NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

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. Lymphoma Action
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 Graham Collins, Consultant Haematologist and lymphoma MDT lead – clinical expert, nominated by Gilead (company)
   b. Dr Tobias Menne, Consultant Haematologist – clinical expert, nominated by NCRI-ACP-RCP-RCR
8. **Evidence Review Group critique of company response to technical engagement** prepared by Aberdeen HTA Group

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 low-grade non-Hodgkin lymphoma [ID1685]

Document B

Company evidence submission

January 2022

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Tables and figures

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

B.1.1. Decision problem

This submission covers the technology's full anticipated marketing authorisation for this indication. Further details are provided in the decision problem summary presented in Table 1.

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 non-Hodgkin lymphoma	[redacted]	The anticipated marketing authorisation for axicabtagene ciloleucel is for the treatment of '[redacted] As such, this submission is focused on FL, a subtype of indolent non-Hodgkin lymphoma, and specifically on FL patients who have received three or more prior lines of therapy (4L+ patients)
Intervention	Axicabtagene ciloleucel	Axicabtagene ciloleucel	Not applicable
Comparator(s)	• Rituximab monotherapy • Rituximab in combination with chemotherapy • Obinutuzumab with bendamustine • Lenalidomide with rituximab • Clinical management without axicabtagene ciloleucel including chemotherapy (such as cyclophosphamide, fludarabine, bendamustine or chlorambucil) • Best supportive care	• Rituximab in combination with chemotherapy • Obinutuzumab with bendamustine • Lenalidomide with rituximab • Clinical management without axicabtagene ciloleucel including chemotherapy (such as cyclophosphamide, fludarabine, bendamustine or chlorambucil)	Rituximab monotherapy is only recommended as an option for the treatment of r/r FL when all alternative treatments have been exhausted (that is, if there is resistance to or intolerance of chemotherapy). If it was being considered for use in patients with r/r FL after three or more lines of systemic therapy, it would be reserved for patients not fit enough to receive intensive active treatment as is the case for best supportive care, thereby constituting a cohort of patients widely considered not suitable or appropriate for consideration of CAR T-cell therapy. Indeed, clinical experts note that by the time patients reach the 4L+ treatment setting, they will have received

			rituximab monotherapy multiple times and, thereby, additional rituximab monotherapy would most likely be ineffective in this setting.[1] Neither rituximab monotherapy nor best supportive care are therefore relevant comparators for patients being considered for axicabtagene ciloleucel Of the other comparators listed, we would expect obinutuzumab with bendamustine and lenalidomide with rituximab to typically be used earlier in the treatment pathway than the 4L+ treatment setting. In addition, we would expect that chemotherapy (clinical management without axicabtagene ciloleucel) would be used after the 4L+ setting, following approval of axicabtagene ciloleucel. However, we have considered these as part of a blended comparator representing current care in the decision problem addressed.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	Health-related quality of life data were not collected in ZUMA-5 and are therefore informed by the existing literature base
Key: 4L+, fourth-line plus (three or more lines of prior therapy); CAR T-cell, chimeric antigen receptor T-cell; FL, follicular lymphoma; NICE, National Institute for Health and Care Excellence; r/r, relapsed or refractory.			

B.1.2. Description of the technology being appraised

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

The draft Summary of Product Characteristics (SmPC) for the relapsed or refractory (r/r) follicular lymphoma (FL [r/r FL]) indication is presented in Appendix C. The European Public Assessment Report for this indication can be provided on receipt.

Axi-cel was the first in a breakthrough class of chimeric antigen receptor (CAR) T-cell (CAR T-cell) therapies that are manufactured from patients' own T-cells and engineered ex vivo to express antigen-specific CAR, 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 linked to CD3ζ and CD28 T-cell activating domains; CD19 is a B-cell-specific cell surface antigen ubiquitously expressed in B-cell malignancies, including FL.[2]

Axi-cel is given as a single infusion treatment. The timescale from collection of the patient's T-cells by leukapheresis, through transportation to the manufacturing facility, product manufacture, and delivery to the clinical centre in Europe is typically [redacted].[3]

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.

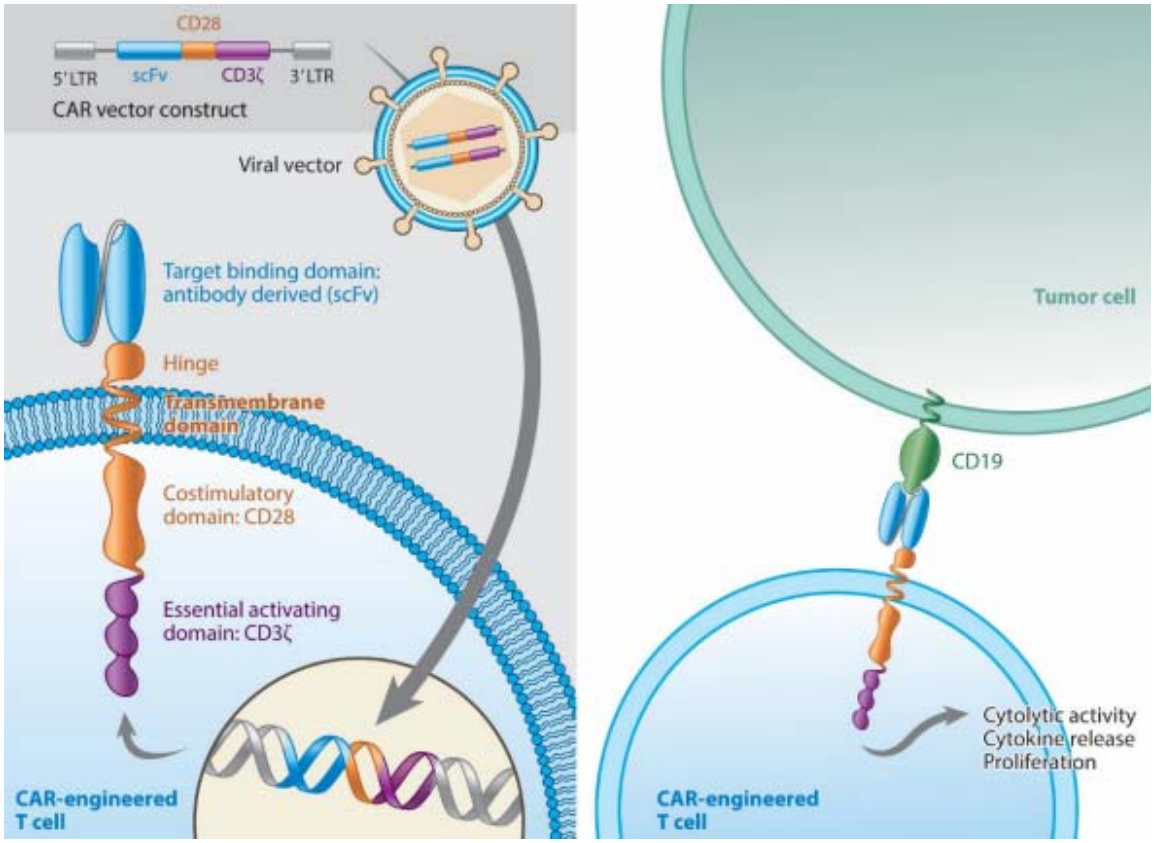
Table 2: Technology being appraised

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 monoclonal antibody (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 single-chain variable region fragment (scFv); the partial extracellular domain and complete transmembrane and intracellular signalling domains of human CD28, a lymphocyte co-stimulatory receptor that plays an important role in optimising T-cell survival and function; and the cytoplasmic portion, including the signalling domain, of human CD3ζ, a component of the T-cell receptor complex.[4] 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 antigen expressed on the cell surface of the target B-cell malignancies as well as normal B-cells. Following engagement with CD19-expressing target cells, the CD3ζ domain activates the downstream signalling cascade that leads to T-cell activation, proliferation and acquisition of effector functions, such as cytotoxicity. The intracellular signalling domain of CD28 provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including IL-2 production.[5] Together, these signals act in concert resulting in proliferation of the axi-cel CAR T-cells and apoptosis and necrosis of the CD19 expressing target cells. In addition, activated T-cells secrete cytokines and other molecules that can recruit and activate additional antitumour immune cells[6]
Marketing authorisation	A FL variation was submitted to the EMA on 23 July 2021 CHMP opinion is expected in April 2022 The application for GB filing will be submitted in April 2022 for a marketing authorisation extension of Yescarta to [redacted] The anticipated date of marketing authorisation for this indication is [redacted] Axi-cel is already indicated for the treatment of adult patients with r/r diffuse large B-cell lymphoma DLBCL and PMBCL, after two or more lines of systemic therapy

Indications and any restriction(s) as described in the 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
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 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 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 paracetamol 500–1,000 mg oral and diphenhydramine 12.5–25 mg intravenous or oral approximately 1 hour prior to axi-cel infusion is also recommended
Additional tests or investigations	Patients will be considered for axi-cel eligibility by a panel of expert clinicians following referral from a specialist doctor, with treatment provided in one of the 12 CAR-T centres currently set up to deliver CAR T-cell therapy across NHS England 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 is to 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	List price: £280,451 Average cost of a course of treatment including leukapheresis, bridging therapy, conditioning chemotherapy, acquisition (with PAS) and infusion and monitoring hospitalisation costs: [redacted]
Patient access scheme (if applicable)	[redacted]

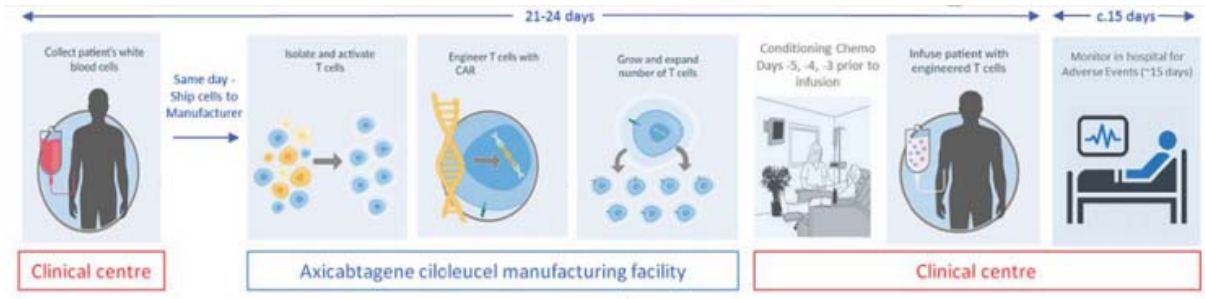
Key: CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FL, follicular lymphoma; GB, Great Britain; NHS, National Health Service; SmPC, Summary of Product Characteristics; PMBCL, primary mediastinal large B-cell lymphoma; r/r, relapsed or refractory; r/r FL, relapsed or refractory follicular lymphoma.

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



Key: CAR, chimeric antigen receptors; scFv, single-chain variable region fragment.

Figure 2: Process of manufacturing and administering axi-cel



Key: CAR, chimeric antigen receptors

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

B.1.3.1. Disease overview

Non-Hodgkin lymphoma (NHL) comprises a diverse group of cancers of the lymphatic system.[7] Indolent NHL (iNHL) describes slower growing lymphomas of this group; these lymphomas generally have longer survival times but are less likely to be cured compared with faster growing lymphomas.[7] FL is the most common type of iNHL that arises from B-lymphocytes (making it a B-cell malignancy) and accounts for approximately 19% of all cases of NHL.[8 9] It mainly affects adults over the age of 60, with no clear gender difference.[8, 9] Diagnosis and monitoring of FL includes assessment of several features that can help predict the likely disease course and thus inform treatment decisions.[8] These include grading and staging of disease, and risk categorisation based on demographic and basic disease characteristics; classification systems specific to FL are summarised in Table 3.

Table 3: Classification systems for follicular lymphoma

WHO/REAL	Cotswolds modified Ann Arbor	FLIPI score
Grade 1: 0–5 centroblasts **Grade 2**: 6–15 centroblasts **Grade 3**: >15 centroblasts **Grade 3B**: absence of centrocytes	**Stage I:** single lymph node group or organ **Stage II**: multiple lymph node groups/organ on same side of diaphragm **Stage III**: multiple lymph node groups/organ on both sides of diaphragm **Stage IV**: bone marrow or distant organ involvement. **Stage X:** bulky disease with nodal mass >10 cm **Stage E**: extra-nodal extension or single isolated site of extra-nodal disease **Stage A/B**: absence or presence of symptoms – B-symptoms include weight loss >10%, fever, drenching night sweats	**Factors (1 point for each variable present):** • Age >60 years • Ann Arbor Stage III–IV • Haemoglobin level <12 g/dl • LDH level >ULN • ≥4 nodal sites of disease **Risk category (factors):** • **Low** (0–1) • **Intermediate** (2) • **High** (3–5)
Key: FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; REAL, Revised European-American Lymphoma; ULN, upper limit of normal; WHO, World Health Organization. **Source:** Hernandez-Ilizaliturri 2020.[10]		

The FL disease course is one of interspersing remissions and relapses and nearly all patients will ultimately relapse. With each relapse the disease becomes more

resistant to treatment, leading to shorter remission periods over time.[11-14] UK clinical experts estimate approximately 10% of patients diagnosed with FL go on to receive ≥4 lines of therapy, with an estimated period of 10 years between the first and fourth-line treatment.[1] These estimates are generally aligned to real-world evidence from the prospective observational LymphoCare study in the US, which reported that 9% of patients diagnosed with FL received fourth-line treatment after a median follow-up of 8 years (range: 0.02–10.34).[13]

Despite its commonly indolent nature, FL is highly heterogeneous and there is a subpopulation of approximately 10-20% of patients who experience a more aggressive disease trajectory, characterised by multiple relapses, treatment refractoriness, short remission periods and an overall shortened lifespan.[15, 16] Patients with FL who experience progression of disease within 2 years of receiving front-line chemoimmunotherapy (defined as 'POD24') have a particularly poor prognosis, with only a 50% overall survival (OS) estimate at 5 years, compared with 90% OS estimate at 5 years for those without POD24.[15, 17, 18] Other high-risk sub-populations of FL include patients who are chemoimmunotherapy resistant and fail to achieve a response within 6 months of completion of initial chemoimmunotherapy (treatment refractory) or have double-refractory disease (that is, patients with FL who are refractory to the first two lines of therapy, notably including both an alkylating agent and an anti-CD20 monoclonal antibody). Given that all patients with r/r FL who require ≥ 4 lines of active treatment are a heterogenous group for whom there is no established standard of care (see Section B.1.3.4) and who represent a significant unmet need, in this appraisal, all of the 4L+ patients are the population of interest, irrespective of them having any high-risk prognostic factors.[11-14] Furthermore, aligning to the patient population enrolled to the ZUMA-5 trial introduced in Section B.2, FL patients to be considered for treatment with axi-cel are expected to have Grade 1–3A, Stage III–IV disease of any risk category (after three or more lines of systemic therapy [4L+] as per the anticipated marketing authorisation outlined in Table 2).

B.1.3.2. Prognosis of patients with r/r FL after three or more lines of systemic therapy

An estimated 2,200 patients are newly diagnosed with FL each year in the UK[19]; of these, an estimated 220 will receive at least four lines of therapy (approx.10% of all patients diagnosed).[1] Approximately 198 of these 220 patients are assumed to receive treatment in England or Wales (based on 90% of patients in the UK residing in England or Wales).[20]

The prognosis of patients with 4L+ r/r FL is generally poor and there is no established standard of care in this setting (see Section B.1.3.4). The LymphoCare study in the US recently reported median progression-free survival (PFS) of 0.69 years (95% confidence interval [CI]: 0.50, 0.97) in patients with FL receiving fourth-line treatment (n = 229).[13] A further retrospective analysis in the US recently reported median PFS of 0.90 years (95% CI: 0.59, 1.10) and median event-free survival of 0.56 years (95% CI: 0.48, 0.84) in FL patients receiving fourth-line treatment (n = 198) (event-free survival defined as time to progression, change of treatment or death).[11] Clinical experts noted that median PFS on current fourth-line plus (4L+) care in the UK is estimated to be notably lower, at 0.31–0.46 years.[1]

Retrospective analysis in the US further reported median OS for FL patients receiving fourth-line treatment at 5.34 years (95% CI: 3.51, not reached).[11] This is higher than clinical experts expect for UK FL patients receiving fourth-line treatment, for whom they estimate a median OS of approximately 3 years.[1] The LymphoCare study did not report OS data by treatment line. The only other study identified that reported such data in the published literature base was a retrospective analysis of patients with r/r FL in Japan. This study reported a median OS of 1.01 years in patients with r/r FL after fourth-line chemotherapy.[12]

These varied data reported in the current published literature reinforce the heterogeneity of the disease course in FL.[11] It should also be acknowledged that the current evidence base is largely retrospective in nature, with small patient numbers and strong variability in the type and number of prior lines per country that had been received; taken together, these differences of the evidence base further reflect the heterogenous nature of r/r FL. In the SCHOLAR-5 study introduced in Section B.2.9,

patients receiving fourth-line treatment in real-world practice across Europe and the US had a median OS of [redacted] months (Table 15).[21]

B.1.3.3. Burden of disease

Alongside reduced life expectancy, FL is associated with several physical and psychological symptoms that affect patients' health-related quality of life (HRQL). The most common symptom of FL is a painless swelling in the lymph nodes of the neck, armpit or groin, but it can also be associated with 'B-symptoms' such as night sweats, erratic fever and weight loss.[8] Patients with FL presenting with multiple sites of lymphadenopathy can endure restricted movement, disfigurement, pain, and bone marrow disease that can result in anaemia, leukopenia and thrombocytopenia.[22, 23]

In addition to physical symptoms FL negatively affects the mental health of patients, with depression and stress commonly reported.[24-26] As a generally accepted chronic, incurable and progressive condition, this can also be emotionally unsettling to FL patients. Indeed, HRQL diminishes with each treatment relapse and UK clinical experts note that patients with r/r FL reaching the 4L+ treatment setting are likely to have a lower quality of life due to the fewer treatment options available.[1] In a UK cross-sectional study using a variety of patient-reported outcome instruments to assess HRQL, patients with relapsed FL were more likely to experience worse HRQL compared with FL patients who were newly diagnosed, in partial or complete remission or disease-free.[22] Patients with relapsed FL had lower mean physical, emotional, functional and social wellbeing scores and reported statistically significantly higher levels of anxiety, depression and activity impairment levels compared with disease-free patients.[22] As such, the burden of illness in patients with three or more lines of systemic therapy is expected to be particularly high (though data is limited, Section B.3.4)

HRQL is further affected by treatment toxicity effects; for example, chemotherapy has specifically been shown to worsen health functioning ($p = 0.004$), depressive symptoms ($p = 0.005$) and activity impairment ($p = 0.009$) compared with FL patients in remission but not on treatment.[22] Patients receiving active chemotherapy for disease progression displayed considerable impairment (daily activity impairment > 50%) including in overall work productivity.[27]

Alongside the burden on patients, FL also poses a substantial burden on carers. In a Canadian cross-sectional cohort of patients with iNHL, including FL, the majority of care (74%) was unpaid assistance from a partner or spouse, relative or friend.[27] This group of unpaid caregivers provided a mean of 9.8 days of care in the 30 days prior to data collection, with a mean of 11.3 days of absenteeism.

B.1.3.4. Clinical pathway of care

Table 4 summarises the National Institute for Health and Care Excellence (NICE) recommendations for the treatment of symptomatic advanced-stage FL. However, despite there being national guidance and recommendations in place, there is significant variability in how patients are managed therapeutically in the r/r FL setting, and notably, beyond the 3L setting there is no consensus or standard of care available in the clinical management pathway.[1, 28]

Table 4: NICE recommendations for the treatment of symptomatic advanced-stage follicular lymphoma

	Guidance	TA#	Recommendations
First-line treatment and first-line maintenance treatment	Rituximab for the first-line treatment of Stage III–IV follicular lymphoma	TA243	Rituximab in combination with: • CVP • CHOP • Mitoxantrone, chlorambucil and prednisone • Cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α or • Chlorambucil These are recommended as an option for the treatment of symptomatic Stage III and IV FL in previously untreated patients
	Rituximab for the first-line maintenance treatment of follicular non-Hodgkin lymphoma	TA226	Rituximab maintenance therapy is recommended as an option for the treatment of patients with follicular non-Hodgkin lymphoma that have responded to first-line induction therapy with rituximab in combination with chemotherapy
	Obinutuzumab for untreated advanced follicular lymphoma	TA513	Obinutuzumab is recommended as an option for untreated advanced FL in adults (that is, as first induction treatment with chemotherapy, then alone as maintenance therapy), only if: • The person has a FLIPI score of 2 or more

	Guidance	TA#	Recommendations
			• The company provides obinutuzumab with the discount agreed in the PAS
Treating relapsed or refractory disease	Rituximab	TA137	Rituximab, within its marketing authorisation, in combination with chemotherapy is recommended as an option for the induction of remission in patients with relapsed Stage III or IV follicular non-Hodgkin lymphoma Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of patients with relapsed Stage III or IV follicular non-Hodgkin lymphoma in remission induced with chemotherapy with or without rituximab Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of patients with r/r Stage III or IV follicular non-Hodgkin lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy)
	Lenalidomide with rituximab for previously treated follicular lymphoma	TA627	Lenalidomide with rituximab is recommended, within its marketing authorisation, as an option for previously treated follicular lymphoma (Grade 1–3A) in adults, only if the company provides lenalidomide according to the commercial arrangement
	Obinutuzumab with bendamustine for treating follicular lymphoma after rituximab	TA629	Obinutuzumab with bendamustine followed by obinutuzumab maintenance is recommended, within its marketing authorisation, as an option for treating FL that did not respond or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen, but only if the company provides it according to the commercial arrangement

Key: CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; r/r, relapsed or refractory.
Source: NICE Pathways – Treating follicular lymphoma.[29]

Newly diagnosed FL patients are typically treated with rituximab plus a chemotherapy backbone (R-chemo) followed by rituximab maintenance for up to 2 years, in responding patients. At first relapse, patients who had a good response to initial R-chemo treatment are typically retreated with a different R-chemo regimen

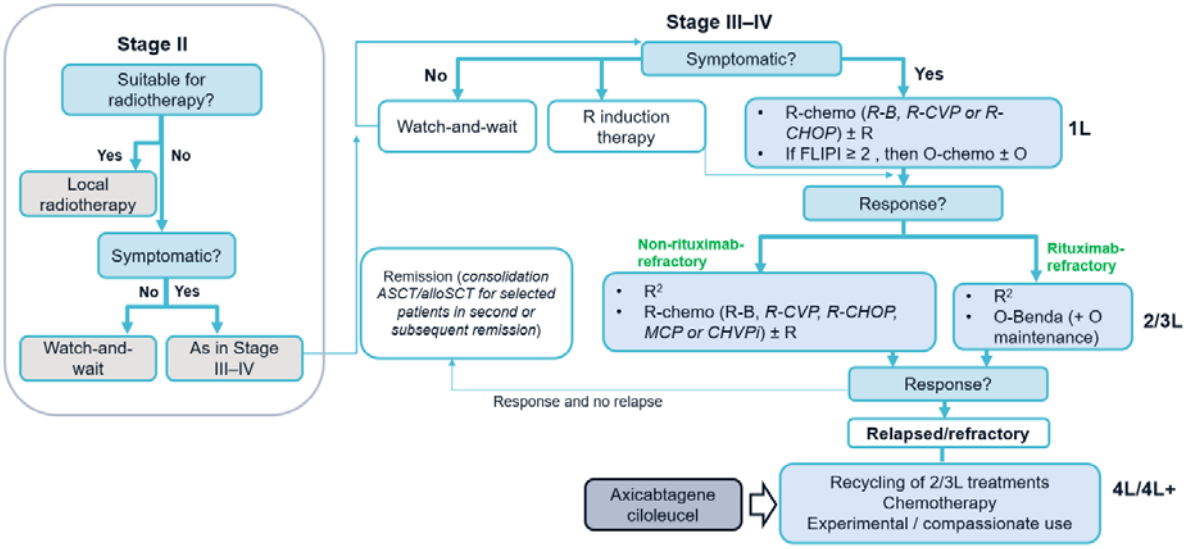
(followed by rituximab maintenance in responding patients). Patients who did not have a good response to initial R-chemo treatment are typically treated with lenalidomide plus rituximab (R^2) or obinutuzumab with bendamustine. Although rituximab monotherapy is also considered as a treatment option for relapsed FL, it is rarely used outside of the maintenance setting in the UK, with an observed lack of clinical effect as a remission inducing treatment. This is reflected in its recommended use, that is, only when all alternative treatment options have been exhausted (i.e. if there is resistance to or intolerance of chemotherapy).[1, 30]

At second relapse, the same regimens are considered with treatment decisions made on a case-by-case basis. Consolidation with autologous stem cell transplantation (auto-SCT) is recommended at second or subsequent remission (complete or partial) for patients who have not already had a transplant and who are fit enough for transplantation.[29] Allogeneic stem cell transplant can also be considered at second or subsequent remission (complete or partial) for patients who are fit enough for transplantation and for whom a suitable donor can be found when auto-SCT has not resulted in remission or is inappropriate.[29] However, it should be noted that allogeneic stem cell transplant needs to be carefully considered due to the notable morbidity and mortality in the r/r setting.[1]

By the time patients reach third relapse, that is they have received three prior systemic therapies, they have typically exhausted recommended treatment options. It must also be noted that by the 4L+ setting FL patients will very likely have received multiple rituximab-based regimens throughout their treatment course and, therefore, it is expected (and as validated by UK clinical experts) that their response to further rituximab-based treatment will be suboptimal at best. In the absence of an established standard of care, current 4L+ therapy consists of recycling earlier-line treatment options for FL (Table 4) or resorting to generic haemato-oncology or experimental/compassionate use treatments. Treatment decisions are made on a case-by-case basis, considering factors such as patient fitness, treatment goals, response and durability of response to prior therapy.

