach to axi-cel, auto and allo-SCT to maintain consistency of approach. Resource based costing should only be applied to auto and allo-SCT if the company can adequately demonstrate that the NHS reference costs exclude important resource use.

Other minor discrepancies between ERG and company base case analyses

The company response to technical engagement has focused on the key issues raised in the ERG report executive summary. However, there remain some additional areas of disagreement between the company and ERG preferred base cases.

1) The ERG prefers that the distribution of post-event treatments to be consistent with the data provided in the ZUMA-7 study, whereas the company base case post technical engagement prefers the use of clinical expert opinion. The justification for the ERG preferred approach is to ensure that the treatment costs applied in the model are consistent with the treatments used in the study to generate the modelled treatment benefits.
2) The ERG preferred approach is to use utility data from ZUMA-1 study (pre-progression) rather than the company preferred approach to use data from the JULIET study. The impact of alternative sources on the ICER is minor.
3) The proportion of patients in the SOC arm who receive salvage chemotherapy. The company preferred base case assumes 100% whereas the ERG preferred base case prefers to use data from the ZUMA-7 study ([redacted]. The impact on the ICER is minor.

Summary.

In summary, the ERG and company preferred base case analyses are aligned with regards to the most appropriate cross-over adjustment model to use for standard of care OS and the ERG is satisfied that the revised post FDA analyses are appropriate. However, the company and ERG remain in disagreement with regards to the inclusion of axi-cel retreatment costs, the most appropriate MCM for axi-cel OS, the most appropriate approach to cost SCT treatments. There is also minor disagreement around the source of post-event treatment

distribution and utility as well as the proportion of SOC arm patients who would receive salvage chemotherapy. In general, throughout our assumptions, the ERG prefers to maintain consistency in costing with the treatments used to deliver the modelled benefits based on the treatments used in the ZUMA-7 study.

Furthermore, a remaining area of residual uncertainty relates to the most appropriate costing approach for delivery and management of axi-cel patients in the hospital setting. Table 4 below provides the company preferred base case analysis and a set of scenarios showing the impact on the ICER of each difference between the company and ERG preferred approach. A further scenario analysis is added that explores the impact of applying a tariff price to the axi-cel arm, following the assumptions outlined in Table 3 above.

Table 4: Company and ERG preferred ICERs post technical engagement (post-FDA analysis)

Sc.	Scenario	Incremental Costs	Incremental QALYs	ICER
	Company preferred base case post FDA analysis	[redacted]	[redacted]	£51,154
1	Apply ERG preferred post-event treatment distribution (based on Zuma 7)	[redacted]	[redacted]	£51,467
2	Utility source: Zuma-1 pre-progression	[redacted]	[redacted]	£50,955
3	Include axi-cel re-treatment costs	[redacted]	[redacted]	£54,006
4	Apply NHS reference costs for auto-SCT	[redacted]	[redacted]	£52,881
5	Apply an additional consultation for Neurological adverse events	[redacted]	[redacted]	£51,159
6	Apply log-logistic MCM for axi-cel OS	[redacted]	[redacted]	£52,144
7	ERG preferred base case post FDA analysis (Scenarios 1-6 combined)	[redacted]	[redacted]	£57,172
Additional scenario analyses applied to ERG base case analysis				
8	ERG base case (Sc 7) + CAR-T tariff	[redacted]	[redacted]	£76,533
9	SOC OS; RPSFTM, no re-censoring (HR = [redacted])	[redacted]	[redacted]	£79,626
10	SOC OS; RPSFTM, re-censoring switchers only (HR = [redacted])	[redacted]	[redacted]	£79,273
11	SOC OS; IPCW, robust SE, wide intervals (HR = [redacted])	[redacted]	[redacted]	£87,564
12	SOC OS; IPCW, robust SE, 2-day intervals (HR = [redacted])	[redacted]	[redacted]	£79,097

Abbreviations: FDA = Food and drug administration; ICER = Incremental cost-effectiveness ratio; MCM = Mixture cure model; QALY = Quality adjusted life year

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy [ID1684]

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

Produced by: Aberdeen HTA Group

Correspondence: Dwayne Boyers,
Senior Research Fellow
Health Economics Research Unit
University of Aberdeen,
Foresterhill,
Aberdeen, AB25 2ZD
Email: d.boyers@abdn.ac.uk

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Overview

The purpose of this document is to summarise the ERG's understanding and critique of the CAR-T tariff information provided by NHS England prior to the first appraisal committee meeting for topic ID1684. The ERG considers the balance of uncertainty around the true axi-cel infusion hospital costs and explores a range of alternative scenarios to inform committee discussions. Results of ICERs applied to the company and ERG preferred base case analyses are provided in this document and a confidential appendix considers the same analyses incorporating confidential CMU prices for other treatments included in the economic model.