Axi-cel would offer a new treatment option in this 4L+ setting, as depicted in Figure 3.

Figure 3: Clinical care pathway for patients with follicular lymphoma and proposed axi-cel positioning



Key: 1L, first-line; 2L, second-line; 4L, fourth-line; alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplant; Benda, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP, cyclophosphamide, vincristine and prednisolone; FLIPI, Follicular Lymphoma International Prognostic Index; MCP, mitoxantrone, chlorambucil and prednisolone; NICE, National Institute for Health and Care Excellence; O, obinutuzumab; R, rituximab; R-B, rituximab with bendamustine; R^2, lenalidomide with rituximab.
Source: NICE Pathways – Treating follicular lymphoma.[29]

B.1.3.5. Unmet need

Patients with r/r FL who have received three or more lines of systemic therapy represent a difficult-to-treat patient group who often follow an aggressive, chemotherapy-resistant disease course, with poor prognosis and no established standard of care.

Current 4L+ treatment options in England are limited to recycling earlier-line treatments to which patients may have reduced tolerance, as well as reduced effectiveness; or resorting to generic haemato-oncology treatments with little expectation of effect or experimental treatments with no proven benefit. Patients in England actually have fewer treatment options at later lines than those in Wales and Scotland, where idelalisib (a licensed Pi3Kδ inhibitor) is an additional treatment available through routine baseline commissioning to patients with FL that is refractory to two prior lines of treatment.[31, 32] This is in contrast to England, where

NICE, in its final appraisal document (FAD), did not recommend idelalisib for treating FL that has not responded to two prior lines of treatment in adults.[33]

Although survival expectations depend on several factors, including previous treatment regimens received and response to previous treatment, patients are generally not expected to survive beyond approximately 3 years with current 4L+ care options that are currently available in England.[1]

B.1.4. Equality considerations

No equality issues for axi-cel are foreseen, but as noted above there are existing inequalities in current non-immunochemotherapy treatment options available in England compared with Wales and Scotland. Through provision of a non-immunochemotherapy treatment option to patients in England (as well as Wales and Scotland), recommendation of axi-cel could help reduce this current inequality across the devolved nations of the UK.[31, 32]

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 axi-cel.

B.2.2. List of relevant clinical effectiveness evidence

Table 5 summarises the clinical effectiveness evidence supporting axi-cel for the treatment of adult patients with r/r FL on the 4L+ treatment pathway.

Table 5: Clinical effectiveness evidence

<table>
<tr><td>Study (NCT)</td><td colspan="5">ZUMA-5 (NCT03105336)</td></tr>
<tr><td>Study design</td><td colspan="5">ZUMA-5 is an ongoing Phase II, multicentre, open-label study evaluating the efficacy and safety of axi-cel in r/r iNHL.</td></tr>
<tr><td>Population</td><td colspan="5">Adult subjects with r/r B-cell iNHL of FL or MZL histological subtypes who have received 2 or more prior lines of therapy. The FL cohort of patients who have received three or more lines of prior therapy is the focus of this submission.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Axi-cel</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Not applicable</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-5 presents the pivotal, regulatory, clinical evidence in support of axi-cel in r/r FL</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Overall survival
• Progression-free survival
• Response rate
• Adverse effects of treatment
• Health-related quality of life</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Incidence of anti-CD19 CAR antibodies
• Levels of anti-CD19 CAR T-cells in blood
• Levels of cytokines in serum</td></tr>
<tr><td colspan="6">Key: FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; r/r, relapsed/refractory.
Notes: bolded outcomes are those used in the economic modelling.</td></tr>
</table>

As ZUMA-5 is a single-arm study, comparator data are provided by an international, multicentre, external control cohort study, SCHOLAR-5, designed to provide

comparative evidence in patients with r/r FL meeting the ZUMA-5 eligibility criteria. SCHOLAR-5 is described in more detail in Section B.2.9.

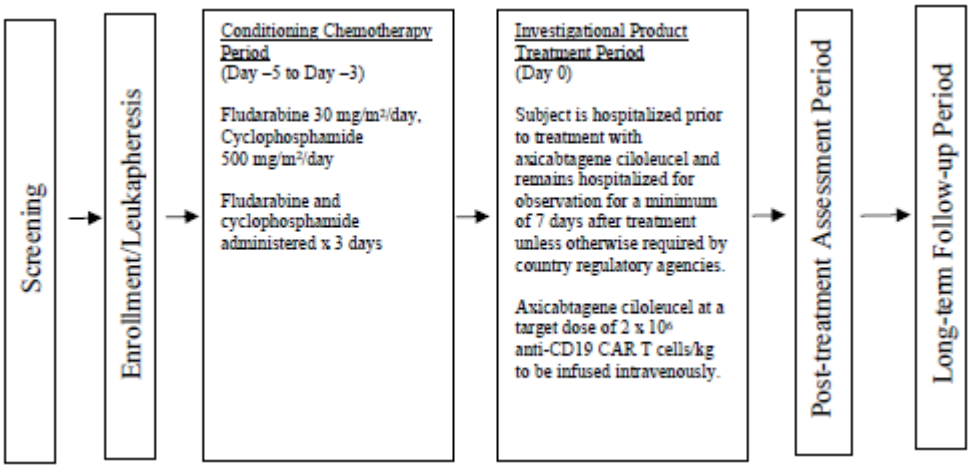
B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Table 6 provides a summary of the trial methodology for ZUMA-5.

ZUMA-5 is a Phase II, multicentre, open-label study evaluating the efficacy of axi-cel in adults with either r/r B-cell iNHL of the histological subtypes FL or marginal zone lymphoma (MZL).[34] This submission focuses solely on patients with r/r FL who have received three prior therapies (aligning with the anticipated market authorisation).

Up to approximately 125 patients with FL were to be enrolled and treated with axi-cel at a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg body weight.[34] Each patient was to proceed through the study periods depicted in Figure 4.

Figure 4: Study scheme for ZUMA-5



Key: CAR, chimeric antigen receptor.
Source: ZUMA-5 Clinical Study Protocol.[34]

The primary endpoint of the ZUMA-5 trial was the overall response rate, defined as the incidence of patients achieving complete response (CR) or partial response (PR) as determined by independent central review per Lugano classification (hereafter referred to as central assessment).[34] Secondary endpoints included CR rate, ORR and CR rate in patients who received three or more lines of prior therapy, ORR by

investigator assessment, duration of response (DOR), PFS, OS, and safety (Table 6).

Table 6: Summary of trial methodology for ZUMA-5

Trial number (acronym)	NCT03105336 (ZUMA-5)
Location	A total of 19 centres located in the US and France
Trial design	ZUMA-5 is a Phase II, multicentre, single-arm, open-label study evaluating the efficacy of axi-cel in patients with r/r iNHL Up to approximately 160 patients, including approximately 125 patients with FL with at least 80 patients with FL in the inferential analysis set, will be enrolled and treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2 x 10^6, anti-CD19 CAR T-cells per kg body weight
Eligibility criteria for participants	**Key inclusion criteria:** • Local histological confirmed diagnosis of B-cell iNHL, with histological subtype limited to FL Grade 1, Grade 2 or Grade 3a or MZL nodal or extra-nodal, based on criteria established by the WHO 2016 classification • r/r disease after two or more prior lines of therapy – Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent (single agent anti-CD20 antibody will not count as line of therapy for eligibility) – Stable disease (without relapse) >1 year from completion of last therapy is not eligible • At least one measurable lesion • Platelet count ≥75,000/μL • Creatinine clearance (as estimated by Cockcroft Gault) >60 mL/min • Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an ECHO, and no clinically significant ECG findings • Baseline oxygen saturation > 92% on room air **Key exclusion criteria:** • Transformed FL or MZL • FL histological Grade 3b • Known history of infection with HIV or Hepatitis B (HBsAG positive) or Hepatitis C virus (anti-HCV positive). A history of Hepatitis B or Hepatitis C is permitted if the viral load is undetectable per standard serological and genetic testing • History of a seizure disorder, cerebrovascular ischaemia/haemorrhage, dementia, cerebellar disease, cerebral oedema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement • Presence of fungal, bacterial, viral or other infection that is uncontrolled or requiring IV antimicrobials for management

	Note: other protocol defined Inclusion/exclusion criteria applied
Settings and locations where the data were collected	• Patients were to be hospitalised for treatment with axi-cel and were to remain in hospital for a minimum of 7 days after treatment • Patients were to remain hospitalised until all axi-cel-related non-haematological toxicities had returned to Grade ≤1 or baseline. Patients were also to remain hospitalised for ongoing axi-cel-related fever, hypotension, hypoxia or an ongoing central neurological toxicity if the event severity was Grade >1 or if deemed necessary by the treating investigator • Patients may have been discharged with non-critical and clinically stable or slowly improving toxicities if the event was Grade >1, if deemed appropriate by the investigator • All data was collected in an electronic CRF system • Routine laboratory assessments were to be performed by the local institutional laboratory. Prior to site activation, laboratory licensures and normal ranges were to be collected by the sponsor and stored in the Trial Master File • An independent Data Safety Monitoring Board had ongoing oversight of the study and monitored data throughout
Study periods and trial drugs	• Screening • Enrolment/leukapheresis: patients were considered enrolled in the study when they commenced leukapheresis – At least 12–15 L were to be processed to obtain approximately 5–10 x 10^9 mononuclear cells • Conditioning chemotherapy: all patients were to receive a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day for 3 days • Investigational product treatment: all patients were to receive a single IV infusion of axi-cel at a target dose of 2 x 10^6, anti-CD19 CAR T-cells per kg body weight after a 2-day rest period post-completion of conditioning chemotherapy – assigned as Day 0 – The following medications were to be administered 1 hour prior to infusion (i) acetaminophen 650 mg PO (ii) diphenhydramine 12.5–25 mg IV or PO • Post-treatment assessment: beginning at Week 2 (±2 days) and completing at Month 3 (±1 week) • Long-term follow-up period: beginning at Month 6
Concomitant medication	• Investigators could prescribe any other concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (for example, G-CSF) • Corticosteroid therapy at a pharmacologic dose (≥5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs were to be avoided for 7 days prior to leukapheresis and 5 days prior to axi-cel administration unless used for bridging therapy • 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 may interfere with evaluation of the axi-cel, such as non-steroidal anti-

	inflammatory agents should also be avoided for the same time period unless medically necessary • Treatment for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation and high-dose corticosteroid, other than defined/allowed in this protocol, and other investigational agents are prohibited except as needed for treatment of disease progression after axi-cel infusion
Primary outcome	• ORR, defined as the incidence of CR or PR by independent central review per Lugano classification • Response assessment (via PET-CT scan) began 4 weeks (±3 days) after the KTE-X19 infusion and are to be conducted every 3 months up until Month 24 • Response assessment will also be conducted at any point up to Month 24 when there is clinical concern for disease progression and after Month 24, if disease recurrence is suspected
Other outcomes used in the economic model/specified in the scope	• CR rate, defined as the incidence of CR by independent central review per Lugano classification • ORR for those patients who had three or more lines of therapy by central assessment • CR rate for those patients who had three or more lines of prior therapy by central reader • ORR by investigator assessment • DOR, defined as the time from first objective response to disease progression or death (by central and investigator assessment) • PFS, defined as the time from axi-cel infusion date to the date of disease progression or death from any cause (by central and investigator assessment) • OS, defined as the time from axi-cel infusion date to the date of death from any cause. – Survival status was assessed every 3 months up to Month 24, every 6 months from Month 24 to Month 60 and every 12 months from Month 60 to Year 15 • Safety assessments, including the incidence of AEs and clinically significant changes in laboratory values occurring throughout the conduct of the study. AEs were coded with the MedDRA Version 23.0 and severity was graded using the NCI's CTCAE Version 4.03

Pre-planned subgroup analyses	• Selected efficacy and safety endpoints were performed in subgroups defined by baseline covariates, including time to relapse (<24 vs ≥24 months) and double-refractory (defined as refractory to the first two lines of therapy)
Key: AE, adverse event; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CRF, case report form; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; FL, follicular lymphoma; G-CSF, granulocyte-colony stimulating factor; HIV, human immunodeficiency virus; IAS, inferential analysis set; iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; MZL, marginal zone lymphoma; NCI, National Cancer Institute; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PET, positron emitting tomography; PO, oral administration; PR, partial response; r/r, relapsed or refractory; SAS, safety analysis set; TTNT, time to next therapy; WHO, World Health Organisation. **Source:** ZUMA-5 Clinical Study Protocol.[34]	

B.2.3.1. Baseline characteristics

Table 7 provides a summary of baseline characteristics, including demographic and clinical characteristics, for FL patients.

The FL populations presented here are:

- **The full analysis set:** all patients who were enrolled in the trial
- **The safety analysis set (SAS):** all patients treated with any dose of axi-cel
- **The inferential analysis set (IAS):** the first ≥80 patients enrolled into the study who met the eligibility criteria for the pivotal cohort were treated with any dose of axi-cel, and had the opportunity to be followed for 18 months post axi-cel infusion

Baseline characteristics are presented for patients with two or more lines of prior therapy (as per ZUMA-5 eligibility criteria) and patients with three or more lines of prior therapy (as per anticipated marketing authorisation).

The demographics and clinical characteristics of patients were largely consistent across all analysis sets. A high proportion of patients had high-risk Follicular Lymphoma International Prognostic Index (FLIPI) scores (that is FLIPI Scores ≥ 3), and the majority of patients were refractory to prior therapy and had received at least three prior lines.[35] The majority of patients had progression of disease within 24 months of completion of first anti-CD20-based chemoimmunotherapy (i.e. POD24) and approximately a third had double-refractory disease. Clinical experts in the UK confirmed the baseline characteristics of patients enrolled to ZUMA-5 were generally

representative of patients who would typically be considered for axi-cel within its anticipated marketing authorisation in clinical practice.[1]

Table 7: Baseline characteristics of FL patients in ZUMA-5

Characteristics	FL patients with two or more lines of prior therapy			FL patients with three or more lines of prior therapy		
	FAS (n = 127)	SAS (n = 124)	IAS (n = 86)	FAS (n = 80)	SAS (n = 78)	IAS (n = 60)
Median age, years (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aged ≥65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FL histological category at trial entry, n (%)						
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FLIPI total score, n (%)						
Low risk (0–1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate risk (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk (3–5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapsed/refractory disease[a], n (%)						
Relapsed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Double-refractory subgroup[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median no. of prior therapies (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy, n (%)						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior auto-SCT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior PI3K inhibitor, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	FL patients with two or more lines of prior therapy			FL patients with three or more lines of prior therapy		
	FAS (n = 127)	SAS (n = 124)	IAS (n = 86)	FAS (n = 80)	SAS (n = 78)	IAS (n = 60)
Prior anti-CD20 single agent, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior alkylating single agent, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-CD20 + alkylating agent, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to relapse from first therapy[b], n (%)						
≥24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior lenalidomide, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow assessment at baseline, n (%)[c]						
Lymphoma present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphoma present but not FL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphoma not present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: auto-SCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; FL, follicular lymphoma; IAS, inferential analysis set; PI3K, phosphoinositide 3-kinase

Notes: [a] Patients with FL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Patients with FL who progressed >6 months of completion of the most recent prior treatment are defined as relapsed. Patients with FL who progressed within 6 months of completion each of the first 2 lines of prior treatment are defined as double-refractory. [b] from first anti-CD20-chemotherapy combination. [c] bone marrow assessment at baseline for lymphoma presence is based on investigator reported Lugano bone marrow assessment/bone marrow assessment using aspirate or core biopsy at screening. If these are not available, lymphoma presence is based on diagnosis history of bone marrow involvement.

Source: ZUMA-5 CSR 18-Month Addendum.[35]

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

Table 8 provides a summary of the statistical analysis and definitions of analysis sets in ZUMA-5.

Approximately 160 patients were to be enrolled and treated with axi-cel, including 125 FL patients, with at least 80 patients with FL in the IAS.[34] The trial used a single-

arm design to investigate the ORR in patients with r/r B-cell iNHL treated with axi-cel with a hypothesised target response rate in patients with FL of 60%.

The primary analysis was performed when at least 80 patients with FL were enrolled into the IAS, and patients had had the opportunity to be followed up for at least 12 months following the first disease assessment. After the primary analysis, additional follow-up analyses of efficacy and safety were to be performed, as needed to satisfy regulatory requirements and to perform long-term efficacy, safety and OS follow-up.

- Follow-up Analysis 1 was planned when at least 80 patients with FL in the IAS had had the opportunity to be followed up for 18 months
- Further analyses are planned (follow-up Analysis 2) when at least 80 patients with FL in the IAS have had the opportunity to be followed up for 24 months

This submission presents data from follow-up Analysis 1 (i.e. the 18-month analysis). Although all patients would have had the opportunity to be followed for 18 months after axi-cel infusion, some might have <18 months of actual follow-up because they were unable to attend the 18-month study visit.[35] For any patient unable to attend the 18-month study visit, an additional patient was added to the IAS to ensure that at least 80 patients had ≥18 months of follow-up. The IAS, therefore, included the first 86 patients to account for patients who were unable to reach the 18-month study visit per protocol.

Table 8: Summary of statistical analyses for ZUMA-5

Hypothesis objective	Four hypotheses were tested using a fixed sequence procedure in terms of ORR and CR to control the overall Type I error at one-sided alpha level of 0.025 with the following test order: • Hypothesis 1 (H1): test for ORR as determined by central review, if significant then • Hypothesis 2 (H2): test for CR rate as determined by central review, if significant then • Hypothesis 3 (H3): test for ORR as determined by central review in the subjects who have had three or more prior lines of therapy, if significant then • Hypothesis 4 (H4): test for CR rate as determined by central review in the subjects who have had 3 or more prior lines of therapy

	The hypotheses H1 through H4 will be assessed at the time of the interim Analysis 3, 4 and 5, and the primary analysis The H1 is that the ORR, as determined by central review, to axi-cel is significantly greater than 40% in patients with the FL histological subtype in the IAS The H2 is that the CR rate, as determined by central review, to axi-cel is significantly greater than 15% in patients with the FL histological subtype in the IAS The H3 is that the ORR, as determined by central review, to axi-cel is significantly greater than 40% in patients with FL in the IAS who have had three or more prior lines of therapy The H4 is that the CR rate, as determined by central review, to axi-cel is significantly greater than 15% in patients with FL the IAS who have had three or more prior lines of therapy
Statistical analysis	For the primary endpoint of ORR, the patient incidence of objective response was calculated and two-sided 95% CIs calculated with the Clopper–Pearson method. An exact binomial test was used to compare the ORR per central read among the patients with FL and among the patients with FL who had three or more lines of prior therapy to the hypothesised historical control rate of 40% Kaplan–Meier methods were applied to time to event analyses including DOR, PFS and OS. Kaplan–Meier plots, estimates and two-sided 95% CIs were generated, and the number of patients censored or having events summarised
Analysis sets	**IAS**: all enrolled patients treated with any dose of axi-cel who met the eligibility criteria: – Histologically confirmed diagnosis of B-cell iNHL, with histological subtype limited to FL Grade 1, Grade 2 or Grade 3a based on criteria established by the WHO 2016 classification – r/r disease after two or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent. SD (without relapse) >1 year from completion of last therapy was not eligible This analysis set was used for all analyses of the primary endpoint of objective response and endpoints based on objective response (ORR, BOR rate including CR rate, DOR, PFS) and OS for the study
	SAS: all patients treated with any dose of axi-cel. The safety analysis set was used for all safety analyses for the study and was used for the sensitivity analyses of ORR, BOR rate, DOR, PFS and OS.
	FAS: all enrolled (leukapheresed) patients. This set was used for sensitivity analyses of ORR, BOR rate, CR rate, DOR, PFS and OS; this set was also used for patient listings of death

	Retreatment analysis set: all patients who underwent retreatment with axi-cel; this set was used for all retreatment safety and efficacy analyses. Patients in the retreatment analysis set were not included in any other analysis set
Sample size, power calculation	Up to approximately 160 patients, including approximately 125 with FL, with at least 80 patients with FL in the IAS were to be enrolled and treated The primary efficacy endpoint for this study in at least 80 patients with FL in the IAS has 93% power to test the null hypothesis that the ORR is 40% vs the alternative hypothesis that the ORR is 60% with a one-sided alpha level of 0.0237
Data management, patient withdrawals	For the primary endpoint of ORR, patients who did not meet the criteria for an objective response by the analysis cut-off date, including those with not estimable assessment data and those without any assessment, were considered non-responders Standard censoring methods were applied to time to event analyses for those patients without an event at the time of analysis
Key: BOR, best overall response; CIs, confidence intervals; DOR, duration of response; FAS, full analysis set; FL, follicular lymphoma; IAS, inferential analysis set; iNHL, indolent non-Hodgkin lymphoma; PFS, progression-free survival; OS, overall survival; SAS, safety analysis set; SD, standard deviation; WHO, World Health Organization. **Source:** ZUMA-5 Clinical Study Protocol.[34]	

B.2.4.1. Patient disposition data

Figure 5 provides a summary of patient disposition data for FL patients in ZUMA-5.