NHS England CAR-T Tariff

Summary of information provided

NHS England have provided some further details on the figures underpinning their CAR-T tariffs. The following information is available to the ERG:

1) An expenditure spreadsheet that appears to summarise items of expenditure against staff resource use for six different trusts, used to calculate the original tariff inflated to 2022/23 prices: (£97,598);
2) A revised, reduced tariff calculation spreadsheet with the reduced tariff (£64,515) distributed across different categories of resource use in the pre-infusion, treatment (up to day 28) and post-infusion (day 28-100).

From the information provided, the ERG has the following understanding. The starting point is a set of per patient expenditures, as estimated by 6 NHS trusts, required to establish, and deliver a CAR-T service. The cost per patient appears to have been estimated based on an allocation of an average of 24 patients per centre per year.

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

NHS England have provided some further details on how they have now revised/adjusted the current tariff. They state that they have removed overheads which were fully absorbed in the original lines of expenditure (adding 30% to directly incurred salary and consumable costs).

The effect of this is to reduce the total expenditure (and tariff) by approximately 23% (i.e. from £97,598 to £75,076). NHS England note that the revised tariff now represents the marginal cost of treating a patient.

NHS England note further adjustments to account for changes in assumptions around: 1) length of stay and acuity of care; 2) the proportion of patients able to receive pre-conditioning in an ambulatory setting; and 3) the percentage of patients who are well enough to spend some of the first 28 days post-infusion outside of hospital (often in a local hotel instead). These adjustments translate into a 20% reduction in preconditioning costs (-£1,734), a 33% reduction in inpatient admission costs (-£9,749), but a corresponding 171% increase in hotel costs (+£1,867). The net impact on the tariff is a further reduction of £9,616 (£75,076 – £9,616 = £65,415). A further breakdown is provided which apportions the £65,415 across different components of the patient's treatment pathway (to 100 days post-infusion) as illustrated in Table 1.

Table 1: Summary of revised CAR-T tariff cost breakdown

Resource category	**Value (GBP, 2022)**	**Proportion of tariff distributed**
Identification and work-up	£6,514	9.96%
Leukapheresis	£2,459	3.76%
Pre-conditioning	£6,935	10.6%
Inpatient admission up to day 28	£19,499	29.81%
Early follow up close to treatment centre up to day 28	£11,588	17.71%
Adverse events up to day 28	£13,070	19.98%
Follow up post discharge to day 100	£5,351	8.18%
Total	**£65,415**	**100%**

ERG critique of the CAR-T tariff methods

The CAR-T tariff clearly accounts for higher staffing ratios than those accounted for in more general malignant lymphoma admission costs that the company use to estimate their infusion

admission costs in the economic model. The tariff also includes hotel costs, to allow patients to stay within the locality of the treatment centre, which are not included in the company model. The ERG considers it likely to be appropriate that the staff resource, treatment facilities, equipment and hotel costs associated with delivering a CAR-T service are higher than for more general malignant lymphoma admissions (as applied in the company's economic model).

Whilst it is likely that the company costs are under-estimated, the ERG view is that there is insufficient detail on the actual methods used to derive the original and revised CAR-T tariffs, and the methods used to distribute the tariff across resource use categories. These concerns mean it is difficult for the ERG to judge whether the CAR-T tariff should be applied in the economic model. The ERG raises the following specific concerns with regard to the CAR-T tariff given currently available information:

- *We are not party to the assumptions and methods originally used by trusts to estimate their expenditures against the different elements of resource, or how these equate with the actual quantities of resource use that are currently required to deliver of CAR-T therapy. It would have been preferable to have access to the estimates of resource use underpinning the expenditures detailed, but the ERG is unclear as to whether these data are available to NHS England or not.*

- *The expenditure figures do not reveal the quantities of resource assumed or the corresponding costing assumptions, or exactly what the costs incorporate. It is unclear how the proportions for each category of resource use have been derived. A robust costing analysis would require the allocation to different categories of resource to be based on data provided from the trusts for the original tariff. However, the ERG is unclear whether this was the case, or whether the tariff was apportioned to resource use categories retrospectively. If the apportionment was conducted retrospectively, it is unclear how the allocation to each category of resource was derived. Furthermore, the tariff breakdown appears to be inconsistent with the original tariff. For example, the guidance in the original summary spreadsheet suggests trusts were instructed to exclude lymphodepletion from reported expenditures but then the breakdown for the revised tariff apportions 10.6% of overall expenditure to pre-conditioning.*

- *It is not clear if the original expenditure estimates provided by trusts are based on actual data/experience, or projections of what they thought they would need to treat a given number of patients. There is a note in the summary worksheet suggesting that costs were to be based on PLICs, which may suggest they were based on experience of treating patients.*

- *The throughput for calculating expenditure per patient, and potential for economies of scale is not clear. If the calculations account for fixed investment costs for setting up a new service, economies of scale may be realised as provision/throughput increases. Per patient costs may further reduce if new infrastructure is shared across other specialties and indications.*

- *NHS England state that as part of their revisions, overheads have been removed from the original costs, but this would seem inappropriate. It is recognised that costs included in an economic evaluation should reflect the value of all resources used: staffing, capital, consumables, and an appropriate allocation of shared overheads. So, to remove overheads does not seem well justified.*

- *The stated adjustments to costs for pre-conditioning care, length of stay (for infusion), and acuity of care are not transparently described or justified, and the original assumptions are not clear on this either, i.e., what has been assumed originally with respect to length of stay and acuity of care for estimating expenditures?*

Any application of the original or revised CAR-T tariff in the company's economic model requires careful consideration about the items of resource that are / are not included in the tariff to avoid the risk of double counting resource use already considered in the company's model. Table 2 summarises the ERGs assumptions about the items of resource that are included in the tariff. In scenario analyses where the tariff is applied, the resource use items assumed to be covered by the tariff are otherwise set to zero in the company's model.

Table 2: ERG assumptions about components of costs included / excluded from the new CAR-T tariff.

Resource	**Included in tariff?**
Leukapheresis	Yes
Conditioning chemo (admin)[A]	No
Conditioning chemo (drug)[A]	No
Bridging chemo (admin)	Yes
Bridging chemo (drug)	Yes
Axi-cel infusion costs + hospital stay	Yes
Hotel costs	Yes
Aes (CRS and b-cell aplasia) [B]	No
Aes (other)	Yes
Hospital health state costs over first 100 days [C]	Yes
Subsequent treatment costs over first 100 days	No

[A] It is unclear whether the tariff includes conditioning chemotherapy costs. Guidance notes for the original tariff suggest that it does not, but the breakdown assigns an allocated cost. The ERG assumes that the information in the original guidance to trusts is correct and has been followed, and hence the conditioning chemotherapy costs are excluded from the tariff.

[B] CRS and b-cell aplasia costs are assumed to be excluded from the tariff on the grounds that CRS treatments (toculizumab – high cost drug and ICU admission are not included) and for b-cell aplasia, the main treatment (IVIg) is assumed to not be covered under the tariff.

[C] Analyses applying the CAR-T tariff remove the pre and post-event healthcare utilisation costs for hospital incurred resource use for the first 3 (monthly) cycles of the model. Resource use excluded are: outpatient visits, specialist nurse visits, inpatient days, and CT scans.