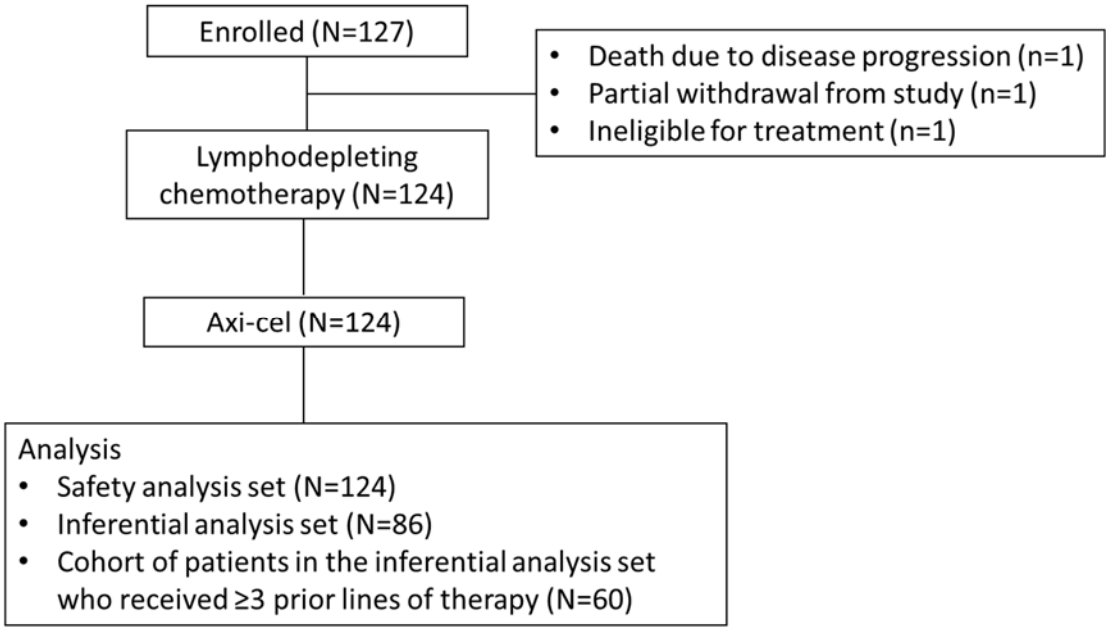
In total, [redacted] patients with FL were enrolled into the ZUMA-5 trial (that is, underwent leukapheresis).[35] Axi-cel was successfully manufactured for all [redacted] (100%) FL patients; there were no delays in infusion due to manufacturing issues. For patients who received axi-cel, the median time from leukapheresis to delivery of axi-cel to the study site was [redacted] days (range: [redacted]), and the median time from leukapheresis to administration was [redacted] days (range: [redacted] days).

At the data cut-off date for follow-up Analysis 1 (the 18-month analysis), [redacted] patients with FL had received lymphodepleting chemotherapy and proceeded to axi-cel infusion.[35] [redacted] patients did not receive either lymphodepleting chemotherapy or axi-cel infusion for the following reasons:

- Patient death ([redacted])

- Ineligible for treatment due to low platelet levels and was subsequently treated in a compassionate use study ([redacted])
- Partial withdrawal from the study at data cut-off; however, this patient may be treated in the future ([redacted])

Figure 5: Patient disposition data for FL patients enrolled in the ZUMA-5 trial



Key: FL, follicular lymphoma.
Source: Adapted from the ZUMA-5 CSR 18-Month Addendum.[35]

Bridging therapy was received by four FL patients between enrolment and lymphodepleting chemotherapy; all four had documented measurable disease after bridging therapy.[35]

Of the [redacted] FL patients enrolled, [redacted] had received three or more prior lines of therapy; [redacted] of whom were treated with axi-cel and [redacted] of whom had at least 18 months of follow-up at the time of 18-month analysis.

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

Quality assessment of ZUMA-5 was conducted using the Downs and Black checklist, full details of which are provided in Appendix D.

Within the context of a single-arm study design, the overall risk of bias in ZUMA-5 is thought to be low. The primary endpoint (ORR) was determined by independent central review as per the Lugano classification and provides an objective estimate of treatment effect of relevance to clinical practice (where response to treatment is the primary measure of effect). The single-arm design does, however, necessitate a need for an indirect treatment comparison to provide relative treatment-effect estimates required for decision-making that is associated with higher uncertainty than a controlled trial would otherwise stipulate. This is further discussed in Section B.2.13. In terms of intervention, the axi-cel treatment schedule adopted in ZUMA-5 reflects the administration and dosing practice of axi-cel in clinical practice. Of note, there would be no additional impact or requirement for further FL-specific site qualification or referrals/monitoring and related processes, over and above what already exists for DLBCL/PMBCL patients in England.

B.2.6. Clinical effectiveness results of the relevant trials

ZUMA-5 patient groups and analysis sets for which data are presented are summarised in Table 9.

Efficacy data are presented for the IAS of FL patients with two or more lines of prior therapy as this was the predefined primary efficacy analysis set. However, to align with the anticipated marketing authorisation and target population for reimbursement, efficacy data are also presented for the IAS and SAS of FL patients with three or more lines of prior therapy; for efficacy analyses this latter population is referred to as the modified intent-to-treat (mITT) population from hereon in.

This submission presents data from follow-up Analysis 1 (the 18-month analysis).

Table 9: Summary of ZUMA-5 cohorts and analysis sets presented

Patient group	Analysis set	N	Data available	Submission location
FL patients with two or more lines of prior therapy	IAS	86	Efficacy	Section B.2.6
FL patients with two or more lines of prior therapy	SAS	124	Safety	Section B.2.10

Patient group	Analysis set	N	Data available	Submission location
FL patients with three or more lines of prior therapy	IAS	60	Efficacy	Section B.2.6
FL patients with three or more lines of prior therapy	mITT[a]	78	Efficacy	Section B.2.6
FL patients with three or more lines of prior therapy	SAS[a]	78	Efficacy	Section B.2.6

Key: FL, follicular lymphoma; IAS, inferential analysis set; mITT, modified intent-to-treat; SAS, safety analysis set.
Notes: [a] mITT analyses in FL patients with three or more lines of prior therapy were post-hoc for all endpoints other than ORR and CR rate. IAS includes the first 86 patients treated with any dose of axi-cel who had the opportunity to be followed for at least 18 months from first disease assessment date. SAS/mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

B.2.6.1. FL patients with two or more lines of prior therapy

B.2.6.1.1. Response and duration of response (IAS)

The primary efficacy endpoint of ORR in patients with r/r FL who had the opportunity to be followed for at least 18 months from first disease assessment date following axi-cel treatment was [redacted] patients ([redacted]%). This ORR was statistically significantly greater than the pre-specific historical control rate of [redacted]% ([redacted]).[35] The CR rate was [redacted] patients ([redacted]%). This CR was statistically significantly greater than the pre-specified control rate of [redacted]% ([redacted]).

Among the [redacted] patients who achieved a CR or PR, the median time to first objective response was <1 month.[35] Of patients who initially had a PR (n = [redacted]), [redacted] later achieved a CR. The median DOR in all responders (n = [redacted]) was not reached and [redacted] patients ([redacted]%) had an ongoing response at data cut-off (minimum follow-up of 18 months from first disease assessment; median follow-up of [redacted] months for DOR). The median DOR in CRs (n = [redacted]) was not reached and [redacted] patients ([redacted]%) had an ongoing response at data cut-off.

A summary of response and duration of response data are presented in Table 10.

Table 10: Summary of response using central assessment per Lugano classification; FL patients with two or more lines of prior therapy, IAS

	N = [redacted]
Objective response rate (CR + PR), n (%) [95% CI]	[redacted]
p-value vs historical control rate	[redacted]
Best objective response	
Complete response rate, n (%) [95% CI]	[redacted]
Partial response, n (%) [95% CI]	[redacted]
Stable disease, n (%) [95% CI]	[redacted]
Progressive disease, n (%) [95% CI]	[redacted]
Time to response	
Median time to response in all responders, months (range)	[redacted]
Median time to response in CRs, months (range)	[redacted]
Duration of response	
Median duration of response in all responders, months (range)	[redacted]
Median duration of response in CRs, months (range)	[redacted]

Key: CI, confidence interval; CR, complete response; CSR, clinical study report; FL, follicular lymphoma; IAS, inferential analysis set; NE, not evaluable; PR, partial response.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

The Kaplan–Meier plots for DOR and DOR by best response for all patients in the IAS are provided in Appendix L.

B.2.6.1.2. Progression-free survival (IAS)

Median PFS [redacted] in patients with r/r FL who had the opportunity to be followed for at least 18 months from first disease assessment date, and had a median follow-up time for PFS of [redacted] months (reverse Kaplan–Meier approach).[35]

At the time of analysis, [redacted] patients ([redacted]%) had progressed or died.[35] The estimated 12-month PFS rate was [redacted]% (95% CI: [redacted], [redacted]) and the estimated 18-month PFS rate was [redacted]% (95% CI: [redacted], [redacted]).

Among the [redacted] patients who achieved a CR, [redacted] ([redacted]%) had progressed or died.[35] The estimated 12 and 18-month PFS rates in CRs were [redacted]% (95% CI: [redacted]%, [redacted]%) and [redacted]% (95% CI: [redacted]%, [redacted]%), respectively.

The Kaplan–Meier plots for PFS and PFS by best response for all patients in the IAS are provided in Appendix L.

B.2.6.1.3. Overall survival (IAS)

Median OS [redacted] in patients with r/r FL who had the opportunity to be followed for at least 18 months from first disease assessment date following axi-cel treatment, and had a median follow-up time for OS of [redacted] months (reverse Kaplan–Meier approach).[35]

At the time of analysis, [redacted] patients ([redacted]%) had died. The estimated 12-month OS rate was [redacted]% (95% CI: [redacted], [redacted]) and the estimated 18-month OS rate was [redacted]% (95% CI: [redacted], [redacted]).

Among the [redacted] patients who achieved a CR, [redacted] patients ([redacted]%) had died. The estimated 12- and 18-month OS rates in CRs were [redacted]% (95% CI: [redacted]%, [redacted]%) and [redacted]% (95% CI: [redacted]%, [redacted]%), respectively.

The Kaplan–Meier plots for OS and OS by best response for all patients in the IAS are provided in Appendix L.

B.2.6.1.4. Retreatment data (IAS)

Overall, [redacted] FL patients were retreated with axi-cel after disease progression. [redacted] of these patients achieved a CR to retreatment and the remaining [redacted] achieved a PR.[35] At the time of analysis, [redacted] patents ([redacted] CRs and [redacted] PR) had an ongoing response to retreatment and neither the median DOR nor the median PFS had been reached.

B.2.6.1.5. Subsequent therapy (SAS)

[redacted] ([redacted]%) patients with FL in the safety analysis set had subsequent anticancer therapy.[35] No single regimen was used to treat more than [redacted], further demonstrating the lack of established standard of care at later-line settings. A summary of the regimens that were given is provided in Appendix L.

[redacted] ([redacted]%) patients with FL in the safety analysis set had a stem cell transplant after treatment with axi-cel ([redacted] auto-SCT and [redacted] allogeneic stem cell transplant). [redacted] of these patients initially had a PR but then progressed; the [redacted] was a non-responder whose disease progressed.

B.2.6.2. FL patients with three or more lines of prior therapy

B.2.6.2.1. Response and duration of response (IAS)

The secondary efficacy endpoint of ORR in patients with FL who had received three or more lines of prior therapy and had the opportunity to be followed for at least 18 months from first disease assessment date following axi-cel treatment was [redacted] patients ([redacted]%). This ORR was significantly greater than the pre-specific historical control rate of [redacted]% ([redacted]).[35] The CR rate was [redacted] patients ([redacted]%), significantly greater than the pre-specified control rate of [redacted]% ([redacted]).

The median DOR in all responders (n = [redacted]) was not reached and [redacted] patients ([redacted]%) had an ongoing response at data cut-off (minimum follow-up of 18 months from first disease assessment, median follow-up of [redacted] months for DOR).[35] The median DOR in CRs (n = [redacted]) was not reached and [redacted] patients ([redacted]%) had an ongoing response at data cut-off.

A summary of response and duration of response data are presented in Table 11.

Table 11: Summary of response using central assessment per Lugano classification; FL patients with three or more lines of prior therapy, IAS

	N = [redacted]
Objective response rate (CR + PR), n (%) [95% CI]	[redacted]
p-value vs historical control rate	[redacted]
Best objective response	
Complete response rate, n (%) [95% CI]	[redacted]
Partial response, n (%) [95% CI]	[redacted]
Stable disease, n (%) [95% CI]	[redacted]
Progressive disease, n (%) [95% CI]	[redacted]
Duration of response	
Median duration of response in all responders, months (range)	[redacted]
Median duration of response in CRs, months (range)	[redacted]

Key: CI, confidence interval; CR, complete response; CSR, clinical study report; FL, follicular lymphoma; IAS, inferential analysis set; NE, not evaluable; PR, partial response.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

The Kaplan–Meier plots for DOR and DOR by best response for FL patients with three or more lines of prior therapy in the IAS are provided in Appendix L.

B.2.6.2.2. Progression-free survival (IAS)

Median PFS [redacted] in patients with FL who had received three or more lines of prior therapy and had the opportunity to be followed for at least 18 months from first disease assessment date following axi-cel treatment, and a median follow-up time for PFS of [redacted] months (reverse Kaplan–Meier approach).[35]

At the time of analysis, [redacted] patients ([redacted]%) had progressed or died.[35] The estimated 12-month PFS rate was [redacted]% (95% CI: [redacted], [redacted]) and the estimated 18-month PFS rate was [redacted]% (95% CI: [redacted], [redacted]).

Among the [redacted] patients who achieved a CR, [redacted] ([redacted]%) had progressed or died.[35] The estimated 12 and 18-month PFS rates in CRs were [redacted]% (95% CI: [redacted]%, [redacted]%) and [redacted]% (95% CI: [redacted]%, [redacted]%), respectively.

The Kaplan–Meier plots for PFS and PFS by best response for FL patients with three or more lines of prior therapy in the IAS are provided in Appendix L.

B.2.6.2.3. Overall survival (IAS)

Median OS [redacted] in patients with FL who had received three or more lines of prior therapy and had the opportunity to be followed for at least 18 months from first disease assessment date following axi-cel treatment, and had a median follow-up time for OS of [redacted] months (reverse Kaplan–Meier approach).[35]

At the time of analysis, [redacted] patients ([redacted]%) had died.[35] The estimated 12-month OS rate was [redacted]% (95% CI: [redacted], [redacted]) and estimated 18-month OS rate was [redacted]% (95% CI: [redacted], [redacted]).

Among the [redacted] patients who achieved a CR, [redacted] ([redacted]%) had died. The estimated 12 and 18-month OS rates in CRs were [redacted]% (95% CI: [redacted]%, [redacted]%) and [redacted]% (95% CI: [redacted]%, [redacted]%), respectively.

The Kaplan–Meier plots for OS and OS by best response for FL patients with three or more lines of prior therapy in the IAS are provided in Appendix L.

B.2.6.2.4. Response and duration of response (mITT)

Post-hoc analyses of ORR in patients with FL who had received three or more lines of prior therapy and were treated with axi-cel was [redacted] patients ([redacted]%). This ORR was significantly greater than the pre-specific historical control rate of [redacted]% ([redacted]). The CR rate was [redacted] patients ([redacted]%), significantly greater than the pre-specified control rate of [redacted]% ([redacted]). The median DOR in all responders (n = [redacted]) was not reached with a median follow-up time of [redacted] months (reverse Kaplan–Meier approach).

A summary of response and duration of response data is presented in Table 12.

Table 12: Summary of response using central assessment per Lugano classification; FL patients with three or more lines of prior therapy, mITT

	[redacted]
Objective response rate (CR + PR), n (%) [95% CI]	[redacted]
Best objective response	
Complete response rate, n (%) [95% CI]	[redacted]
Partial response, n (%) [95% CI]	[redacted]
Stable disease, n (%) [95% CI]	[redacted]
Progressive disease, n (%) [95% CI]	[redacted]
Duration of response	
Median duration of response in all responders, months (range)	[redacted]

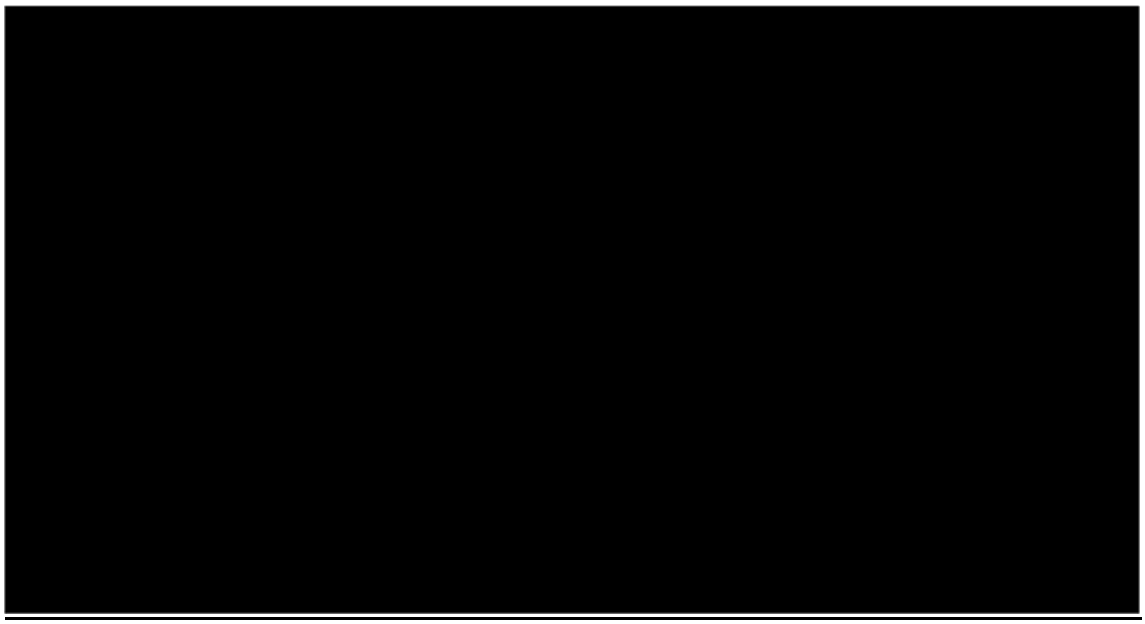
Key: CI, confidence interval; CR, complete response; CSR, clinical study report; FL, follicular lymphoma; mITT, modified intent-to-treat; NE, not evaluable; PR, partial response.
Notes: mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-month addendum.[35]

The Kaplan–Meier plots for DOR and DOR by best response for FL patients with three or more lines of prior therapy in the mITT are provided in Figure 6 and Figure 7.

Figure 6: Kaplan–Meier plot for duration of response; FL patients with three or more lines of prior therapy, mITT

Key: CI, confidence interval; FL, follicular lymphoma; mITT, modified intent-to-treat; NE, not evaluable
Notes: mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-month addendum[35] and data on file.

Figure 7: Kaplan–Meier plot for duration of response by best response; FL patients with three or more lines of prior therapy, mITT



Key: CI, confidence interval; CR, complete response; FL, follicular lymphoma; mITT, modified intent-to-treat; NE, not evaluable; PR, partial response.
Notes: mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-month addendum[35] and data on file.

B.2.6.2.5. Progression-free survival (mITT)

Median PFS [redacted] in patients with FL who had received three or more lines of prior therapy and were treated with axi-cel, after a median follow-up time for PFS of [redacted] months (reverse Kaplan–Meier approach).

At the time of analysis, [redacted] patients ([redacted]%) had progressed or died. The estimated 12-month PFS rate was [redacted]% (95% CI: [redacted], [redacted]) and the estimated 18-month PFS rate was [redacted]% (95% CI: [redacted], [redacted]).

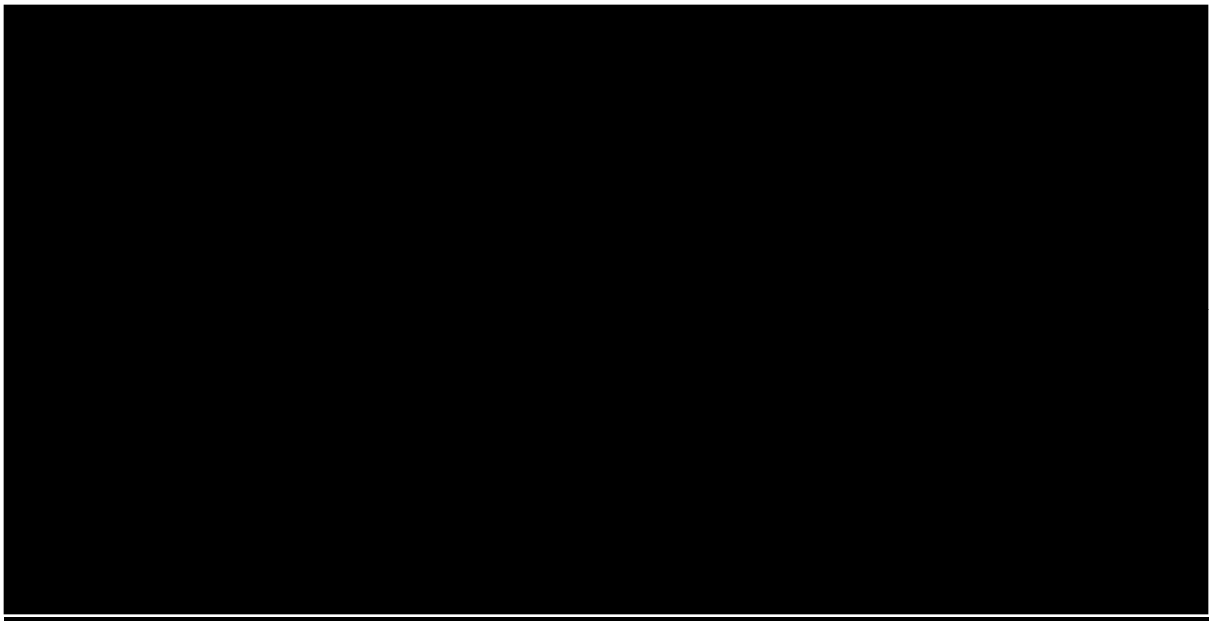
Among the [redacted] patients who achieved a CR, [redacted] ([redacted]%) had progressed or died. The estimated 12 and 18-month PFS rates in CRs were [redacted] (95% CI: [redacted] and [redacted]% (95% CI: [redacted] respectively.

The Kaplan–Meier plots for PFS and PFS by best response for FL patients with three or more lines of prior therapy treated with axi-cel are provided in Figure 8 and Figure 9.

Figure 8: Kaplan–Meier plot for progression-free survival; FL patients with three or more lines of prior therapy, mITT

Key: CI, confidence interval; FL, follicular lymphoma; mITT, modified intent-to-treat; NE, not evaluable.
Notes: mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-month addendum[35] and data on file.

Figure 9: Kaplan–Meier plot for progression-free survival by best response; FL patients with three or more lines of prior therapy, mITT



Key: CI, confidence interval; CR, complete response; FL, follicular lymphoma; mITT, modified intent-to-treat; NE, not evaluable; PR, partial response.
Notes: mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-month addendum[35] and data on file.

B.2.6.2.6. Overall survival (mITT)

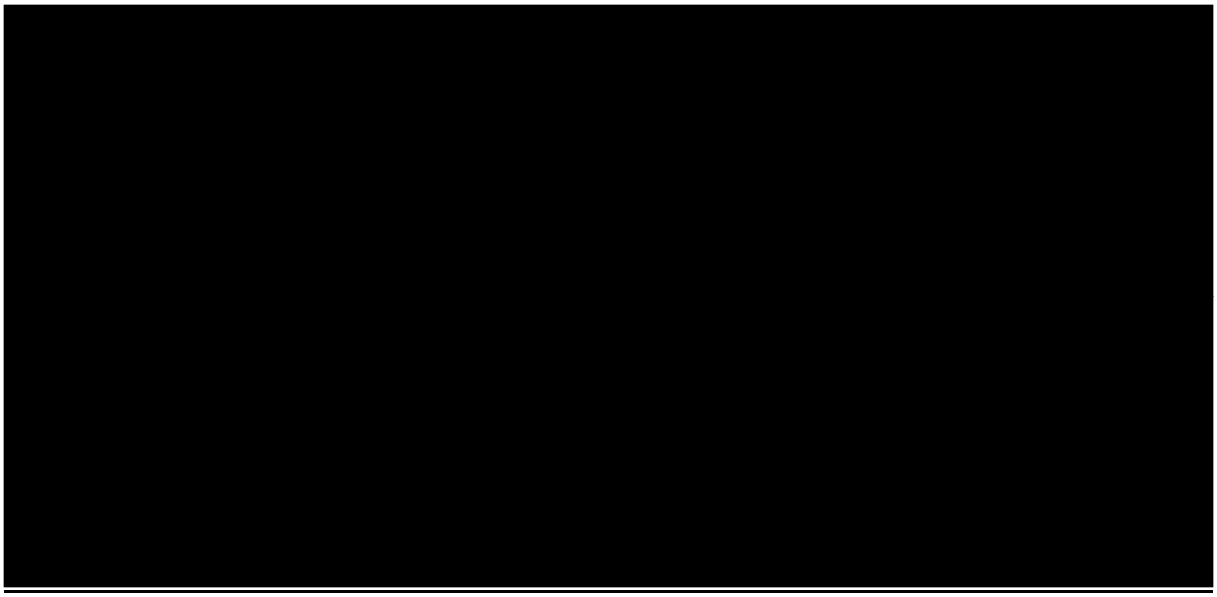
Median OS [redacted] in patients with FL who had received three or more lines of prior therapy and were treated with axi-cel, after a median follow-up time for OS of [redacted] months (reverse Kaplan–Meier approach).