Additional ERG scenarios around the CAR-T tariff and axi-cel treatment infusion costs

Whilst the ERG raises several concerns with the CAR-T tariff costs, it is also likely that the company's approach to costing is an underestimate of the true opportunity costs of axi-cel treatment and infusion. Further review of the company's administration costs, and calculation formulae has identified several concerns with the company approach:

1) The company's inpatient costs are calculated based on a "per day" cost. The company first obtained a weighted average elective inpatient reference cost (2019/20 reference costs) for malignant lymphoma, as the weighted average of HRG codes, weighted according to HRG codes SA31 (A-F), uplifted for inflation to 2021 values (cost post inflation adjustment of £7,528.93). The company then assumed that the average length of stay was equivalent to dividing the tariff value by the excess bed day cost for the corresponding HRG codes (excess bed day cost post uplift = £468.12), generating an assumed length of stay for an average lymphoma ward of 16.1 days. However, the corresponding HES data indicate an average length of stay of 10.4 days. This has important implications because the company approach uses an average cost per day based on lymphoma admissions divided through by CAR-T length of stay, effectively assuming that the cost per day for CAR-T therapy is less than the cost per day on a lymphoma ward. This lacks face validity. The ERG preferred approach is to apply the average hospital length of stay for a patient with a diagnosis of diffuse large b-cell lymphoma (Average LOS: 10.4 days based on HES data for ICD 10 code: C833). Note: This should be considered an approximation only as it is not weighted for severity of disease in the same way as the weighted average NHS reference cost. The implication of adopting the ERG alternative approximation is to increase the average cost per day of admission for CAR-T from £468.12 in the company base case analysis to £723.94 in the ERG preferred analysis. When multiplied through by the axi-cel LOS of [redacted] days, this change alone increases the company's treatment costs from [redacted] to [redacted].

2) The company's model does not account for the costs of hotel stays during the first 28 days post infusion for a proportion of patients who do not live close to the CAR-T centre. The ERG therefore considers it appropriate to include hotel accommodation

costs at £150 per night (including accommodation and subsistence costs) for a proportion of patients (assume 50%) who do not live locally to a CAR-T centre, from time of discharge to 28 days post treatment (i.e 28-[redacted] = [redacted] days), leading to an additional cost of [redacted] per patient.

3) Even adjusting the cost per bed day as outlined above may be an under-estimation of costs. It assumes that the cost per bed day in a ward treating lymphoma patients incurs the same resource use as a cost per day on a CAR-T ward. This is highly unlikely to be the case and is likely an under-estimate of the true resource use, such as staff to patient ratios, use of multi-disciplinary teams, provision of infrastructure and equipment. One plausible scenario is to assume that the staffing ratios are resource requirements may be more like a ward where auto-sct is delivered. The ERG does not have access to detailed breakdowns of these costs by category, but one approach may be to assume that the cost per day is more similar to a patient receiving auto SCT than for lymphoma more generally. Using the same calculation approach as described in (1) above, this would result in a cost per day of £16,668.47 (HRG: SA26A) / 20.2 days (mean length of stay, HES 2019/20 data, OPCS code: X33.4) = Average cost per day: £825.17. Applying this daily cost would further increase the costs of axi-cel infusion in the model to [redacted] (without local accommodation costs) or £[redacted] (with accommodation costs included).

4) A final scenario considered by the ERG is one where the cost per bed day (obtained from 1 above) is uplifted to illustrate the impact of further increased staffing requirements, equipment, consumables etc. The challenge here is determining and justifying an appropriate inflation factor for the admission costs. Assuming the base HRG for lymphoma reflects admissions to general haematology wards with nurse-to-patient ratios of 1:6, and that CAR-T therapy admissions on balance require a nursing ratio more in line with high dependency (level 2) critical care (1:2), then nursing costs can be expected to be approximately 3 times higher for CAR-T admissions. Assuming medical time and other resources are also increased by this factor, we assess a scenario that inflates the company's infusion admission cost per day estimate by 3, but otherwise retains the company's other cost assumptions. Note, this is a rough calculation which has not been clinically validated but is provided for discussion and illustrates the impact of increased resource use assumptions on the ICER.

5) Despite the ERGs reservations about the CAR-T tariffs and what they include, they are based on submissions of costs from trusts where CAR-T is delivered and thus probably represent trust's best attempts to categorise costs (though this information is not transparently reported in terms of resource use and assumptions). The ERG thus provides two further scenarios (A) applying the original tariff and (B) applying the revised tariff from NHS England for information. Scenarios applying the CAR-T tariff incorporate the assumptions outlined in Table 2 above.