At the time of analysis, [redacted] ([redacted]%) had died. The estimated 12-month OS rate was [redacted]% (95% CI: [redacted], [redacted]) and the estimated 18-month OS rate was [redacted]% (95% CI: [redacted], [redacted]).

Among the [redacted]patients who achieved a CR, [redacted] patients ([redacted]%) had died. The estimated 12 and 18-month OS rates in CRs were [redacted]% (95% CI: [redacted]%, [redacted]%) and [redacted]% (95% CI: [redacted] respectively.

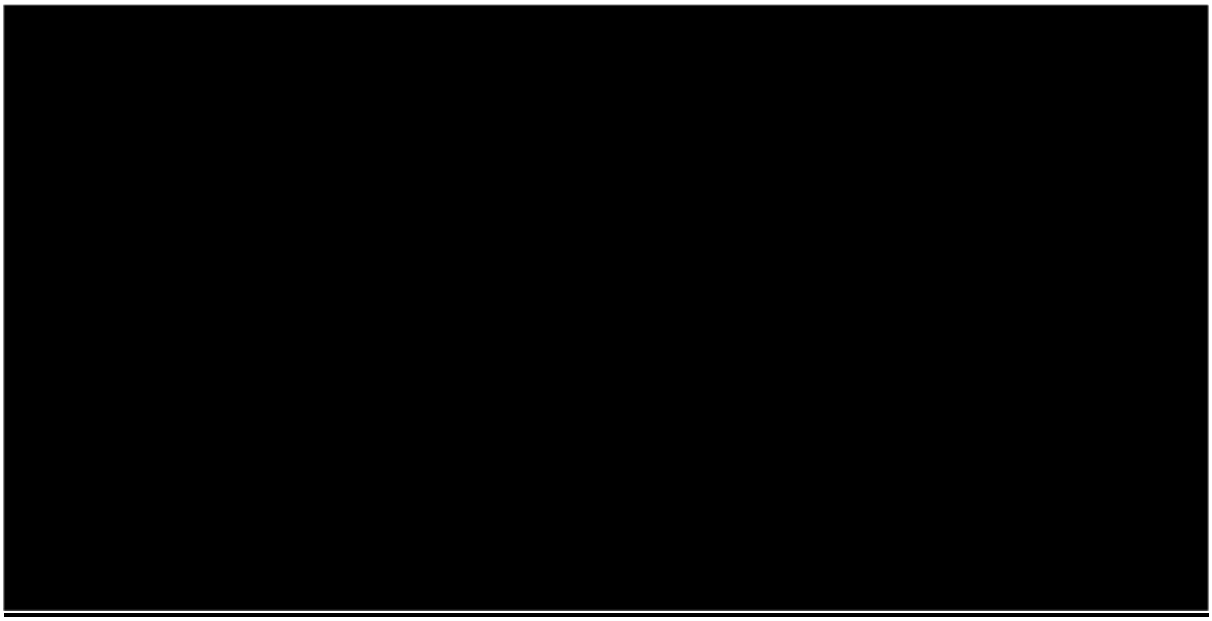
The Kaplan–Meier plots for OS and OS by best response for FL patients with three or more lines of prior treated with axi-cel are provided in Figure 10 and Figure 11.

Figure 10: Kaplan–Meier plot for overall survival; FL patients with three or more lines of prior therapy, mITT



Key: CI, confidence interval; FL, follicular lymphoma; mITT, modified intent-to-treat; NE, not evaluable.
Notes: mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-month addendum[35] and data on file.

Figure 11: Kaplan–Meier plot for overall survival by best response; FL patients with three or more lines of prior therapy, mITT



Key: CI, confidence interval; CR, complete response; FL, follicular lymphoma; mITT, modified intent-to-treat; NE, not evaluable; PR, partial response.
Notes: mITT includes all patients treated with any dose of axi-cel.
Source: ZUMA-5 CSR 18-month addendum[35] and data on file.

B.2.7. Subgroup analysis

Subgroup analyses demonstrated consistent ORR and CR rates across subgroups, with rates that were generally comparable with the those observed in the overall population. Subgroup analyses were only conducted on the total FL population.

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

B.2.8. Meta-analysis

Not applicable.

B.2.9. Indirect and mixed treatment comparisons

A systematic literature review identified a paucity of clinical evidence for patients with FL who have received at least three prior therapies (Appendix D). Three potentially relevant studies that may have been used for comparative efficacy data were identified:

- Batlevi et al. (2020)[11]
- Link et al. (2019)[13]
- Fuji et al. (2020)[12]

However, all three studies were considered highly limited in their suitability as a source of comparative efficacy data for axi-cel in patients with 4L+ r/r FL in England. Firstly, none of the studies reported baseline characteristics in the 4L+ FL setting. Secondly, none of the studies were in a European setting, which may have led to unobserved biases due to both differences in the natural history of disease and potentially differing treatment patterns. As a result, no matching comparison for treatment-effect modification has been conducted for these three studies.

B.2.9.1. SCHOLAR-5

B.2.9.1.1. Methods

An international, multicentre, external control cohort study, SCHOLAR-5, was designed to provide comparative evidence for axi-cel in patients with r/r FL meeting ZUMA-5 eligibility criteria.[21] SCHOLAR-5 was also designed to help characterise the natural history of FL and current treatment patterns.

The SCHOLAR-5 cohorts were created from multiple data sources:

- Cohort A – retrospective cohort created from electronic medical records of six sites, including university hospitals and cancer centres with two sites based in the UK and other sites based in France, Spain, Portugal and the US
- Cohort B – retrospective cohort created from the Vanderbilt University Medical Center's Synthetic Derivative: a fully de-identified database derivative of electronic medical records from the university
- Cohort C – prospective cohort created from an open-label Phase II study, DELTA, that enrolled patients with r/r FL who had not responded to or were refractory to rituximab and an alkylating agent and were treated with idelalisib

Adult patients with r/r FL or MZL starting third or later-line therapy on or after April 2011 to July 2014 (depending on source) were eligible for the SCHOLAR-5 cohort.[21] Before analysis set construction, cohorts were restricted to FL patients who had received at least three prior lines of therapy, aligning to the anticipated marketing authorisation for axi-cel.

Two analysis sets were initially constructed to meet the study objectives. The real-world analysis set contained Cohort A and B patients (n = 58) and was used to characterise the natural history of FL and current treatment patterns.[21] The effectiveness analysis set (EAS) contained Cohort A, B and C patients with FL (n = 82) and was used to provide primary comparative analysis. A modified EAS was also constructed that contained EAS patients who had a recorded Eastern Cooperative Oncology Group score and age range within the patients of ZUMA-5 (n = 67).

The primary effectiveness endpoint was predefined as ORR within a line of treatment, but a variety of methods were used to assess response across cohorts.[21] Secondary effectiveness endpoints of interest included CR rate, DOR, PFS and OS.

Propensity scoring methods, specifically standardised mortality ratio (SMR) weighting, were applied to account for imbalances of confounders between the ZUMA-5 and SCHOLAR-5 populations prior to comparative analyses. Full details of the propensity scoring methods and outcomes are provided in the SCHOLAR-5 technical report in the reference pack.[21] Sensitivity analyses using propensity score

matching rather than SMR weighting are also described in the SCHOLAR-5 technical report.

B.2.9.1.2. Natural history and treatment pattern outcomes

Natural history and real-world treatment pattern data from SCHOLAR-5 are summarised in Table 13, Figure 12 and Figure 13.

The lack of standard of care in later-line settings is clear to see in real-world treatment pattern data, with fourth-line treatments consisting of a varied mix of immunochemotherapy, chemotherapy and experimental treatments.[36] In post-hoc analyses of the UK cohort of patients ([redacted]), a similar mix of immunochemotherapy, chemotherapy and experimental treatments were reported, along with what we assume is compassionate use of PI3Ki-based treatment[21] (as such treatment is not routinely reimbursed in National Health Service [NHS] England[33]).[21]

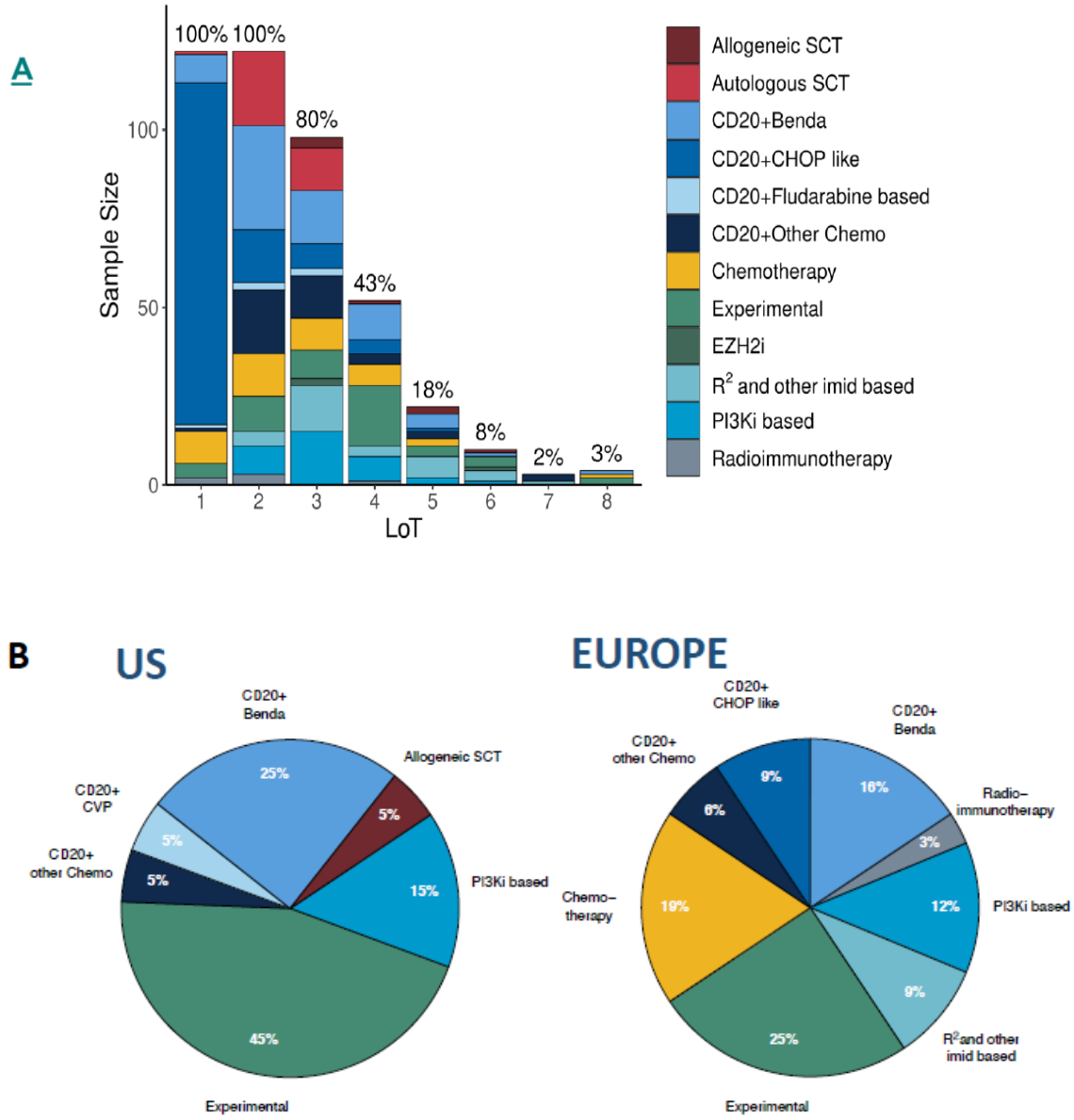
Natural history data from SCHOLAR-5 further demonstrate the reduced effectiveness of treatment over time, as observed in previous studies.[11-13] ORR reduced from 66% with third-line treatment to 53% and 37% with fourth and fifth or later-line treatments, respectively (Table 13).[36] Survival outcomes similarly reduced with each line of treatment (Figure 12 and Figure 13). The proportion of patients alive at 18-months reduced from 83% with third-line treatment to 72% and only 36% with fourth and fifth or later-line treatment, respectively (Table 13).[36]

Table 13: Natural history represented by response by line of therapy

Outcome	Line of treatment		
	3L (n = 98)	**4L (52)**	**≥ 5L (n = 27[a])**
ORR, % (95% CI)	66% (55, 76)	53% (38, 67)	37% (22, 56)
CR, % (95% CI)	43% (32, 54)	33% (20, 48)	17% (8, 33)
18 months OS, % (95% CI)	83% (76, 91)	72% (61, 86)	36% (22, 60)
PFS Median, months (95% CI) 18 months PFS, % (95% CI)	 11.0 (8.6, 17.1) 31% (21, 46)	 7.4 (5.3, 15.1) 23% (13, 41)	 4.0 (3.1, 114) 4% (1, 23)

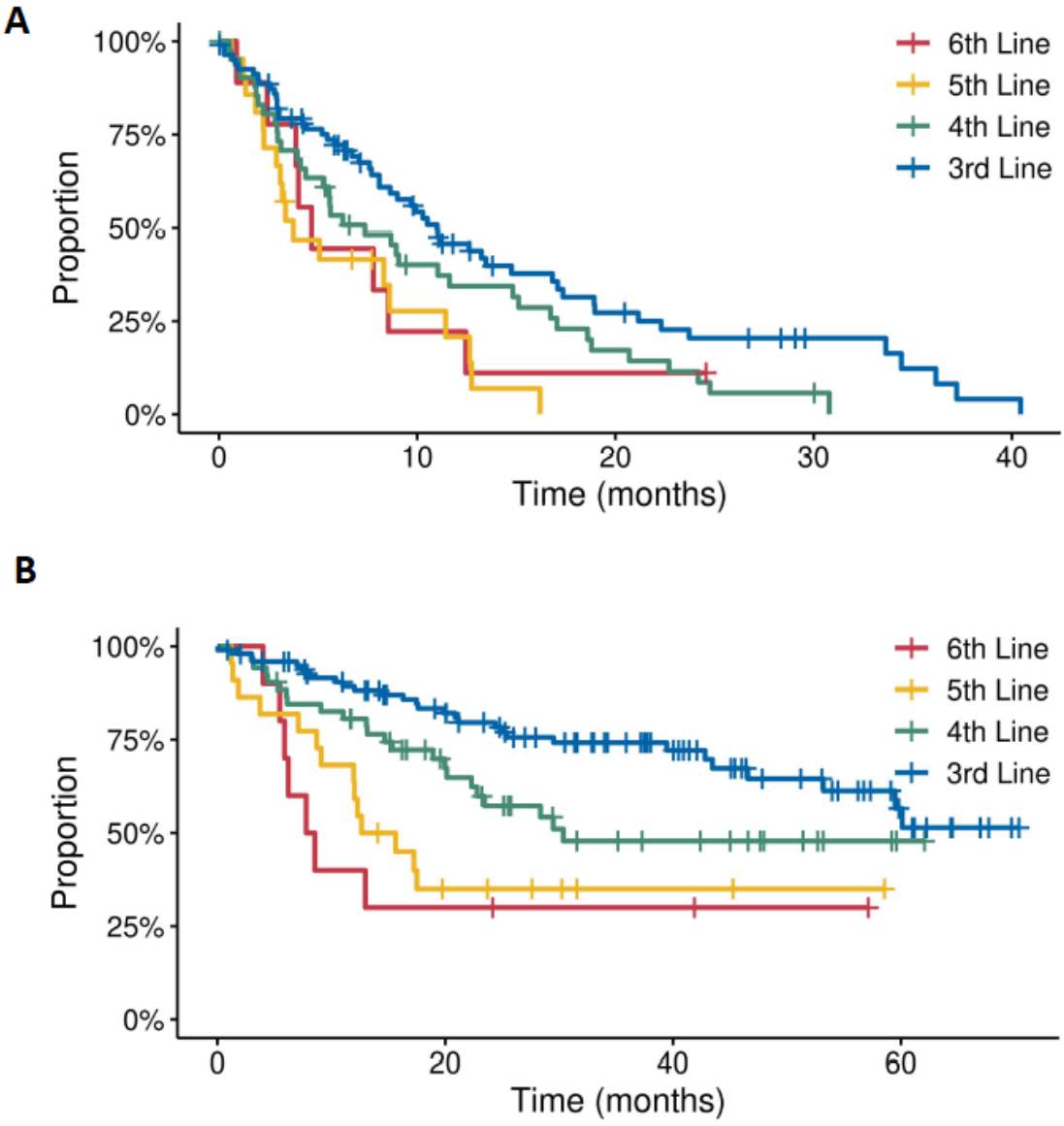
Key: 3L, third line of treatment; 4L, fourth line of treatment; ≥ 5L, fifth or later line of treatment; CI, confidence interval; CR, complete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
Notes: [a] for ≥5 line of treatment, 39 eligible lines from 27 patients were included in the model, except for OS which included the first eligible line per patient.
Source: Ghione et al. (2021).[36]

Figure 12: (A) Real-world clinical site treatment patterns by line of therapy[a,b] and (B) fourth line treatment patterns by region (US and Europe)



Key: Benda, bendamustine; Chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP, cyclophosphamide, vincristine and prednisolone; LoT, line of therapy; R^2, lenalidomide with rituximab; SCT, stem cell transplant.
Note: [a], All SCHOLAR-5 patients (i.e. excludes DELTA trial data); [b], percentage values represent proportion of patients with line of treatment
Source: Ghione et al. (2021a)[37]; Ghione et al. (2021b).[36]

Figure 13: Natural history represented by (A) progression-free survival (B) overall survival by line of therapy



Source: Ghione et al. (2021).[36]

B.2.9.1.3. Comparative analyses

Baseline characteristics of patients pre- and post-weighting are provided in Table 14. Both the IAS and the mITT of ZUMA-5 were used for weighting and comparative analyses; IAS data are provided in Appendix M and mITT data are provided below. Before weighting, significant differences were observed in POD24 status, the number of prior lines of therapy and the proportion of patients >65 years of age ([redacted]

[redacted]).[21] After applying SMR weights, the effective sample size for SCHOLAR-5 reduced from 82 patients to 77, but there were no significant differences remaining in baseline characteristics.

Note: It was not feasible to compare patients from SCHOLAR-5 to ZUMA-5 based on double-refractory status as the SCHOLAR-5 protocol did not include double-refractory status as a variable. It is acknowledged that this is a limitation as double-refractory status is a recognised poor prognostic indicator in the r/r FL treatment setting. However, UK clinical experts agreed that POD24, tumour bulk, time since last treatment and age are highly appropriate prognostic factors to which comparative analyses between SCHOLAR-5 and ZUMA-5 have been conducted.

Table 14: Baseline characteristics of patients pre- and post-weighting; FL patients with three or more lines of prior therapy, SCHOLAR-5 EES, ZUMA-5 mITT

Characteristics	Pre-weighting			Post-weighting		
	SC-5 (n = 82)	Z-5 (n = 78)	p-value [SMD]	SC-5 (EES = 77)	Z-5 (n = 78)	p-value [SMD]
POD24, n (%)						
Yes	[redacted]					
No						
Missing						
Prior lines of therapy						
Mean (SD)	[redacted]					
Median (range)						
Relapsed/refractory to prior line of therapy						
Relapsed	[redacted]					
Refractory						
Missing						

Characteristics	Pre-weighting			Post-weighting		
	SC-5 (n = 82)	Z-5 (n = 78)	p-value [SMD]	SC-5 (EES = 77)	Z-5 (n = 78)	p-value [SMD]
Prior SCT						
Yes						
No						
Missing						
Tumour bulk ≥ 7 cm						
Yes						
No						
Missing						
Time since last treatment, months						
Mean (SD)						
Median (range)						
CR or PR to prior line of therapy						
Yes						
No						
Missing						
Age ≥ 65 years						
Yes						
No						
Missing						
Prior anti-CD20 + alkylator combination						
Yes						
No						
Missing						

Key: CR, complete response; ESS, estimated sample size; mITT, modified intent-to-treat; POD24, progressed disease within 24 months after initiation of first-line anti-CD20 chemo combination therapy; PR, partial response; SC-5, SCHOLAR-5; SCT, stem cell transplant; SD, standard deviation; SMD, standardised mean difference; Z-5, ZUMA-5.
Note: Percentages may not add up to 100% due to rounding.
Source: SCHOLAR-5 Technical Report.[21]

Comparative analysis results are summarised in Table 15, and Kaplan–Meier curves for PFS and OS are shown in Figure 14 and Figure 15.

ORR and CR rates were markedly higher in ZUMA-5 than SCHOLAR-5, with odds ratios of [redacted] and [redacted] respectively, which were statistically significant at the [redacted][21] Although median PFS, OS and DOR were not reached for ZUMA-5, first quartile estimates exceeded the medians reached in SCHOLAR-5 for all time to event outcomes.

Cox model hazard ratios predict an [redacted]% reduction in risk of disease progression or death ([redacted]) and a [redacted]% reduction in risk of death alone ([redacted]) with axi-cel treatment versus current care.[21] For DOR, cox model hazard ratios predict a [redacted]% reduction in the risk of relapse after response ([redacted]).

Table 15: Comparative analysis summary; FL patients with three or more lines of prior therapy, SCHOLAR-5, EES, ZUMA-5 mITT

Outcome	SCHOLAR-5 (n = 77)	ZUMA-5 (n = 78)	Relative treatment-effect estimate (95% CI)	p-value
ORR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CR rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median DOR, months	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; DOR, duration of response; EES, estimated sample size; FL, follicular lymphoma; M, month; mITT, modified intent-to-treat; NE, not estimable; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, risk reduction.
Source: SCHOLAR-5 Technical Report.[21]

Figure 14: Progression-free survival for axi-cel (ZUMA-5) and current 4L+ care (propensity score weighted SCHOLAR-5)

Key: 4L+, fourth-line plus; mITT, modified intent-to-treat.
Source: Gilead data on file

Figure 15: Overall survival for axi-cel (ZUMA-5) and current 4L+ care (propensity score weighted SCHOLAR-5)

Key: 4L+, fourth-line plus; mITT, modified intent-to-treat.
Source: Gilead data on file

Sensitivity analyses across different analysis sets from SCHOLAR-5 and ZUMA-5 are provided in the appendices of the SCHOLAR-5 technical report.[21] Irrespective of the analysis set used, axi-cel demonstrated a significant response and survival benefit compared with current care for the treatment of FL patients who had received at least three lines of prior therapy.

B.2.9.2. Uncertainties in the indirect and mixed treatment comparisons

Comparative analyses clearly indicate improved response and survival outcomes with axi-cel compared with current care, but the wide CIs around point estimates indicate that the exact magnitude of improvement is unclear. Robustness of comparative analyses are, however, supported with consistent findings across primary and sensitivity analyses exploring different weighting methods and analysis sets across the two studies.

All comparisons of real-world data to clinical trial data are subject to common limitations relating to differences in disease assessment approaches across these settings. Real-world data response and progression outcomes from SCHOLAR-5 are likely inflated compared with ZUMA-5 owing to significant differences in the way such data are sourced and collected in the real-world versus a controlled trial environment. Response and progression outcomes in clinical practice are typically derived and interpreted on a centre-by-centre basis by an individual treating physician based on a heterogenous schedule of when that patient is available for follow-up, and typically without bone marrow confirmation. Further inherent limitations with the real-world data set of SCHOLAR-5 included missing baseline characteristic data for some potentially confounding factors, such as FLIPI score, particularly at later lines of therapy, and variation in line of therapy definitions. The latter resulted in a loss of sites and patients in the feasibility phase of the study.

Finally, the highly variable treatment approach at fourth and later-line prevents any treatment-specific comparisons to be conducted. However, the blended comparator approach to comparative analyses offers a high degree of external validity and generalisability considering the lack of standard of care in current 4L practice.

In the absence of clinical evidence for patients with FL who have received at least three prior therapies in the existing evidence base, SCHOLAR-5 provides the strongest evidence on which to form comparative effectiveness conclusions for axi-cel versus current care.

B.2.10. Adverse reactions

B.2.10.1. Safety summary

Table 16 presents an overview of safety outcomes from ZUMA-5 at the time of the 18-month analysis.

In total, [redacted] ([redacted]%) of all FL patients in the SAS experienced at least one adverse event (AE); [redacted] ([redacted]%) patients experienced worst Grade 3 or higher AEs, and [redacted] ([redacted]%) had serious AEs (SAEs).[35] As of the 18-month analysis data cut-off date, [redacted] Similar safety outcomes were observed in FL patients with at least three prior lines of therapy in the SAS (Table 16).

Table 16: Safety summary for FL patients in ZUMA-5

N (%)	FL patients with two or more lines of prior therapy SAS (n = 124)		FL patients with three or more lines of prior therapy SAS (n = 78)	
	Any grade	≥Grade 3	Any grade	≥Grade 3
TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Serious treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]
Death due to treatment-related TEAE	[redacted]	[redacted]	[redacted]	[redacted]

Key: FL, follicular lymphoma; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

B.2.10.2. Common adverse events

Table 17 presents the most common AEs (occurring in ≥ 30% of patients with FL) following treatment with axi-cel.

The most common any grade AEs of all FL patients in the SAS were pyrexia ([redacted] patients [[redacted]%]), hypotension ([redacted] patients [[redacted]%]) and headache ([redacted] patients [[redacted]%]); whereas the most common Grade 3 or above AEs were neutropenia ([redacted] patients

[%]) and anaemia (patients [%]).[35] A similar safety profile was observed in FL patients with at least three prior lines of therapy in the SAS (Table 17).

Table 17: Common adverse events occurring in ≥ 30% of FL patients in ZUMA-5

	FL patients with two or more lines of prior therapy SAS (n = 124)		FL patients with three or more lines of prior therapy SAS (n = 78)	
	Any grade	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Pyrexia				
Hypotension				
Headache				
Fatigue				
Nausea				
Anaemia				
Neutropenia				
Sinus tachycardia				
Tremor				

Key: AEs, adverse events; FL, follicular lymphoma; SAS, safety analysis set.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

SAEs that occurred in ≥ 2% of patients are summarised in Appendix N.

Among all FL patients in the SAS, the most common SAEs were pyrexia (patients [%]), pneumonia (patients [%]), encephalopathy (patients [%]) and confusional state (patients [%]).[35] The most common Grade 3 or higher SAEs were encephalopathy (patients [%]), pneumonia (patients [%]) and confusional state (patients [%]).

Among FL patients with at least three prior lines of therapy in the SAS, the most common SAEs were pyrexia (patients [%]), pneumonia (patients [%]), confusional state (patients [%]) and encephalopathy (patients [%]).[35] The most common Grade 3 or higher SAEs were encephalopathy (patients [%]), pneumonia (patients [%]) and confusional state (patients [%]).

B.2.10.3. Treatment-related adverse events

Table 18 presents the most common treatment-related AEs (occurring in ≥ 20% of patients with FL) following treatment with axi-cel.

The most common any grade treatment-related AEs of all FL patients in the SAS were pyrexia ([redacted] patients [redacted%]), hypotension ([redacted] patients [redacted%]) and headache ([redacted] patients [redacted%]); whereas the most common Grade 3 or above treatment-related AEs were hypoxia ([redacted] patients [redacted%]) and neutropenia ([redacted] patients [redacted%]).[35] A similar safety profile was observed in FL patients with at least three prior lines of therapy in the SAS (Table 18).

Table 18: Common treatment-related adverse events occurring in ≥ 20% of FL patients in ZUMA-5

	FL patients with two or more lines of prior therapy SAS (n = 124)		FL patients with three or more lines of prior therapy SAS (n = 78)	
	Any grade	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Tremor	[redacted]	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]

Key: AEs, adverse events; FL, follicular lymphoma; SAS, safety analysis set.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

B.2.10.4. Adverse events of special interest

B.2.10.4.1. Cytokine release syndrome

CRS is an AE induced by the activated T-cells upon engagement with the CD19 target, and therefore is generally considered to be related to treatment with CAR T-cell therapy. In ZUMA-5, the severity of CRS was graded according to a modification of the grading system proposed by Lee et al.[38]

Table 19 presents CRS rates and the most common symptoms of CRS (occurring in ≥ 4% of patients with FL) following treatment with axi-cel.

CRS was experienced by [redacted] ([redacted]%) FL patients, of which [redacted] ([redacted]%) had worst Grade 3 or higher CRS and [redacted] ([redacted]%) had worst Grade 5 CRS.[35] The most common symptoms of CRS Grade 3 or higher were hypoxia ([redacted] patients [redacted]%]), pyrexia ([redacted] patients [redacted]%]) and hypotension ([redacted] patients [redacted]%]). The most common serious CRS symptoms by any grade were pyrexia ([redacted] patients [redacted]%]), hypoxia ([redacted] patients [redacted]%]) and hypotension ([redacted] patients [redacted]%]).

The median time to onset of CRS in FL patients was [redacted] days (range: [redacted]) following axi-cel infusion.[35] At the 18-month analysis data cut-off date, CRS had resolved in [redacted] in ZUMA-5; [redacted]. For the [redacted] patients with FL whose CRS had resolved, the median duration of CRS was [redacted] days (range: [redacted]).

A similar CRS profile was observed in FL patients with at least three prior lines of therapy in the SAS (Table 19).

Table 19: Summary of CRS symptoms and events occurring in ≥ 4% of FL patients in ZUMA-5

N (%)	FL patients with two or more lines of prior therapy SAS (n = 124)			FL patients with three or more lines of prior therapy SAS (n = 78)		
	Any grade	Grade ≥ 3	Grade 5	Any grade	Grade ≥ 3	Grade 5
Any CRS event[a]	[redacted]					
Symptoms of CRS[b]						
Pyrexia	[redacted]					
Hypotension	[redacted]					
Chills	[redacted]					
Hypoxia	[redacted]					
Sinus tachycardia	[redacted]					
Headache	[redacted]					
Tachycardia	[redacted]					
Nausea	[redacted]					
Vomiting	[redacted]					
Fatigue	[redacted]					
Malaise	[redacted]					
Alanine aminotransferase increased	[redacted]					
Myalgia	[redacted]					

Key: CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; FL, follicular lymphoma; SAS, safety analysis set; TE, treatment-emergent.
Notes: [a] CRS events are graded according to a modification of the criteria of Lee et al. (2014). Percentages are calculated using the total number of patients in the analysis set as the denominator. [b] individual CRS symptoms are coded using MedDRA Version 23.0 and graded per CTCAE Version 4.03. Percentages are calculated using the number of patients with any TE CRS of any grade.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

B.2.10.4.2. Neurological events

Neurological events are a commonly reported AE of CAR T-cell therapy, manifesting through a diverse range of symptoms. It is strongly recommended that patients are systematically monitored and undergo neurological assessments both prior to and following CAR T-cell infusion. In ZUMA-5, neurological events were identified based on a modification of the search strategy by Topp et al.[39]

Table 20 presents neurological event rates and symptoms of neurological events following treatment with axi-cel.

In total, [redacted] patients ([redacted]%) had at least one neurological event of any grade, [redacted] ([redacted]%) had worst Grade 3 neurological events and [redacted]([redacted]%) patients had worst Grade 4 neurological events.[35] [redacted] had a Grade 5 neurological event. The most common Grade 3 or higher neurological events were encephalopathy ([redacted] patients [[redacted]%]), confusional state ([redacted] patients [[redacted]%]) and aphasia ([redacted] patients [[redacted]%]). The most common serious neurological events by any grade were encephalopathy ([redacted] patients [[redacted]%]), confusional state ([redacted] patients [[redacted]%]), somnolence, aphasia, agitation and immune effector cell-associated neurotoxicity syndrome ([redacted] patients each [[redacted]%]).

The median time to onset of neurological event in FL patients was [redacted] days (range: [redacted]); [redacted] had neurological events with an onset >80 days after the axi-cel infusion.[35] Of note, consulted clinical experts noted that the delayed/late-onset, low-grade neurological events observed in the handful of FL patients, was not likely to have any considerable impact.[1] At the 18-month analysis data cut-off date, neurological events had resolved in [redacted] patients ([redacted]%). Of the [redacted] with unresolved neurological events, [redacted]. For the 67 patients with FL whose neurological event had resolved, the median duration of the event was [redacted] days (range: [redacted]).

A similar neurological event profile was observed in FL patients with at least three prior lines of therapy in the SAS (Table 20).

Table 20: Summary of neurological events occurring in FL patients in ZUMA-5

N (%)	FL patients with two or more lines of prior therapy SAS (n = 124)			FL patients with three or more lines of prior therapy SAS (n = 78)		
	Any grade	Grade ≥ 3	Grade 5	Any grade	Grade ≥ 3	Grade 5
Any neurological event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of neurological event, n (%)						
Tremor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N (%)	FL patients with two or more lines of prior therapy SAS (n = 124)			FL patients with three or more lines of prior therapy SAS (n = 78)		
	Any grade	Grade ≥ 3	Grade 5	Any grade	Grade ≥ 3	Grade 5
Agitation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disturbance in attention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Delirium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hallucination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: FL, follicular lymphoma; SAS, safety analysis set.
Source: ZUMA-5 CSR 18-Month Addendum.[35]

Cytopenia

Table 21 presents the incidence of cytopenia following treatment with axi-cel. Cytopenias were consistent with the known toxicities of the conditioning regimen of cyclophosphamide and fludarabine. Grade ≥ 3 neutropenia, thrombocytopenia and anaemia occurred in [redacted]%, [redacted]% and [redacted]% of FL patients, respectively. A similar cytopenia profile was observed in FL patients with at least three prior lines of therapy in the SAS (Table 21). Prolonged (duration >30 days) Grade ≥ 3 neutropenia, thrombocytopenia and anaemia occurred in [redacted]%, [redacted]% and [redacted]% of FL patients, respectively. For FL patients whose events had resolved, the mean (standard deviation) and median (range) times to onset of cytopenias were [redacted] ([redacted]) and [redacted] ([redacted]) days after axi-cel infusion. The median duration of cytopenias were [redacted] (range: [redacted]) days. Similar findings were observed in FL patients with at least three prior lines of therapy in the SAS.

Table 21: Incidence of cytopenia in FL patients in ZUMA-5

N (%)	FL patients with two or more lines of prior therapy SAS (n = 124)		FL patients with three or more lines of prior therapy SAS (n = 78)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Patients with any cytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Patients with neutropenia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Patients with thrombocytopenia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Patients with anaemia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: FL, follicular lymphoma; SAS, safety analysis set; SMQ, standardised MedDRA queries.
Note: multiple incidences of the same adverse event in one patient are counted once at the worst grade for this patient. Events (neutropenia, thrombocytopenia or anaemia) with onset on or after axicabtagene ciloleucel infusion date are summarised. Thrombocytopenia is identified using the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for haematopoietic thrombocytopenia (narrow search). Neutropenia is identified using MedDRA search terms defined by Kite. Anaemia (including aplastic anaemia) is identified using the SMQ haematopoietic erythropenia (broad search).
Source: ZUMA-5 CSR 18-Month Addendum.[35]

B.2.10.4.3. Infections

Normal B-cells can be eliminated by CAR T-cell therapy alongside malignant B-cells, leading to B-cell aplasia that can put patients at increased risk of infection and hypogammaglobulinaemia (immunoglobulin <4g/L).

Infections were experienced by [redacted] ([redacted]%) of the FL patients, of which [redacted] ([redacted]%) had worst Grade 3 infections, and [redacted] ([redacted]%) had worst Grade 4 infection.[35] [redacted] The most common infections were pneumonia ([redacted] patients [[redacted]%]), upper respiratory tract infection ([redacted] patients, [[redacted]%]), and oral candidiasis, sinusitis and urinary tract infection ([redacted] patients each, [[redacted]%]). Worst Grade 3 events included pneumonia ([redacted] patients [[redacted]%]) and urinary tract infection

([redacted] patients, [redacted%]). The single worst Grade 4 event was sepsis ([redacted] patient, [redacted%]). [redacted]

B.2.10.5. Concomitant medication

Among FL patients, [redacted] patients ([redacted%]) were treated with corticosteroids (with or without tocilizumab), [redacted] ([redacted%]) were treated with tocilizumab (with or without corticosteroids) and [redacted] patients ([redacted%]) were treated with corticosteroids and tocilizumab.[35] [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-5 is like that observed with axi-cel in diffuse large B-cell lymphoma (DLBCL) and other CAR T-cell therapies, for which there are established risk management guidelines.

Since the approved access of axi-cel and other CAR T-cell therapies through the Cancer Drugs Fund (CDF) in NHS England, clinicians are increasingly comfortable with toxicity management for this CD19-directed CAR-T therapy class. Real-world data for patients with high-grade lymphoma treated with CD19 CAR T-cell therapy in NHS England showed lower rates of Grade ≥ 3 CRS and Grade ≥ 3 neurological events, with increased use of tocilizumab and steroid use, than reported across the pivotal clinical trials of tisagenlecleucel-T (JULIET) and axi-cel in this indication (ZUMA-1).[40, 41] Of note, in ZUMA-5 [redacted] had low-grade neurological events with an onset >80 days after the axi-cel infusion. However, UK clinical experts confirmed that they did not expect this to have much impact on patient management nor was it of particular concern in terms of any detriment this could have on the quality of life of patients specifically within the scope of this appraisal.[1]

Further real-world data from King's College Hospital and, as evidenced through wider national UK clinical practice, has showed that most patients treated with CD19 CAR T-cell therapy in practice do not appear to have an increased risk of early or late infections, despite CRS and administration of tocilizumab and steroids.[42] Immunoglobulin levels also remained above 4g/L in most patients, suggesting that

the humoral immune system can be restored despite initial B-cell aplasia, which was significant both pre and post-CAR T-cell therapy. Only three patients (6%) required regular immunoglobulin replacement post-CAR T-cell therapy; two for recurrent chest infections. This is also consistent with European guideline recommendations around the use of intravenous immunoglobulins following CAR T-cell therapy only for those patients with ongoing/recurrent infections, to which this represents a small minority of patients in clinical practice.

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 is to 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.[43]

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.

B.2.11. Ongoing studies

The ZUMA-5 study is ongoing; data from the follow-up Analysis 2 (that is, 24-month data cut) is expected to become available in December 2021.

B.2.12. Innovation

Axi-cel is a personalised, transformative medicine in which the patients' own T-cells are engineered ex vivo to target and kill cancer cells, upon return to the patient via a single infusion.

Axi-cel was the first of the breakthrough class of CAR T-cell therapies to receive European Medicines Agency and US Food and Drug Administration approval; it now

represents a breakthrough treatment for patients with r/r FL, providing a novel treatment option in later-line settings where there is currently no established standard of care. This was also recognised by NICE, which noted that there is no established clinical care in this setting when issuing the final scope for this appraisal following amendments made at draft scope (see Table 1).[1] Instead, current care options are limited to recycling earlier-line treatments to which patients may now have a reduced tolerance, as well as reduced effectiveness; or resorting to generic haemato-oncology treatments with little expectation of effect or experimental treatments with no proven benefit.[1]

Despite the more indolent nature of FL compared with previous CAR T-cell indications, it can still be an aggressive disease in a not insignificant proportion (approximately 10–20%[15, 16]) of patients and prognosis by the time of third relapse is typically poor, with patients unlikely to survive beyond approximately 3 years.[1, 21] Axi-cel is expected to offer a significant extension to this life expectancy and while survival benefit will be captured in the quality-adjusted life years (QALY), the truly innovative nature of axi-cel and the difference it could make to lives is difficult to truly reflect in such a calculation. FL is an emotionally unsettling disease due to its chronic and progressive nature and the hope that axi-cel could offer is likely to provide positive value independent of expected survival and health status.[44] There are also clear administration benefits of a single treatment infusion with CAR-T versus the recurrent cyclic nature of conventional treatments that are unlikely to be fully captured in the QALY. Indeed, the potential benefits of this “one-time” infusion versus patients returning regularly for recurrent therapy until progression, should not be underestimated for patients and their quality of life (especially so in the 4L+ FL setting), and this has been expressed by practising UK CAR-T physicians as potentially preferable both for patient care and long-term healthcare resourcing/capacity (Gilead data on file).

The innovation of axi-cel has been previously recognised by NHS England and NICE, and its introduction was considered a step change in the DLBCL pathway.[45] A similar step change could be achieved with the introduction of axi-cel to the FL pathway.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Principal findings from the clinical evidence

The vast majority ([redacted]% depending on analysis set) of FL patients who had received at least three prior therapies and were treated with axi-cel in ZUMA-5 responded to treatment, and the CR rate was [redacted]% (depending on analysis set). ORR and CR rates across analysis sets were significantly greater than pre-specified control rates. At the time of the 18-month analysis data cut-off, [redacted]% of responders and [redacted]% of complete responders with a minimum follow-up of 18 months, had an ongoing response (IAS data).

Median PFS and OS are yet to be reached in any analysis set. At the time of the 18-month analysis data cut-off, [redacted]% of FL patients who had received at least three prior therapies in the IAS were alive, and [redacted]% of patients were alive and progression-free; in the mITT, [redacted] were alive and [redacted] of patients were alive and progression-free. These proportions increased to [redacted]% and [redacted]%, respectively, in complete responders in the IAS; in the mITT the proportions increased to [redacted]% and [redacted]%, respectively

ORR and CR rates were markedly higher with axi-cel compared with current care in SCHOLAR-5, with odds ratios of [redacted] and [redacted], respectively. DOR, PFS and OS analyses showed a clinically meaningful and statistically significant reduction in the risk of relapse post response, as well as the risk of disease progression or death, and of death alone of [redacted]%, [redacted]% and [redacted]%, respectively ([redacted]) with axi-cel compared with current care.

B.2.13.2. Strengths and limitations of the evidence base

ZUMA-5 provides prospective clinical trial data demonstrating the clinical benefit of axi-cel treatment for FL patients who have had three prior therapies: a difficult-to-treat group of patients who often have an aggressive, chemotherapy-resistant disease course and for whom there is no current standard of care.

Although ZUMA-5 does not provide head-to-head clinical trial data, an attempt was made to address this evidence gap through the utilisation of data from SCHOLAR-5, an external control cohort study which used established, widely recognised methodology. Along with comparative effectiveness analyses, SCHOLAR-5 provides

further data supporting a lack of standard of care in r/r FL and a diminished treatment effect with each line of therapy in FL, as previously reported.[11-13, 28]

A limitation of both ZUMA-5 and SCHOLAR-5 is the lack of HRQL data collection. Quality-of-life outcomes as recorded by direct documentation in electronic medical records were to be defined as exploratory endpoints in SCHOLAR-5, but there were insufficient data for analysis as most sites did not collect any patient-reported outcome data. However, [redacted]

A further limitation of ZUMA-5 is the immaturity of data with median DOR, PFS or OS yet to be reached within the current 18-month follow-up data. While a positive signal for the longer-term benefits of axi-cel treatment for r/r FL, there is uncertainty around the magnitude of this benefit in clinical practice. In other lymphomas, axi-cel survival curves are starting to plateau, representing the possibility of healthy long-term survival for a proportion of patients.[46, 47] Although this is yet to be demonstrated in an indolent lymphoma setting, it is expected that this long-term survival benefit will translate to the r/r FL setting, based on the unique mechanism and transformative nature of CAR T-cell therapy. This expectation is supported by clinical experts, who noted that it is reasonable to assume a proportion of patients with r/r FL (25%) who are treated with axi-cel may have mortality hazards that behave more in line with the general population after a given time point (see Section B.3).[1] However, in recognition of the current uncertainty, we acknowledge that axi-cel is likely to be a CDF candidate. As a CDF drug, axi-cel would offer clinicians with a much-needed effective treatment option for patients who otherwise face a very uncertain outcome and poor quality of life. It would also allow time for further data collection needed to robustly assess the cost-effectiveness before a final decision on routine reimbursement is made. [redacted]

B.2.13.3. Applicability of clinical evidence to practice

The trial population of ZUMA-5 represents a patient group with an aggressive disease course, with a high proportion of the FL patients who had received at least

three prior lines of therapy having chemo resistant ([redacted]% refractory; [redacted]% double-refractory) and early relapse disease ([redacted]% were POD24) (IAS data).[35] Clinical validation confirms that the patients enrolled into ZUMA-5 are generally representative of patients in the UK with r/r FL on the 4L+ treatment pathway who would be considered for CAR-T treatment[1], despite the lack of UK sites involved in this trial.

The total trial population is broader than the target population for reimbursement, but predefined and post-hoc analyses provide a complete data set for adult patients with r/r FL on the 4L+ treatment pathway; this is the anticipated marketing authorisation indication. There are also several analysis sets explored in ZUMA-5; data are presented for patients treated with axi-cel who have at least 18 months of follow-up in the latest data cut-off (IAS), and for all patients treated with axi-cel (mITT) in preceding clinical sections. mITT data are used in the economic model base case as the more conservative and most representative analysis set for all patients potentially to be treated in clinical practice, as compared to the IAS set.

Comparator data taken from SCHOLAR-5 are believed to offer a high degree of external validity and generalisability, with the blended comparator representative of the lack of standard of care in current practice and treatments received across the primary analyses cohort generally reflected in the UK cohort. Although at face value the inclusion of PI3Ki treatments (12%; Figure 12) suggests a misalignment with clinical practice in England, where such treatment is not routinely reimbursed and is anticipated to come from existing (but no longer) compassionate access to idelalisib in England around the time of receiving its European licence.

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 and NHS England service provisions for CAR T-cell therapies are well established, with no or very minimal impact on further site qualification, patient referral or management expected with the introduction of axi-cel in FL at fourth-line setting. For the treatment of adult patients with r/r FL on the 4L+ treatment pathway, axi-cel is expected to fit into the current service provisions and there are no additional or different infrastructure or personnel needs.

B.2.13.4. Axi-cel as an end-of-life therapy

With increasing relapses and lines of treatment, patients with FL face the stark reality of a progressively shortened lifespan.[11-14] The emotional impact of this devastating reality must be heavily felt by patients who reach ≥ 4 lines of treatment, where there is no established standard of care and patient prognosis is extremely poor.[1, 28] When approved, axi-cel is expected to create a step change for the treatment of adult patients with r/r FL after receiving 4L+ care. Furthermore, at this late-stage of the treatment pathway, Gilead believes axi-cel would be adopted by clinicians as an end-of-life therapy in NHS England.

Based on SCHOLAR-5 data that provide the most up to date and comparable estimates for current care in the axi-cel target population, and clinical expert elicitation, the current life expectancy of these patients is short, at approximately 3 years.[21] While Gilead acknowledges that this is slightly longer than the NICE criteria of a short life expectancy, which is "normally less than 24 months"[48], Gilead believes that in real terms, patients with r/r FL receiving ≥ 4 lines of treatment have a strikingly short life expectancy, which is approximately 3 years. Furthermore, axi-cel is expected to extend life expectancy by at least the requisite 3 months, based on first quartile estimates and economic model extrapolations. Table 22 summarises the data for axi-cel with regards to the NICE criteria for life-extending treatment at the end of life.