Table 3 summarises the scenario analyses undertaken by the ERG. Tables 4 and 5 provide the results of those scenarios applied to the company and ERG base case analyses.

Table 3 Alternative costing scenarios applied to the company's preferred costing approach

Sc.	Additional costs	%	Unit cost	per	No. units	Axi-cel admission costs	Notes
0	**Company axi-cel admin costs**	**100%**	**£468.12**	**Day**	[redacted]	[redacted]	
1	ERG adapted approach to length of stay calculation and assumptions about cost per day (applied to malignant lymphoma: HRG code: SA31 (A-F)	100%	£723.94	Day	[redacted]	[redacted]	HRG code as per company approach. Length of stay data obtained from HES, ICD 10 code: C883 (diffuse large b-cell lymphoma)
2	1 + Hotel costs close to treatment centre	50%	£150	Day	[redacted] (28-[redacted])	[redacted]	Assume NHS pays the costs of local accommodation from the point of discharge up to day 28 following infusion. Assume 50% of patients do not live locally and require accommodation. Unit cost of £150 per night is an ERG conservative assumption about per night costs of accommodation and subsistence.
3	Cost per bed day increased to assume that resource requirement is more similar to Auto-SCT than lymphoma HRGs	100%	£825.17	Day	[redacted]	[redacted]	Assumes that the additional resource use required to deliver CAR-T therapy may be more closely aligned to auto-SCT than to broader treatment for diffuse large b-cell lymphoma, cost per bed day obtained from HRG: SA26A, Auto SCT, and mean length of stay obtained from HES (OPCS code X33.4).
4	3 + Hotel costs close to treatment centre	50%	£150	Night	[redacted] (28-[redacted])	[redacted]	

Sc.	Additional costs	%	Unit cost	per	No. units	Axi-cel admission costs	Notes
5	1 + Assuming a nurse: patient ratio in the base lymphoma tariff of 1:6; and CAR-T of 1:2, then staff costs could be uplifted by a factor of 3. Assuming all other resources increase by a similar factor would increase the company's costs by a factor of 3.	100%	£723.94 x 3	Bed day	[redacted]	[redacted]	Multiplier of 3 applied to lymphoma HRG costs.
6	Analysis 5 + hotel stay costs					[redacted]	
7	Original CAR-T tariff applied					--	Applied across multiple items of resource use in the company model as detailed in Table 2.
8	Revised CAR-T tariff applied					--	Applied across multiple items of resource use in the company model as detailed in Table 2.

Table 4 Scenario analyses applied to company preferred base case

Scenario no.	**Scenario**	Incremental costs	Incremental QALYs	ICER
0	Company base case	[redacted]	[redacted]	£51,155
1	Cost per day based on HES LOS data for malignant lymphoma	[redacted]	[redacted]	£52,548
2	1 + include hotel costs	[redacted]	[redacted]	£52,710
3	Cost per bed day similar to auto-sct	[redacted]	[redacted]	£52,981
4	3 + Hotel costs	[redacted]	[redacted]	£53,143
5	1 + cost per bed day x 3	[redacted]	[redacted]	£58,733
6	5 + hotel costs	[redacted]	[redacted]	£58,894
7	Original CAR-T Tariff (£97.598)	[redacted]	[redacted]	£68,011
8	Revised CAR-T Tariff (£64,515)	[redacted]	[redacted]	£60,620

Table 5 Scenario analyses applied to ERG preferred base case

Scenario no.	**Scenario**	Incremental costs	Incremental QALYs	ICER
0	ERG base case post-FDA update	[redacted]	[redacted]	£57,172
1	Cost per day based on HES LOS data for malignant lymphoma	[redacted]	[redacted]	£58,649
2	1 + include hotel costs	[redacted]	[redacted]	£58,827
3	Cost per bed day similar to auto-sct	[redacted]	[redacted]	£59,125
4	3 + Hotel costs	[redacted]	[redacted]	£59,303
5	1 + cost per bed day x 3	[redacted]	[redacted]	£65,453
6	5 + hotel costs	[redacted]	[redacted]	£65,631
7	Original CAR-T Tariff (£97.598)	[redacted]	[redacted]	£74,647
8	Revised CAR-T Tariff (£64,515)	[redacted]	[redacted]	£66,925