Table 22: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Current care survival estimates from SCHOLAR-5: Median months = [redacted]	Section B.2.9.1.3 Page 55
	Clinical expert expectations with current care: 3 years of survival	Section B.1.3.2 Page 16
	Current care survival estimates from economic modelling: Median undiscounted survival = [redacted] months 24-month survival rate [redacted]	Section B.3.3 Page 101
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-5: Median months = [redacted] months	Section B.2.6.2.3 Page 39
	Comparative survival estimates for axi-cel versus current care: [redacted]	Section B.2.9.1.3 Page 55
	Axi-cel survival estimates from economic modelling: Median undiscounted survival = [redacted] months 24-month survival rate [redacted] Median undiscounted survival gain with axi-cel versus current 4L+ care = [redacted]	Section B.3.3 Page 98
Key: CI, confidence interval; NHS, National Health Service.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

A systematic review of the literature was conducted to identify economic evaluations/cost-effectiveness analyses of relevance to the decision problem. Searches were initially conducted in May 2020, with an update performed in May 2021 to align with NICE requirements. Full search strategies, inclusion and exclusion criteria and the Preferred Reporting Items for Systemic Reviews and Meta-Analyses flow diagram are provided in Appendix G. To identify relevant literature, the following electronic databases were searched (in addition to conference proceedings and health technology assessment databases):

- MEDLINE® In-Process
- Embase® and MEDLINE
- EconLit
- NHS Economic Evaluation Database

Details of the published cost-effectiveness studies identified in the systemic literature review (SLR) as relevant to this submission are provided in Appendix G.

As shown in Table 23, three prior NICE single technology appraisals in r/r FL published within the last 10 years were identified as relevant to this appraisal. These were TA604 (idelalisib), TA627 (lenalidomide with rituximab) and TA629 (obinutuzumab with bendamustine [TA472 CDF review]).[33, 49-51] Throughout this submission, insights were drawn from these appraisals in r/r FL.

In addition to the prior NICE appraisals in r/r FL, due to the unique mechanism of action and innovative nature of CAR T-cell therapy, insights were drawn from the mock appraisal of regenerative therapies and cell therapy products (such as CAR T-cell therapies) published by Hettle et al. (2017)[52], as well as the three completed NICE single technology appraisals for CAR T-cell therapies in advanced, previously treated lymphoma indications. These appraisals include TA559 (axi-cel in DLBCL and PMBCL), TA567 (tisagenlecleucel-T in DLBCL) and TA677 (KTE-X19 in r/r mantle cell lymphoma [MCL]).[45, 53, 54]

Table 23: Summary list of published NICE appraisals in r/r FL

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA472[49] (reported in TA627)[51]	2017	Markov cohort model (subsequently changed to a partitioned survival analysis model) Health states: • Progression free (on/off treatment) • Progressed disease • Death	62 years	• G-Benda + G – 4.23 • Bendamustine – 2.92	• G-Benda + G – NR (redacted) • Bendamustine – £23,889	• G-Benda + G vs Bendamustine – NR (redacted)
NICE TA604[33]	2019	• Markov cohort – state transition (Comparison A) • Partitioned survival model (Comparison B) • Health states: – Pre-progression (on/off treatment) – Post-progression – Palliative care – Death	62 years	Comparison A: • Chemotherapy – 2.80 • Idelalisib – 3.71 Comparison B: • Chemotherapy – 2.29 • Idelalisib – 5.33	Comparison A: • Chemotherapy – NR (redacted) • Idelalisib – NR (redacted) Comparison B: • Chemotherapy – NR (redacted) • Idelalisib – NR (redacted)	Company: • Comparison A – £26,076 • Comparison B – £19,872 ERG corrected: • Comparison A – £32,882 • Comparison B – £21,559
NICE TA627[51]	2020	Partitioned survival model Health states: • Progression free (on/off treatment) • Progressed disease	63-65 years	Lenalidomide with rituximab: • NR R-CVP • NR	Lenalidomide with rituximab: • NR R-CVP • NR	Versus R-CVP: • £20,156 Versus R-mono: • £17,233

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		• Death		R-mono: NR	R-mono: • NR	
NICE TA629[50] (TA472 CDF review)	2020	Unchanged from TA472	Unchanged from TA472	G-benda+G: • NR (redacted) Bendamustine: • 3.96	G-benda+G: • NR (redacted) Bendamustine: • £21,687	Company: • £17,408 Committee: • £15,587 to £17,322 ERG: • £15,045

Key: CDF, Cancer Drugs Fund; ERG, Evidence Review Group; G-benda+G, obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NR, not reported; PFS, progression-free survival; QALYs, quality-adjusted life years; r/r FL, relapsed/refractory follicular lymphoma; R-CVP, rituximab plus cyclophosphamide, vincristine prednisolone; R-mono, rituximab monotherapy; TA, technology appraisal; vs, versus.
Note: TA472 guidance has been updated and replaced by NICE TA629; however, relevant information on TA472 was reported in TA627.

B.3.2. Economic analysis

B.3.2.1. Patient population

The patient population considered in the analysis is [redacted], in line with the anticipated marketing authorisation for axi-cel. As discussed in Section B.1.1, the wording in the final NICE appraisal scope is 'adults with r/r non-Hodgkin lymphoma'. As such, this submission focusses on a subtype of iNHL, those with r/r FL.

As described in Section B.2.3, ZUMA-5 evaluated the safety and efficacy of axi-cel for the treatment of patients with r/r iNHL. Specifically, ZUMA-5 included patients with r/r FL (Grades 1–3a) or MZL (nodal or extranidal) who received two or more prior lines of therapy, including an anti-CD20 monoclonal antibody combined with an alkylating agent.

The economic analysis, which evaluates axi-cel in a 4L+ position, therefore considers a subgroup of the FL population eligible for the ZUMA-5 study; a group in which there is a high unmet need for safe and efficacious treatment.

Two clinical experts were interviewed on 10 September 2021 to ensure the economic modelling approach in this submission was consistent with clinical expectations in NHS England practice. As discussed in Section B.2.3.1, these consultants agreed that the baseline characteristics of patients enrolled in ZUMA-5 were generally representative of patients who would be considered for axi-cel within its anticipated marketing authorisation in clinical practice. However, it was noted that patients enrolled in ZUMA-5 could potentially be considered younger and fitter than the typical 4L+ FL patient in the UK.[1] Although this was the case, it was also noted that the proportion of 4L+ FL patients enrolled in ZUMA-5 who were classified as POD24 was higher than that expected in clinical practice[1], suggesting that the patients within the trial may be higher risk than expected in clinical practice (which is not uncommon in the clinical trial setting).

B.3.2.2. Model structure

A de novo cost-effectiveness model was developed in Microsoft Excel®. The proportion of patients in each health state at a given time point was determined using a partitioned survival analysis modelling approach.

Partitioned survival models in oncology are typically comprised of three health states (pre-progression, progressed disease and death), with the proportion of patients in each health state over time derived directly from the independently modelled OS and PFS projections. This structure reflects the natural history of disease (progressive) and separates the pre- and post-progression states, which in turn helps to capture potential differences in costs and HRQL.

As shown in Table 23, all prior NICE appraisals in r/r FL published within the last 10 years used a progression-based three-state partitioned survival approach. In TA472 (as reported in TA627), the Evidence Review Group considered the manufacturers state transition model unreliable and consequently a partitioned survival analysis was submitted.[51] In TA604, multiple comparisons were submitted with alternative structures; however, the Committee preferred the comparison using a partitioned survival analysis approach.[33] In TA627, a partitioned survival analysis approach was selected.[51] In these appraisals, the alive health states were further divided into on- and off-treatment periods; however, as axi-cel is administered as a one-time infusion in the first model cycle, health states were not explicitly divided by treatment status in this analysis.

Furthermore, the study published by Hettle et al (2017) and the completed single technology appraisals for CAR T-cell therapies in advanced, previously treated lymphoma indications, used a progression-based three-state partitioned survival model.[45, 52-54] Notably, in TA567, an initial decision tree was used to account for patients who received leukapheresis but did not go on to have CAR T-cell therapy.[53] In this analysis, consistent with TA559 and TA677, the costs for patients who underwent leukapheresis but did not go on to receive axi-cel infusion in ZUMA-5 were accounted for using cost multipliers (described further in Section B.3.5.1.1).[45, 54]

Figure 16 presents the model structure diagram. All patients begin in the pre-progressed health state. In each model cycle, patients may remain progression-free,

their disease may progress, or they may enter the death state. Once a patient has experienced disease progression, they may remain in the current state or they may enter the death state. Death is an absorbing health state. Figure 17 graphically represents how OS and PFS extrapolations are used to determine the proportion of patients in each health state at time 'T' in a partitioned survival structure.

In TA559 and TA567, patients with DLBCL who remained pre-progression for 2 years were captured as 'long-term survivors'.[45, 53] It was assumed that long-term survivors, who had a heightened risk of death compared with the age-equivalent general population, did not incur further resource use and experienced improved HRQL. Similarly, in TA677, consistent long-term survivorship assumptions were followed for patients with MCL who remained alive and free of progression at 5 years following CAR T-cell therapy.[54] Here, a similar approach to capturing long-term survivors is undertaken, using the later time point of 5 years in line with TA677.

Figure 16: Model structure diagram

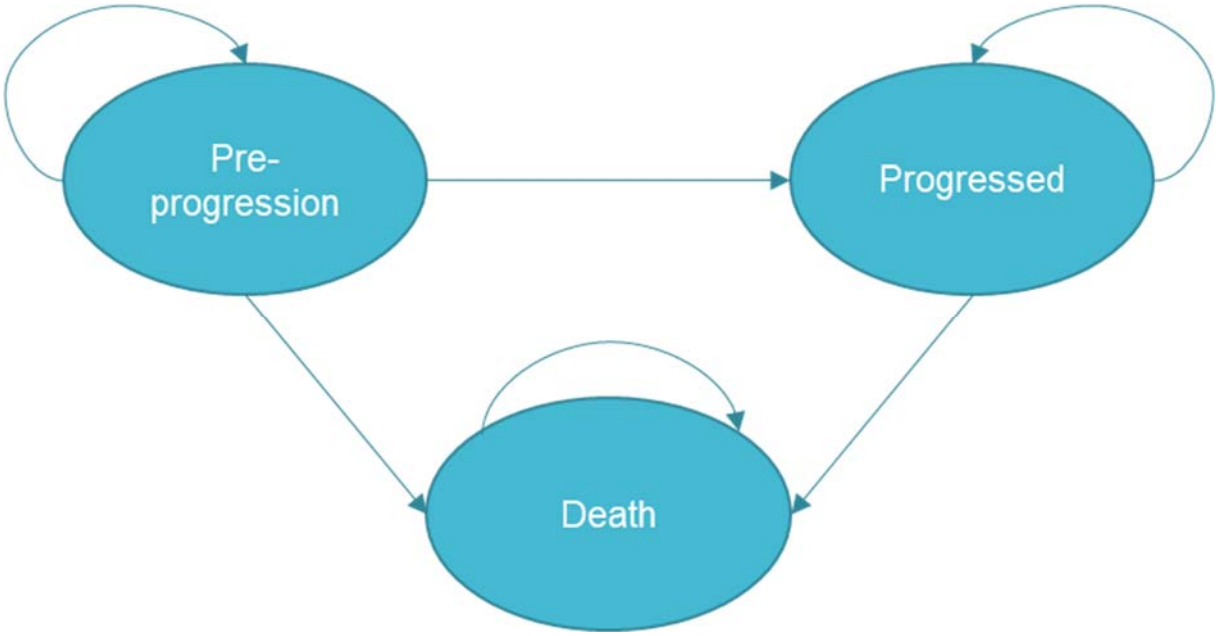
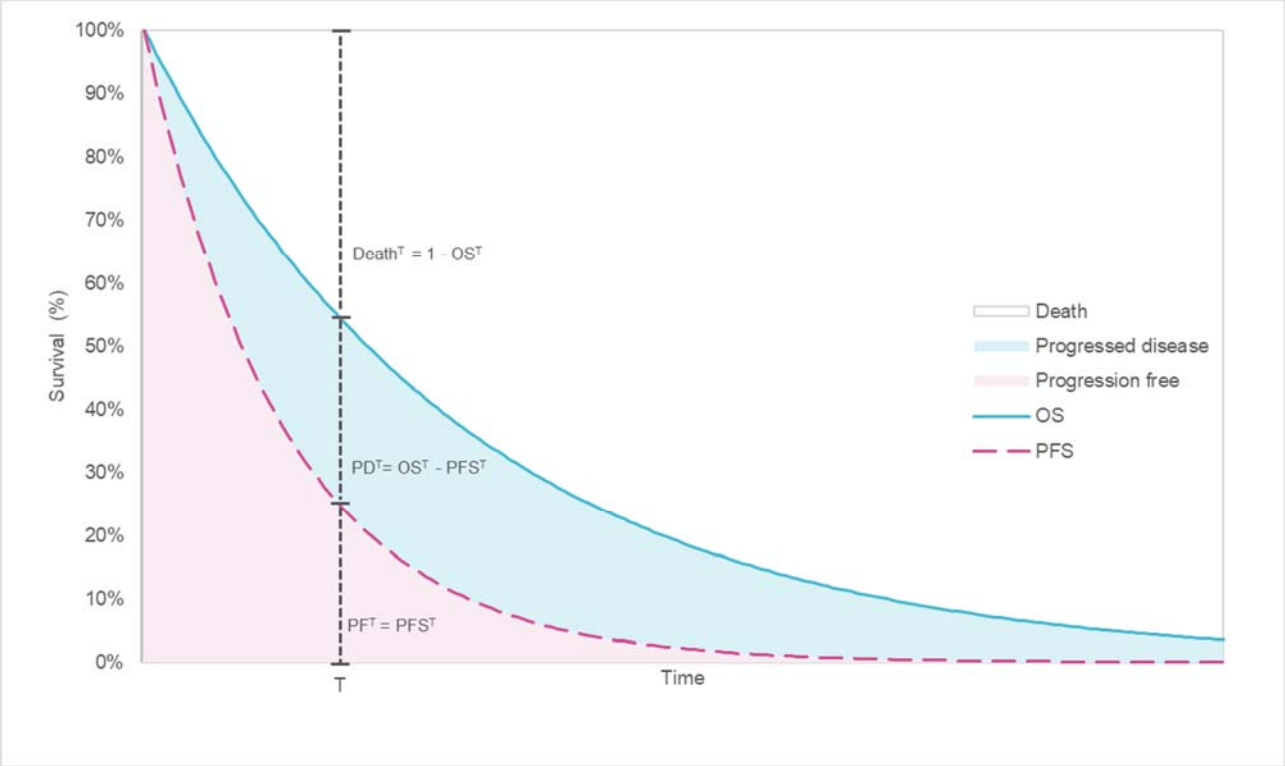


Figure 17: Partitioned survival analysis; health state occupancy example



Key: OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; T, chosen time.
Note: superscript ^{T} denotes 'at time T'.

B.3.2.2.1. Model settings

In line with the NICE reference case, the analysis perspective is that of the NHS and the Personal Social Services (PSS) in England for costs and direct health effects for individual patients for outcomes.[48]

As stated in the NICE reference case[48], the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared; a lifetime horizon is therefore used in the base case. In the analysis, a time horizon of 40 years constitutes a lifetime, based on the starting age of 4L+ patients in ZUMA-5 ([redacted] years) and the modelled OS extrapolations (discussed in Section B.3.3.3).

The model incorporates a cycle length of 28 days, deemed sufficient to capture relevant changes in health. A half-cycle correction is applied to costs and outcomes, except for costs that are known or assumed to occur at the start of the model or at the start of each cycle. Costs applied at the start of the model or cycle include axi-cel

treatment-related costs, comparator costs (acquisition and administration) and AE costs (except for ongoing intravenous immunoglobulin [IVIG] therapy).

Costs and health outcomes are discounted each cycle at an annual rate of 3.5%, as per the NICE reference case.[48] Given the unique mechanism of CAR T-cell therapies and promising implications of sustained disease clearance and potential long-term survivorship, non-reference case discount rates of 1.5% are explored in the scenario analysis.

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention

The intervention considered in the analysis is axi-cel. Axi-cel is incorporated into the economic evaluation according to its anticipated marketing authorisation and in line with the decision problem described in Section B.1.1.

As described in Section B.1.2, axi-cel is an autologous anti-CD19 CAR T-cell therapy that recognises and eliminates all CD19 expressing target cells, including B-cell malignancies and normal B-cells. Axi-cel was the first in a breakthrough class of CAR T-cell therapies. The therapy consists of genetically engineered T-cells which recognise CD19-expressing cancer cells, leading to an immune response which results in the direct killing of the target cancer calls.

Axi-cel was initially indicated by the European Medicines Agency for the treatment of adult patients with r/r DLBCL and PMBCL after two or more lines of systemic therapy.[43] In England, axi-cel is recommended for use via the CDF as an option for r/r DLBCL or PMBCL.[45] As discussed in Table 2, application for a marketing authorisation extension of axi-cel to [redacted] has been submitted.

Axi-cel is a one-time immunotherapy of 2 x 10^6 CAR T-cells/kg of body weight used autologously and administered intravenously. Patients must be treated with a lymphodepleting conditioning chemotherapy consisting of cyclophosphamide 500 mg/m^2 intravenously and 30 mg/m^2 fludarabine intravenously for 3 days before infusion of axi-cel is administered.

B.3.2.3.2. Comparator

As discussed in Section B.1.3, despite the clinical pathway for FL being well established at early treatment lines, there is no established standard of care for adult patients with 4L+ r/r FL. At this stage in the pathway, treatment decisions are made on a case-by-case basis considering factors such as patient fitness, treatment goals, response and durability of response to prior therapy.

Given that there is no true standard of care for patients following treatment with lenalidomide plus rituximab (recommended by NICE in TA627) or obinutuzumab with bendamustine (recommended by NICE in TA629)[50, 51], the comparator considered in the economic model is 'current 4L+ care', which consists of a basket of treatments.

As described in Table 1, rituximab monotherapy and best supportive care were included in the final scope issued by NICE. However, rituximab monotherapy is only recommended as an option for the treatment of r/r FL when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy). As with best supportive care, if rituximab monotherapy was being considered for use in patients with 4L+ r/r FL, it would be reserved for patients not fit enough to receive intensive active treatment, thereby constituting a cohort of patients widely considered not suitable or appropriate for consideration of CAR T-cell therapy. As such, rituximab monotherapy and best supportive care are not considered within the blend of treatments comprising current 4L+ care.

Of the other comparators listed in the final scope, it is expected that obinutuzumab with bendamustine (used for patients who are rituximab-relapsed) and lenalidomide with rituximab would typically be used earlier in the treatment pathway than the 4L+ setting; a sentiment endorsed by the UK Clinical Experts interviewed in September 2021.[1] However, these treatments have been considered as part of the blend which comprises current 4L+ care given the lack of alternative or established treatment approaches in 4L+ care and, thereby, the necessity to potentially resort to their use in these later lines of therapy.

The source of comparative efficacy data for the current 4L+ care arm of the model is described in Section B.3.3.1.2. The basket cost of treatment in the current 4L+ care arm of the model is calculated as a weighted average; derived from the distribution

of treatment regimens that comprise the blend (described in Section B.3.5.1.2). To assess the impact on comparator costs and consequently cost-effectiveness results, the treatments comprising the blend and corresponding distributions are varied in scenario analysis.

B.3.3. Clinical parameters and variables

The clinical parameters used to inform the axi-cel and current 4L+ care arms in the economic model, and their respective sources, are summarised in Table 24 and discussed in more detail throughout this section and, in the case of AE rates, Section B.3.4.3.

As described in Section B.2.3, the primary endpoint of the ZUMA-5 trial was the ORR (defined as the incidence of patients achieving CR or PR as determined by central assessment). In line with prior appraisals of CAR T-cell therapies in advanced lymphoma indications, and in line with the model structure (Section B.3.2.2), ORR is not directly reflected in the cost-effectiveness analysis, but is indirectly captured (with respect to long-term survivorship for patients who respond well to CAR T-cell therapy).

Table 24: Data sources of clinical parameters used in the model

Component	Application with the model	Source(s) for axi-cel	Source(s) for current 4L+ care
PFS (Section B.3.3.2)	Used to fit parametric survival curves to capture lifetime PFS estimates	• ZUMA-5, mITT population (n = [redacted]) • UK lifetables[55] • Literature (Maurer et al. [2014])[56] • Clinical opinion[1]	• SCHOLAR-5, effectiveness analysis set (n = 82) matched to ZUMA-5 mITT analysis set through propensity score weighting • UK lifetables[55]
OS (Section B.3.3.3)	Used to fit parametric survival curves to capture lifetime OS estimates		
AE incidence (Section B.3.4.3)	Informed the proportion of patients who incur the cost and disutility associated with each AE	• ZUMA-5, mITT population (n = 78)	• Clinical trial data (reported in previous NICE TAs)

Key: 4L+, fourth-line plus; AE, adverse event; mITT, modified intent-to-treat; N/A, not applicable; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; TA, technology appraisal.

B.3.3.1. Efficacy overview

B.3.3.1.1. Axi-cel

Axi-cel PFS and OS estimates are based on patient-level data collected in the Phase 2 ZUMA-5 study. Specifically, all survival analyses for axi-cel were conducted using the mITT population in the cohort of 4L+ FL patients of ZUMA-5 (N = [redacted]; all subjects with 4L+ FL treated with axi-cel at a target dose of 2 x 10^6 CAR T-cells/kg).

Latest available (September 2020 database lock) axi-cel PFS and OS Kaplan–Meier data are presented in Section B.2.9.1 (Figure 14and Figure 15, respectively). Despite a considerable follow-up period, data for axi-cel are still relatively immature, with median survival not yet having been reached for any endpoint. An additional ZUMA-5 data cut became available at the time of submission of this dossier, with an additional 6 months of follow-up (i.e. 24 months). It was not possible to include this data prior to submission; however, it is acknowledged that this data may provide a more informative data source for clinical inputs.

As discussed in Section B.2.13, although immaturity of the ZUMA-5 endpoints represents a positive signal for the longer-term benefits of axi-cel treatment for patients with r/r FL, there is uncertainty around the magnitude of this benefit in clinical practice. In other lymphomas, axi-cel survival curves are starting to plateau, representing the possibility of healthy long-term survival for a proportion of patients.[46, 47] Although this is yet to be shown in an indolent lymphoma setting, it is expected that this long-term survival benefit will translate to the r/r FL setting, based on the unique mechanism of action and transformative nature of CAR T-cell therapy.

This expectation of healthy long-term survival for a proportion of patients treated with CAR T-cell therapy was confirmed in interviews with clinical experts from the UK, whereby it was noted that it is reasonable to assume that a proportion of patients with r/r FL who are treated with axi-cel may have mortality hazards that behave more in line with the general population after a given time point.[1] However, as described above, the follow-up duration of the currently available clinical data is not sufficient to fully substantiate this effect in this more indolent lymphoma. As described in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 21, when extrapolating clinical trial data to estimate lifetime outcomes, standard parametric

models are limited with respect to the type of hazards they can represent; more flexible models may be required where mortality hazards are expected to have complex shapes in the longer term.[57]

As described in NICE TSD 21, flexible parametric models using restricted cubic splines can enable hazard and survival functions with complex shapes to be accurately modelled. However, these models will generally provide extremely good fits within the range of the observed data, given a sufficient number of knots have been used, but this does not mean that their extrapolations will be reliable.[57]

In the prior NICE appraisals of CAR T-cell therapies in advanced lymphoma indications, mixture cure models were used to better reflect long-term survival expectations for patients following CAR-T infusion.[45, 53, 54] However, as reported in NICE TA567, robust estimation of mixture cure models require data from studies with sufficient follow-up times that exceed the anticipated time point of cure.

In this case, flexible parametric models or formal mixture cure modelling were not considered plausible due to the immaturity of the ZUMA-5 data at the latest available database lock (September 2020) at the time of submission. Nevertheless, standard parametric models alone cannot capture the expected benefit of axi-cel in the longer term.

To reflect the clinical opinion on long-term outcomes, we take an approach whereby OS and PFS are informed using standard parametric survival extrapolations until a specified time point. After which, for a proportion of patients who are considered long-term survivors, mortality is informed by the age-matched general population adjusted with an SMR. Those who are not captured as long-term survivors continue to follow the hazard of the parametric model. Notably this approach was requested by the Evidence Review Group in prior NICE appraisal for a CAR T-cell therapy in MCL.[54] This approach is also similar to that undertaken in prior NICE appraisals of treatments for acute lymphoblastic leukaemia, whereby it was assumed that patients who survived 4 to 5 years were cured (as reported in TA554).

In line with clinical opinion elicited during the interview to validate the economic modelling approach in this appraisal, it is assumed that 25% of patients treated with axi-cel are captured as long-term survivors in the base case survival estimates. This

value, which is used to estimate respective ‘cure fractions’ for the PFS and OS based on the proportion of patients progression-free/alive at the selected time point (discussed below), is varied in sensitivity and scenario analysis.

As discussed in Section B.3.2.2, in line with the prior NICE appraisal for a CAR T-cell therapy in MCL and in line with clinical validation interviews, a time point of 5 years was selected to explicitly capture long-term survivors. Alternative long-term survivorship timepoints of 2, 7 and 10 years are tested in scenario analysis. The 2-year timepoint is explored in line with TA559 and TA567 (patients with DLBCL), while 7 and 10 years are explored due to the more indolent disease evaluated in this appraisal.

It is not assumed that the mortality rate of long-term survivors would return to that of the age-matched general population, a heightened risk of death for long-term survivors is therefore captured using an SMR. In line with the prior NICE appraisal in DLBCL, in the absence of FL-specific data identified in the literature, an SMR of 1.09 was adopted. Alternative SMRs for long-term survivors of 1 (equivalent to general population) and 1.20 (based on feedback from clinical experts in the UK) are tested in scenario analysis.

It is acknowledged that this approach is yet unproven and suffers from limitations inherent to the use of data with a non-optimal follow-up duration. Further study of CAR T-cell therapy in FL over time will provide more accurate and robust estimates; highlighting that axi-cel is likely to be a candidate for the CDF, whereby additional real-world and ZUMA-5 data collection would reduce some uncertainty in the long-term survival extrapolations. For the purpose of this submission, to reflect this uncertainty, scenario analyses are conducted around the proportion of patients who were captured as long-term survivors, the time point selected and the SMR compared with general population.

B.3.3.1.2. Current 4L+ care

As discussed in Section B.3.2.3.2, as there is no established clinical management in 4L+ r/r FL, the comparator arm in the cost-effectiveness model (current 4L+ care) comprises a blend of multiple therapies. Furthermore, as ZUMA-5 is a single-arm

trial, comparative efficacy data for current 4L+ care were sourced from an alternative data source.

As discussed in Section B.2.9, three published studies were identified as potentially relevant, however all were considered highly limited in their suitability as a source of comparative efficacy data and therefore no matching comparison for treatment-effect modification was conducted for these studies.

B.3.3.1.2.1. SCHOLAR-5

As described in Section B.2.9.1, SCHOLAR-5 is a retrospective, observational, multicentre and patient-level database with two primary objectives: characterising the natural history of iNHL and building an external comparator group to provide comparative data with the ZUMA-5 trial. Details of the SCHOLAR-5 study (including the methods, natural history, treatment patterns and comparative analysis) are described in Section B.2.9.1.

For the comparative analysis, [redacted] patients from SCHOLAR-5 with 4L+ FL were available for analysis against the ZUMA-5 mITT population. Importantly for this appraisal, SCHOLAR-5 patient-level data were readily available to be analysed as a comparative data source to ZUMA-5, enabling the estimation of a relative treatment effect.

The SCHOLAR-5 cohort was used as an external control for the ZUMA-5 clinical trial, after alignment to the ZUMA-5 population using propensity score methods (SMR weighting) to adjust for known confounders. This enabled comparisons to be drawn by balancing patient characteristics between both data sources. Full details of the propensity scoring methods and outcomes are provided in the SCHOLAR-5 technical report provided in the reference pack.[21] Clinical validation was sought regarding the patient characteristics that impact prognosis and thus should be balanced between the two data sources (Table 14).

B.3.3.1.3. Comparative efficacy

Summary Kaplan–Meier plots are presented for PFS and OS for axi-cel (ZUMA-5) and current 4L+ care (propensity score weighted SCHOLAR-5) in Section B.2.9.1.3.

Data from SCHOLAR-5 are relatively mature in comparison to ZUMA-5, due both to a longer available follow-up period and inferior outcomes leading to higher numbers of events taking place earlier in the follow-up. Notably, the PFS data from SCHOLAR-5 reach the x-axis (Figure 14). Note that as the DELTA study did not collect progression data for subsequent lines of therapy, which was used in the SCHOLAR-5 analysis, the number at risk post-weighting for the PFS endpoint is lower (n = [redacted]) than that for OS (n = [redacted]).

B.3.3.1.4. Extrapolation

As the latest PFS and OS Kaplan–Meier data are incomplete (that is, there were patients still alive or progression-free and alive at database lock), extrapolation was required to estimate lifetime PFS and OS.

A range of standard parametric survival models were fitted to both the axi-cel and current 4L+ care PFS and OS data, in line with NICE DSU TSD 14.[58] In addition to the standard models specified in TSD 14, the gamma model was also included (which is equivalent to the generalised gamma model with a shape parameter of 1).[58] The parametric models explored were:

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

As per NICE DSU TSD 14, it is generally considered unnecessary to rely on the proportional hazards assumption when patient-level data are available.[58] Furthermore, given the unique mechanism of action for axi-cel compared with current 4L+ care, it is considered unreasonable to assume proportional hazards between treatments. Curves were therefore fitted separately to each treatment arm.

As per NICE TSD 14[58], goodness-of-fit and plausibility of extrapolation were assessed based on:

- Visual inspection of fitted curves
- Comparisons of Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics
- The plausibility of long-term extrapolation based on clinical expert opinion and expected survival from other data sources

As discussed in Section B.3.3.1, due to the immaturity of the ZUMA-5 data at the latest available data cut, formal mixture cure models were not considered a reasonable approach and therefore not included in the economic analysis. However, standard parametric curves were combined with SMR-adjusted population mortality using a 5-year landmark approach to capture a proportion of long-term survivors.

The following sections detail the approaches to modelling PFS and OS for the axi-cel and current 4L+ care treatment arms.

B.3.3.2. Progression-free survival

A summary of the base case approach to modelling PFS is provided in Table 25.

Table 25: Summary of base case approach used to model PFS, by treatment arm

	Axi-cel	**Current 4L+ care**
Clinical data source(s) to inform the modelling of PFS	• ZUMA-5 mITT PFS data • UK life table data to inform age and gender-matched background mortality • SMR to adjust age and gender-matched background mortality	• SCHOLAR-5 PFS data • UK life table data to inform age and gender-matched background mortality
Extrapolation approach	• Standard parametric extrapolation • General population mortality adjusted with an SMR for a proportion of long-term survivors at 5 years	• Standard parametric extrapolation
Key: mITT, modified intent-to-treat; PFS, progression-free survival; SMR, standardised mortality ratio.		

B.3.3.2.1. Axi-cel

Fitted models are graphically represented alongside ZUMA-5 PFS Kaplan–Meier data in Figure 18. Corresponding smoothed hazard plots are presented in Appendix O. AIC and BIC statistics and landmark estimates are presented in Table 26.

Figure 18: Axi-cel progression-free survival: standard parametric curves

Key: KM, Kaplan–Meier.
Note: standard parametric curves presented have not been corrected for background mortality.

Table 26: Axi-cel, PFS: standard parametric curve AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Mean PFS	Median PFS	Proportion pre-progression at each landmark value			
					6 months	1 year	2 years	5 years

[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival
Notes: mean and median values are provided in units of months. Best statistically fitting model in bold. Selected model in italics. Projected PFS values here are not accounting for background mortality correction.

Based on visual inspection, all curves provide a similar fit to the Kaplan–Meier data. Similarly, the goodness-of-fit statistics are within 5 AIC across all models, and 5 BIC across all models apart from the generalised gamma, suggesting a very similar statistical fit to the observed portion of the data between parametric models.

The exponential, gamma and Weibull curves, which have the most conservative long-term extrapolations, predict similar outcomes, with [redacted] of patients alive and free of progression at 5 years following treatment with axi-cel. In clinical validation interviews, it was suggested that given the uncertainty of the long-term effects of axi-cel and immaturity of the data, the Weibull curve should form the model base case.

As previously discussed, in the interview with clinical experts it was noted that it is reasonable to assume that a proportion of patients with r/r FL who are treated with CAR T-cell therapy (25%) may have mortality hazards that behave more in line with the general population after 5 years.

The selected parametric curve (Weibull) was used to model PFS in the axi-cel arm for all patients up to Year 5. Beyond this point, the SMR-adjusted general population mortality hazard was applied to 25% of patients treated with axi-cel (which equates to approximately [redacted] of the [redacted] of patients in PFS at Year 5). The remaining patients were assumed to follow the mortality hazard of the selected Weibull curve.

The resulting selected axi-cel PFS curve is presented in Figure 19.

Figure 19: Axi-cel PFS: selected curve (25% long-term survivorship)

Key: KM, Kaplan–Meier; PFS, progression-free survival.

In scenario analysis, the impact of capturing all patients who are alive and free of progression at 5 years as long-term survivors is tested (that is, all of the estimated [redacted] of patients in PFS are assumed to be long-term survivors and follow the SMR-adjusted general population mortality hazard).

B.3.3.2.2. Current 4L+ care

Fitted models are graphically represented alongside SCHOLAR-5 PFS Kaplan–Meier data in Figure 20. Corresponding smoothed hazard plots provided in Appendix O. AIC and BIC statistics and landmark estimates are presented in Table 27.

Figure 20: Current 4L+ care PFS: standard parametric curves

Key: 4L+, fourth line or later; KM, Kaplan–Meier; PFS, progression-free survival.
Note: standard parametric curves presented have not been corrected for background mortality.

Table 27: Current 4L+ care: PFS: standard parametric curve AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Mean PFS	Median PFS	Proportion pre-progression at each landmark value			
					6 months	1 year	2 years	5 years

Key: 4L+, fourth line or later; AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival
Notes: Mean and median values are provided in units of months. Best statistically fitting model in bold. Selected model in italics. Projected PFS values here are not accounting for background mortality correction.

Based on the goodness-of-fit statistics and visual interpretation of trends, the exponential model provides the best fit to the Kaplan–Meier data. Goodness-of-fit statistics are within 5 points across models, except for BIC for the generalised gamma and log-logistic models. Given the maturity of the SCHOLAR-5 PFS data, the choice of survival extrapolation does not have a large impact on the long-term PFS estimate, with median PFS ranging from [redacted], and [redacted] of patients remaining alive and free of progression at 5 years across all parametric models.

In the validation interview with clinical experts, it was noted that all current 4L+ care standard parametric PFS curves were clinically plausible.[1] The exponential curve was therefore selected as the model base case based on the goodness-of-fit.

Figure 21 presents the selected axi-cel and current 4L+ PFS curves used in the model base case.

Figure 21: Axi-cel versus current 4L+ care, PFS: selected

Key: 4L+, fourth line or later; KM, Kaplan–Meier; PFS, progression-free survival.

B.3.3.3. Overall survival

A summary of the base case approach to modelling OS is provided in Table 28.

Table 28: Summary of base case approach used to model OS, by treatment arm

	Axi-cel	Current 4L+ care
Clinical data source(s) to inform the modelling of OS	• ZUMA-5 mITT OS data • UK life table data to inform age and gender-matched background mortality • SMR to adjust age and gender-matched background mortality	• SCHOLAR-5 OS data • UK life table data to inform age and gender-matched background mortality
Extrapolation approach	• Standard parametric extrapolation • General population mortality adjusted with an SMR for a proportion of long-term survivors at 5 years	• Standard parametric extrapolation
Key: mITT, modified intent-to-treat; OS, overall survival; SMR, standardised mortality ratio.		

B.3.3.3.1. Axi-cel

Fitted models are graphically represented alongside ZUMA-5 OS Kaplan–Meier data in Figure 22. Corresponding smoothed hazard plots are presented in Appendix O. AIC and BIC statistics and landmark estimates are presented in Table 29.

Figure 22: Axi-cel overall survival: standard parametric curves

Key: KM, Kaplan–Meier.
Note: standard parametric curves presented have not yet been corrected for background mortality.

Table 29: Axi-cel, OS: standard parametric curve AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Mean OS	Median OS	Proportion pre-progression at each landmark value			
					6 months	1 year	2 years	5 years

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival
Notes: Mean and median values are provided in units of months. Best statistically fitting model in bold. Selected model in italics. Projected OS values here are not accounting for background mortality correction.

Based on the goodness-of-fit statistics, the exponential model provides the best fit to the Kaplan–Meier data, although it should be noted the observed OS data at database lock are immature. Furthermore, the AIC and BIC statistics are within 5 points across all models, except for BIC for the generalised gamma and log-normal models. As with PFS, the exponential, gamma and Weibull OS models produce similar longer-term extrapolations, with [redacted] of patients alive at 5-years following treatment with axi-cel.

It was suggested in the validation interview with clinical experts that the generalised gamma and Gompertz curves may be ruled out based on the clinical plausibility of the long-term extrapolations. Similarly, the log-normal model can be excluded based on the plausibility of the long-term extrapolation, with [redacted] of patients modelled to be alive at 40 years prior to any background mortality adjustment.

Consistent with PFS, the Weibull curve was selected in the base case. The selected parametric curve was used to model OS in the axi-cel arm for all patients up to Year 5. Beyond this point, the SMR-adjusted general population mortality hazard was applied to 25% of patients treated with axi-cel (which equates to approximately [redacted] of the [redacted] of patients estimated to be alive at Year 5). The remaining patients were assumed to follow the mortality hazard of the selected Weibull curve.

Figure 23: Axi-cel overall survival: selected curve (25% long-term survivorship)

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

As previously discussed, the impact of assuming all patients who are alive and free of progression at 5-years are long-term survivors is tested in scenario analysis (that is, approximately [redacted] of patients alive at 5 years are assumed to be long-term survivors).

B.3.3.3.2. Current 4L+ care

Fitted models are graphically represented alongside SCHOLAR-5 OS Kaplan–Meier data in Figure 24. Corresponding smoothed hazard plots provided in Appendix O. AIC and BIC statistics and landmark estimates are presented in Table 30.

Figure 24: Current 4L+ care overall survival: standard parametric curves

Key: KM, Kaplan–Meier.
Note: standard parametric curves presented have not been corrected for background mortality.

Table 30: Current 4L+ care: OS: standard parametric curve AIC and BIC statistics and landmark survival estimates

Model	AIC	BIC	Mean OS	Median OS	Proportion pre-progression at each landmark value			
					6 months	1 year	2 years	5 years

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.
Notes: mean and median values are provided in units of months. Best statistically fitting model in bold. Selected model in italics. Projected PFS values here are not accounting for background mortality correction.

Based on the goodness-of-fit statistics and visual interpretation of trends, the generalised gamma model provides the best fit to the Kaplan–Meier data; however both the generalised gamma and Gompertz models may be excluded from contention based on the plausibility of the long-term extrapolation. The generalised gamma and Gompertz models predict [redacted] of current 4L+ care patients are alive at 40 years (aged [redacted]), respectively (prior to any background mortality adjustment).

During the clinical validation interview, the gamma curve was selected as the preferred OS extrapolation based on the plausibility of the extrapolation, with a median OS of [redacted] years and [redacted] of patients alive at 5 years.[1] The gamma curve is therefore used to inform the base case OS extrapolation in the current 4L+ care arm.

Figure 25 presents the selected axi-cel and current 4L+ curves used in the model base case.

Figure 25: Axi-cel versus current 4L+ care, OS: selected

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

B.3.3.4. Summary of selected survival extrapolations

Figure 26 presents a summary of the selected survival extrapolations for PFS and OS, capturing 25% of patients treated with axi-cel as long-term survivors at 5 years.

Figure 26: Axi-cel versus current 4L+ care, OS and PFS: selected

Key: KM, Kaplan–Meier; PFS, progression-free survival; OS, overall survival.

B.3.4. Measurement and valuation of health effects

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

The NICE reference case stipulates that health effects should be expressed in QALYs.[48] To generate QALYs, life years are weighted by a utility value, representative of HRQL. Patient utility is treated as an index, where an index value of 0 represents death and a value of 1 represents full health. As no HRQL data were collected in ZUMA-5 or SCHOLAR-5, utility values identified in the literature were used to inform the analysis (discussed in Section B.3.4.3).

B.3.4.2. Mapping

As there were no HRQL data collected in ZUMA-5, de novo mapping analyses were not conducted for this submission.

B.3.4.3. Health-related quality of life studies

In line with the search for economic evaluations and cost and resource use studies, a systematic review of HRQL evidence in patients with r/r FL was conducted. Original searches were conducted in May 2020, with an updated search run in May 2021. The study identification process, search strategies and a description of the included utility studies is presented in Appendix H. In total, 25 studies identified in the HRQL and utility SLR were included for data extraction. No additional studies of relevance were identified in the updated searches. Of the 25 included studies, 16 reported HRQL elicited via a generic patient-reported outcome instrument; of these 16 studies, 15 included a version of the EQ-5D. The NICE reference case specifies that the EQ-5D is the preferred measure of HRQL in adults.

The SLR identified six studies that reported health state utility scores in a r/r FL population, many of which refer to the same set and source of utility values (Wild et al. [2006]/Pettengell et al. [2007]).[22, 59] As was the case in TA627[51], Wild et al. was not included within the SLR itself as only the abstract is available and utility values are not directly reported in the abstract; however, information on this study has been gathered from many economic evaluations for FL patients.

It is understood that Wild et al. and Pettengell et al. report components of the same study, in which 222 patients (aged 18 years and over with histologically confirmed FL and an Eastern Cooperative Oncology Group performance status of 0–2) were recruited from eight sites across the UK and completed several patient-reported outcome measures. Patients were analysed according to five disease states: 'active disease-newly diagnosed', 'active disease-relapsed', 'partial response', 'complete response' and 'disease free'. Pettengell et al. assessed patient HRQL using the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) instrument and administered the Hospital Anxiety and Depression Scale, to measure psychological morbidity, and the Work Productivity and Activity Impairment Scale to assess the influence of the disease upon activity and productivity. Pettengell et al. identified a clear relationship between disease status and HRQL in their study.

Patients with active relapsed disease reported worse HRQL outcomes across FACT-Lym domains, in comparison to those in remission, partial responders to therapy, and those with newly diagnosed disease. This result was robust to the authors' statistical analyses (ordinary least squares linear regression of the FACT-Lym Total Outcome Score upon scores from each contributory domain). As also reported in TA627, from the Wild et al. study, utility scores were obtained using the EQ-5D questionnaire and by grouping the disease state categories:

- Progression-free utility of 0.805 (standard error: 0.018)
- Progressed (off-treatment) utility of 0.7363 (assuming combined health states of active disease – newly diagnosed/relapsed)
- Progressed (on-treatment) utility value of 0.62 (assuming single health state active disease – relapsed)

In TA604, utility values from Pettengell et al./Wild et al. were used to inform the cost-effectiveness analysis.[33] In TA627, utility values reported in Pettengell et al./Wild et al. were used in the economic model in scenario analysis. However in the TA627 company base case, utility values were derived for R^2 and R-chemo using a mixed effects model fit to HRQL data collected in the AUGMENT study. In the TA627 Final Appraisal Determination, it was reported that patients in AUGMENT had HRQL values that were higher than the general population for the same age group, in all health states. It was noted in the Final Appraisal Determination that clinical experts said someone with FL would not have higher quality of life than a member of the general population in any health state, and at best their quality of life would be equal to a member of the general population at the same age.[51] The TA627 Committee's preferred approach was to cap progression-free utility at the general population and use relative decrements in other health states. In TA629 (TA472 CDF resubmission), utility estimates from the GADOLIN study were used.[54]

Table 31 presents a summary of the utility values identified in the literature for patients with r/r FL. The HRQL data used in the base case analysis and scenario analysis is discussed in Section B.3.4.5.

Table 31: Summary of utility values identified in the literature

Health state	TA627 FAD[60]	AUGMENT (TA627)[51]		Wild et al. (2006)[59]/Pettengell et al. (2008)[22]	GADOLIN (TA629; as reported in TA627)[50, 51]
		R^2	R-mono		
Pre-progression	• Age-matched general population	• 0.847	• 0.840	• 0.805 (0.018)	• On-treatment: 0.822 (0.010) • Off-treatment: 0.807 (0.012)
Progressed disease	• Age-matched general population (with relative decrement)	• Off-treatment: 0.821 • On-treatment: 0.791	• Off-treatment: 0.813 • On-treatment: 0.784	• 0.736 (aggregated) • 0.62 (0.06 – relapsed disease)	• 0.758 (0.024)

Key: FAD, Final Appraisal Determination; R-mono, rituximab monotherapy; R^2, lenalidomide with rituximab; TA, technology appraisal.

B.3.4.4. Adverse reactions

As reported in NICE TA677, since the approved access of CAR T-cell therapies through the CDF in NHS England, clinicians have become increasingly comfortable with toxicity management for CAR T-cell therapies.[54] However, it is acknowledged that there still may be short-term impactful AEs for many patients following treatment with axi-cel. Therefore, a comprehensive approach to capturing these in the model for the axi-cel arm has been taken. For the current 4L+ care arm, a more simplistic approach has been taken.

B.3.4.4.1. Adverse event frequencies

The model attempts to capture the impact of experiencing AEs on both costs and HRQL. The model considers Grade ≥ 3 treatment-related AEs occurring in ZUMA-5 patients. For AEs of clinical importance for CAR T-cell therapies (CRS requiring tocilizumab treatment, and hypogammaglobulinaemia associated with B-cell aplasia), AEs of all grades were included in the model, in line with previous CAR T-cell therapy appraisals.

Specifically, the following AEs were modelled for axi-cel:

- Grade ≥ 3 axi-cel-related AEs occurring in 5% or more of subjects in ZUMA-5
- Grade ≥ 3 treatment-emergent CRS occurring in ZUMA-5 ([redacted] of patients) and any grade CRS requiring treatment with tocilizumab ([redacted] of patients)
- The proportion of patients who received immunoglobulin treatment ([redacted] of patients)

Table 32 presents the incidence of Grade ≥ 3 treatment-related AEs occurring in 5% or more of patients treated with axi-cel, informed by ZUMA-5. For current 4L+ care, AE frequencies were sourced from clinical trial data (reported in NICE TA627) for individual treatments comprising the basket[54], before being weighted by the current 4L+ care treatment distributions (described further in Section B.3.5.1.2). Conservatively, Grade ≥ 3 AEs for the treatments comprising current 4L+ care were only included in the cost-effectiveness analysis if they also occurred in 5% or more of ZUMA-5 patients. Current 4L+ care AEs included in the analysis are presented in Table 33.

Table 32: Grade ≥ 3 adverse event data, axi-cel (ZUMA-5)

Adverse event	Axi-cel, ZUMA-5 ([redacted])
Any axi-cel related Grade ≥ 3 adverse event	[redacted]
Neutropenia	[redacted]
White blood cell count decreased	[redacted]
Neutrophil count decreased	[redacted]
Pyrexia	[redacted]
Hypoxia	[redacted]
Anaemia	[redacted]
Encephalopathy	[redacted]
Platelet count decreased	[redacted]
Confusional state	[redacted]
Leukopenia	[redacted]
Lymphopenia	[redacted]
Thrombocytopenia	[redacted]
Key: 4L+, fourth-line plus; N/A, not applicable.	

Table 33: Adverse event data, current 4L+ care (reported in TA627)

Adverse event	O-benda, GADOLIN (n = 204)	R-CVP, RELEVANCE (n = NR)	R^2, MAGNIFY) (n = 128)	R-CHOP, RELEVANCE (n = NR)
Neutropenia	27.50%	85.30%	42.20%	90.30%
White blood cell count decreased	0.00%	0.00%	3.90%	0.00%
Neutrophil count decreased	NR	NR	NR	NR
Pyrexia	NR	NR	NR	NR
Hypoxia	NR	NR	NR	NR
Anaemia	5.40%	4.50%	3.10%	4.50%
Encephalopathy	NR	NR	NR	NR
Platelet count decreased	NR	NR	NR	NR
Confusional state	NR	NR	NR	NR
Leukopenia	0.00%	16.60%	7.00%	30.80%
Lymphopenia	0.00%	0.00%	3.10%	0.00%
Thrombocytopenia	10.30%	0.00%	5.50%	2.00%
Key: 4L+, fourth-line plus; NR, not reported; TA, technology appraisal.				

B.3.4.4.2. Adverse event utility decrements

Consistent with the approach used by Hettle et al., and the base case approach used in TA559 and TA677, it is assumed that those experiencing Grade ≥ 3 CRS have a quality of life of zero (i.e. the utility decrement is set to be the negative of the utility value in the progression-free health state).[45, 52, 54] The CRS utility decrement, which is applied as a one-off in the first model cycle with other AE utility decrements, was calculated using the median time to CRS resolution observed in ZUMA-5 (6 days).

Also in line with the methods used by Hettle et al. and in TA677, a disutility for hypogammaglobulinaemia was not applied as it is not thought to result in a reduction of HRQL.[45, 52]

For other Grade ≥ 3 AEs occurring in more than 5% of patients, a utility decrement of 0.15 was applied. The utility decrement is consistent with the approach taken in prior NICE appraisals in advanced lymphoma indications (TA677 and TA567)[53, 54], and was originally derived from a cost-effectiveness analysis by Guadagnolo et al. (2006) in patients after primary treatment for Hodgkin lymphoma.[61]

AEs related to the axi-cel arm are expected to occur in the short term after initial treatment; therefore, a one-off QALY decrement is applied in the first model cycle. As a simplifying modelling assumption, AE disutility values in the current 4L+ arm are also applied as a one-off QALY decrement in the first model cycle, despite AEs occurring over the current 4L+ care treatment duration in practice. Table 34 presents the AE durations, which are combined with the AE frequencies and disutility values to calculate the one-off QALY decrement.

Table 34: Adverse event durations

Adverse event	Duration (days)	Source
Neutropenia	47	TA677/TA559 (ZUMA-1)
White blood cell count decreased	40	TA677/TA559 (ZUMA-1)
Neutrophil count decreased	17	TA677/TA559 (ZUMA-1)
Pyrexia	2	TA677/TA559 (ZUMA-1)
Hypoxia	29	Assumed average (TA677)
Anaemia	14	TA677/TA559 (ZUMA-1)
Encephalopathy	12	TA677 (ZUMA-2)
Platelet count decreased	50	TA677/TA559 (ZUMA-1)
Confusional state	12	TA677 (ZUMA-2)
Leukopenia	21	TA677/TA559 (ZUMA-1)
Lymphopenia	29	Assumed average (TA677)
Thrombocytopenia	63	TA677/TA559 (ZUMA-1)

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

In the absence of HRQL data from ZUMA-5, committee-preferred assumptions from the NICE appraisal of lenalidomide with rituximab for treated FL (TA627) were taken into account when forming the base case analysis.[60] As discussed in Section B.3.4.3, in TA627, general population utility values were used in the progression-free state, with relative decrements from AUGMENT used in the progressed state.

A consistent approach was taken here, with age- and sex-matched general population utility values calculated from Ara and Brazier, 2010.[62] The relative decrement for the progressed state (0.969) was calculated as the AUGMENT-derived progression-free utility values for lenalidomide with rituximab (0.847) over the corresponding progressed (off treatment) utility (0.821). In scenario analysis, the impact of calculating the relative decrement for the progressed state using rituximab monotherapy data from AUGMENT (rather than lenalidomide with rituximab data) is explored. Furthermore, a scenario is presented which uses the absolute decrement of -0.026 taken from the AUGMENT mixed effects model to calculate utility in the progressed disease state.

Table 35 describes the utility values applied in the base case cost-effectiveness model and the sources they are taken from.

It is acknowledged that, in the absence of HRQL data collected in the pivotal trial, utility estimates used in the base case analysis are uncertain. Although the assumptions made align with Committee preferences in a recent appraisal in r/r FL, it should be noted that TA627 considered patients at an earlier line of therapy. As such, several scenarios have been explored using alternative utility values identified in the literature:

- Wild et al.
  - Progression-free utility of 0.805 (0.018)
  - Progressed utility of 0.7363 (off-treatment value applied)
- AUGMENT (lenalidomide with rituximab data)
  - Progression-free utility of 0.847
  - Progressed utility of 0.821 (off-treatment value applied)
- AUGMENT (rituximab monotherapy data)
  - Progression-free utility of 0.840
  - Progressed utility of 0.813 (off-treatment value applied)
- GADOLIN
  - Progression-free utility of 0.822 (0.010; on treatment value applied)
  - Progressed utility of 0.758 (0.024)

When alternative values identified in the review of the literature are used to capture utility for patients in the pre-progression and progressed disease health states in scenario analysis, an adjustment is applied over time. This assumes utility declines with age in line with general population trends, as represented by Health Survey for England data modelled by Ara and Brazier.[62]

Table 35: Summary of utility values for cost-effectiveness analysis

	Utility value	Reference in submission	Justification
Health state			
Progression-free	• Age- and sex-matched general population • 0.829 at baseline (60 years)	Section B.3.4.3 and B.3.4.5	• No HRQL data collected in ZUMA-5 • In TA627, the Committee agreed that capping the progression-free survival health state in the economic model to general population values, and using relative decrements from AUGMENT for other health states is appropriate • Alternative progressed utility decrements as tested in scenario analysis • Alternative pre-progression and progressed health state utility values from the literature are tested in scenario analysis
Progressed	• General population with relative decrement derived from AUGMENT • 0.803 at baseline (60 years)	Section B.3.4.3 and B.3.4.5	
Grade ≥ 3 adverse event			
	Utility decrement	**Reference in submission**	**Justification**
CRS	-0.829	Section B.3.4.4.2	Consistent with the approach used by Hettle et al., and the base case approach used prior appraisals of CAR T-cell therapies in advanced lymphoma indications (TA559 and TA677)[45, 52, 54]
Hypogammaglobulinaemia	0.00		
Other adverse events	-0.15		
Key: HRQL, health-related quality of life; r/r FL, relapsed/refractory follicular lymphoma.			

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

A systematic review of the literature was conducted to identify relevant published cost and resource use data. Searches were conducted alongside those presented in Section B.3.1 for economic evaluations. As reported in Appendix I, and in line with the economic evaluation SLR reported in Appendix G, searches were initially conducted in May 2020, with an update performed in May 2021.

Arguably one of the most relevant sources of cost and resource use identification to this appraisal was the most recent NICE STA in previously treated FL (TA627).[51] Furthermore, due to the mechanism of action and innovative nature of CAR T-cell therapies in advanced lymphoma indications, TA559, TA567 and TA677 have also been identified as useful in informing costs and resource use data and assumptions in this economic evaluation.[45, 53, 54]

In line with the NICE reference case, the perspective on costs is that of the NHS and PSS in England.[48] Costs are derived from typical sources for economic evaluations conducted in a UK setting, including:

- The Monthly Index of Medical Specialities (MIMS) for branded treatment costs[63]
- The drugs and pharmaceutical electronic market information tool (eMIT) for generic treatment costs[64]
- National Schedule of NHS costs (or NHS reference costs) 2019/20 for service/healthcare activity costs[65]
- The PSS Research Unit (PSSRU) Unit Costs of Health and Social Care 2020 for staff costs and inflation indices[66]
- Published literature sources

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Axi-cel

As described in Section B.1.2, axi-cel is produced using patient T-cells, which are extracted via leukapheresis. During the manufacturing of a CAR T-cell therapy, some patients may require bridging therapy to remain in a stable condition and eligible for

CAR T-cell infusion. Prior to receiving axi-cel, which is given as a single infusion treatment, patients receive conditioning chemotherapy. In line with ZUMA-5, patients are hospitalised prior to axi-cel administration and are expected to be monitored in an inpatient setting for at least 7 days following infusion.

The following treatment-related costs are therefore 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

As discussed in Section B.2.3, [redacted] patients with 4L+ r/r FL were enrolled in ZUMA-5 (at the commencement of leukapheresis). Of the [redacted] enrolled patients, [redacted] were treated with conditioning chemotherapy and axi-cel.

While axi-cel is administered as a one-off infusion, [redacted] of the [redacted] treated patients in the ZUMA-5 4L+ mITT analysis set were retreated with axi-cel. Despite this observation from the trial, 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 considered relevant to the cost-effectiveness analysis.

As treatment with axi-cel is administered as a single infusion, treatment-related costs in the axi-cel arm of the model are applied as a one-off cost in the first model cycle, for simplicity.

B.3.5.1.1.1. Leukapheresis costs

In alignment with two of the previous NICE appraisals for CAR T-cell therapies in advanced, previously treated lymphoma indications (TA677 and TA559), the cost of leukapheresis was calculated as the weighted average of stem cell and bone marrow harvest.[45, 54] Table 36 presents unit costs sourced from the latest NHS reference costs (2019/2020).[65]

Table 36: Leukapheresis unit costs (NHS reference costs 2019/20)[65]

Description	Number of cases	Cost	Code / setting
Peripheral blood stem cell harvest	2,544	£1,904.30	SA34Z / Total HRGs
Bone marrow harvest	120	£2,993.81	SA18Z / Total HRGs
Weighted average	*2,664*	*£1,953.38*	Calculated
Key: NHS, National Health Service.			

Although [redacted] patients in ZUMA-5 underwent leukapheresis, only [redacted] received axi-cel. To reflect costs more accurately, an uplifting factor of [redacted] was applied to the initial weighted average cost of leukapheresis, resulting in a leukapheresis cost of [redacted] [£1,953.38 x ([redacted])] per patient.

B.3.5.1.1.2. Bridging therapy costs

In ZUMA-5, bridging therapy could be administered to patients between leukapheresis and the administration of conditioning chemotherapy, at the discretion of the treating investigator. Some patients may require bridging therapy to remain in a stable condition and eligible for CAR T-cell infusion. However, in the 4L+ mITT cohort of ZUMA-5, only [redacted] received bridging therapy.

[redacted]. Other bridging therapies included dexamethasone, etoposide, carboplatin, ifosfamide, and mitoxantrone. However, the dose unit and dose frequency were not known for all bridging treatments.

As a simplifying assumption, it was assumed that one dose of rituximab monotherapy is representative of bridging therapy, for the small number of patients who were treated. This is considered a conservative assumption given that rituximab, which is a branded therapy, has higher treatment costs than other generic chemotherapies. The cost of a single dose of rituximab (£1,251.65; see comparator costs in Section B.3.5.1.2 for details) was applied to the proportion of enrolled patients who received bridging therapy in ZUMA-5, resulting in a total bridging therapy cost of [redacted] [£1,251.65 x ([redacted])].

B.3.5.1.1.3. Conditioning chemotherapy costs

A lymphodepleting chemotherapy regimen of intravenous cyclophosphamide 500 mg/m^2 and intravenous fludarabine 30 mg/m^2 on the fifth, fourth, and third day before axi-cel infusion was considered. Table 37 presents conditioning chemotherapy unit costs, sourced from the latest eMIT.[64]

Table 37: Conditioning chemotherapy unit costs (eMIT)[64]

Treatment	Cost per pack	Pack size	Unit	Form
Cyclophosphamide	£8.23	1	500 mg	Vial
	£13.55	1	1,000 mg	Vial
	£27.50	1	2,000 mg	Vial
Fludarabine	£20.28	1	50 mg / 2 ml	Vial
Key: eMIT, Drugs and pharmaceutical electronic market information.				

Drug wastage was considered for conditioning chemotherapy by assuming that patients receive only whole vials, and vial sharing is not permitted. A normal distribution was fitted to mean body surface area (BSA) data to calculate a distribution of the number of vials of cyclophosphamide and fludarabine needed for one administration. Mean BSA (1.99 m^2) was estimated using mean height and weight data from the mITT population of ZUMA-5 in the Du Bois formula.[67] BSA standard deviation was assumed to be 10% of the mean value. The resulting distribution was used to more accurately calculate the number of vials required for the average patient.

The resulting acquisition costs of conditioning chemotherapy were £17.50 and £39.51 for cyclophosphamide and fludarabine, respectively. In line with prior appraisals in CAR T-cell therapies[45, 53, 54], it was assumed conditioning chemotherapy is administered in hospital over 3 days in an elective inpatient setting. A hospitalisation cost per day of £903.20 (see below; Table 38) was applied to the total conditioning chemotherapy cost.

The total cost of 3 days of conditioning chemotherapy, including drug acquisition and hospitalisation, was £2,880.65 per patient.

B.3.5.1.1.4. Axi-cel acquisition costs

Axi-cel has a one-off cost of £280,451.00 (list price), which includes production and delivery (Kite, data on file). A patient access scheme (PAS) of [redacted] (simple discount) for axi-cel has been agreed with NHS England, the resulting one-off acquisition cost is [redacted].

B.3.5.1.1.5. Axi-cel infusion and monitoring hospitalisation costs

Axi-cel is administered as a single infusion within 30 minutes. In line with prior NICE appraisals, CAR T-cell therapies are administered, and patients monitored, in an elective inpatient setting.[45, 54] Table 38 presents the cost of hospitalisation, which was calculated as the weighted average cost for malignant lymphoma, including Hodgkin lymphoma and non-Hodgkin lymphoma from NHS reference costs 2019/2020.[65]

Hospital Episode Statistics 2019/20 report the mean length of stay for malignant neoplasms of lymphoid, haematopoietic, and related tissues (Codes C81-C96) as 8.1 days.[68] As the mean duration of hospitalisation following axi-cel was longer in ZUMA-5 ([redacted] days) than that reported in the Hospital Episode Statistics, a per-day hospitalisation cost was calculated (£903.20) before being applied to the ZUMA-5 hospitalisation duration to avoid the potential underestimation of costs in the axi-cel arm.

Table 38: Hospitalisation unit costs (NHS reference costs 2019/20)[65]

Description	Number of cases	Cost	Code / Setting
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 15+	325	£35,067.13	SA31A / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 10-14	481	£12,841.27	SA31B / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 6-9	1,068	£7,424.34	SA31C / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 4-5	998	£7,121.88	SA31D / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 2-3	1,554	£4,923.93	SA31E / elective inpatient
Malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 0-1	1,818	£2,931.02	SA31F / elective inpatient
Weighted average	*6,244*	*£7,301.52*	*Calculated*
Mean length of stay (Hospital Episode Statistics 2019/20)		8.1 days	Malignant neoplasms of lymphoid, haematopoietic, and related tissues (codes C81-C96)
Average hospitalisation cost per day		**£903.20**	**Calculated**
Key: NHS, National Health Service.			

When using the average length of stay reported in ZUMA-5 ([redacted] days) and the average calculated per-day hospitalisation cost of £903.20, the resulting axi-cel infusion and monitoring costs is [redacted]

B.3.5.1.1.6. Summary of treatment-related axi-cel costs

Table 39 presents a summary of the treatment-related axi-cel costs, applied as a one-off in the first model cycle.

Table 39: Axi-cel treatment costs per patient

Axi-cel cost category	One-off cost	Section
Leukapheresis	[redacted]	B.3.5.1.1.1
Bridging therapy	[redacted]	B.3.5.1.1.2
Conditioning chemotherapy	£2,880.65	B.3.5.1.1.3
Axi-cel acquisition	[redacted]	B.3.5.1.1.4
Infusion and monitoring hospitalisation costs	[redacted]	B.3.5.1.1.5
Total	[redacted]	B.3.5.1.1.6

B.3.5.1.2. Current 4L+ care

As discussed in Section B.3.2.3.2, current 4L+ care is modelled as a basket of therapies, as there is no established standard of care for patients with FL who have received three or more prior lines of therapy. The components of this basket were aligned with SCHOLAR-5 European treatment patterns (

Figure 12). The following assumptions were made regarding SCHOLAR-5 treatment patterns:

- Idelalisib is representative of the 'PI3Ki based' treatment category
- Rituximab plus bendamustine and obinutuzumab plus bendamustine are representative of the 'CD20+Benda' treatment category
- R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) is representative of the 'CD20+CHOP like' treatment category
- Rituximab plus CVP (cyclophosphamide, vincristine and prednisolone) is representative of the 'CD20+other chemo' treatment category
- CVP is representative of the chemotherapy category
- R^2 is representative of the 'R^2 and other immunomodulatory imide drug (IMiD) based' category

However, since SCHOLAR-5 included patients outside of an English setting, some of the observed therapies are not reimbursed by NHS England for the treatment of FL. To better reflect the cost of the comparator mix in practice, all treatments that are not reimbursed by NHS England were removed from the basket. Similarly, SCHOLAR-5

included patients who received experimental treatments, which could not be costed and were therefore removed from the basket.

Finally, in validation interviews with NHS consultants, it was stated that CVP alone is unlikely to be used in 4L+ patients with r/r FL, and that rituximab plus bendamustine use is likely to be twice that of obinutuzumab plus bendamustine at 4L+.[1] These views were taken into consideration when costing current 4L+ care.

Table 40 presents the final re-weighted treatment distributions comprising current 4L+ care costs in the base case analysis.

Table 40: Distribution of current 4L+ care therapies

Treatment	SCHOLAR-5 distribution	Include as comparator?	Re-weighted distribution
Idelalisib	12.0%	No	**0.0%**
Bendamustine + obinutuzumab	5.3%	Yes	**13.3%**
Bendamustine + rituximab	10.7%	Yes	**26.7%**
CVP + rituximab	6.0%	Yes	**15.0%**
Radioimmunotherapy	3.0%	No	**0.0%**
Lenalidomide + rituximab	9.0%	Yes	**22.5%**
R-CHOP	9.0%	Yes	**22.5%**
CVP	19.0%	No	**0.0%**
Experimental	26.0%	No	**0.0%**
Total	100.0%	**Re-weighted total**	**100.0%**

Key: 4L+, fourth-line plus; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SCT, stem cell transplant.

Table 41 and Table 42 present unit costs (list price) and dosing schedules for the set of treatments included in the re-weighted current 4L+ care blend, respectively. In the first instance, generic treatment costs were sourced from eMIT; branded treatment costs were then sourced from MIMS.[63, 64]

As described in Section B.3.5.1.1.3 for conditioning chemotherapy costs, wastage was considered for treatments administered intravenously by assuming that patients require whole vials and that vial sharing is not permitted. For treatments administered per m^2 of BSA, all available vial sizes were included in the model and a

distribution fitted to calculate the average number of vials required for one administration.

For the two included treatments that are administered orally, the most efficient pack size of tablets was included based on the dosing schedule. For lenalidomide, the 21 x 20 mg pack was included; and for prednisolone, the 28 x 20 mg pack was included. Wastage was conservatively not considered for oral treatments in the current 4L+ care arm of the model, by calculating the cost of the number of tablets required for a 28-day model cycle.

Table 41: Current 4L+ care unit costs (list price)

Treatment	Cost per pack	Pack size	Form	Source
Bendamustine	£27.55	5 vials	25 mg powder	eMIT (2021)
	£65.56	5 vials	100 mg powder	
Obinutuzumab	£3,312.00	1 vial	1 g vial	MIMS (2021)
Rituximab	£157.17	1 vial	10mg/ml, 10ml	MIMS (2021)
	£785.84	1 vial	10mg/ml, 50ml	
Cyclophosphamide	£8.23	1 vial	500 mg powder	eMIT (2021)
	£13.55	1 vial	1 g powder	
	£27.50	1 vial	2 g powder	
Doxorubicin	£2.83	1 vial	10 mg/5 ml	eMIT (2021)
	£7.09	1 vial	50 mg/25 ml	
	£20.02	1 vial	200 mg/100 ml	
Vincristine	£12.71	5 vials	1 mg/1 ml	eMIT (2021)
	£19.54	5 vials	2 mg/2 ml	
Prednisolone	£0.41	28 tablets	5 mg	eMIT (2021)
Lenalidomide	£4,168.50	21 tablets	20 mg	MIMS (2021)

Key: 4L+, fourth-line plus; eMIT, drugs and pharmaceutical electronic market information; MIMS, Monthly Index of Medical Specialities.

Table 42: Current 4L+ care – dosing schedules

Treatment component	Dosing schedule	Dose
Bendamustine (with obinutuzumab/rituximab)	• Cycle 1-6 – Day 1 and 2 (28-day cycle)	90 mg/m^2
Obinutuzumab (with bendamustine)	• Cycle 1 – Day 1, 8, 15 (28-day cycles) • Cycle 2-6 – Day 1 (28-day cycle)	1000 mg

Treatment component	Dosing schedule	Dose
	• Maintenance – Once every 2 months for 2 years	
Rituximab (with bendamustine)	• Cycle 1-6 – Day 1 (28-day cycle)	375 mg/m^2
Rituximab (with CVP/CHOP)	• Up to 8 cycles – Day 1 of each 21-day cycle • Maintenance – Once every 3 months for 2 years (or until progression)	375 mg/m^2
Cyclophosphamide	Once each 3-week cycle	750 mg/m^2
Doxorubicin	Once each 3-week cycle	50 mg/m^2
Vincristine	Once each 3-week cycle	1.4 mg/m^2
Prednisolone	Days 1 to 5 of 3-week cycle	100 mg
Rituximab (with lenalidomide)	• Cycle 1 – Day 1, 8, 15, 22 (28-day cycle) • Cycle 2-5 – Day 1 (28-day cycle)	375 mg/m^2
Lenalidomide (with rituximab)	• Up to 12 cycles – Day 1-21 of 28-day cycles	20 mg
Key: 4L+, fourth-line plus; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone.		

Table 43 presents administration costs considered in the cost-effectiveness model. Administration costs for treatments administered intravenously were sourced from NHS reference costs 2019/20.[65] The administration complexity was specified for each treatment, before the cost of subsequent elements of a chemotherapy cycle were applied for the remaining administrations in a given cycle. Oral therapies are conservatively assumed to have zero administration or dispensing costs in the current 4L+ care arm.

Table 43: Administration costs (NHS reference costs 2019/20)[65]

Administration	Description	Activity	Cost	Code / setting
Intravenous – simple	Deliver simple parenteral chemotherapy at first attendance	277,550	£295.92	SB12Z / DCRDN
Intravenous – complex	Deliver more complex parenteral chemotherapy at first attendance	148,545	£329.75	SB13Z / DCRDN
Intravenous – prolonged	Deliver complex chemotherapy, including prolonged infusional treatment at first attendance	172,603	£428.26	SB14Z / DCRDN
Intravenous – subsequent	Deliver subsequent elements of a chemotherapy cycle	205,274	£363.37	SB15Z / DCRDN
Oral	Zero cost	N/A	£0.00	Assumption
Key: DCRDN, Day case and Reg Day/Night; N/A, not applicable; NHS, National Health Service.				

Table 44 summarises the per 28-day model cycle drug and administration costs in the current 4L+ care arm (including drug wastage for intravenous therapies).

Table 44: Drug and administration costs per 28-day model cycle

Treatment	Treatment component	Drug cost per 28 days	Administration cost per 28 days
Bendamustine + obinutuzumab	Bendamustine	£56.05	£659.28
	Obinutuzumab (induction 1)	£9,936.00	£1,154.99
	Obinutuzumab (induction 2)	£3,312.00	£428.26
	Obinutuzumab (maintenance)	£1,656.00	£214.13
Bendamustine + rituximab	Bendamustine	£56.05	£659.28
	Rituximab	£1,251.65	£428.26
CVP + rituximab	Cyclophosphamide	£32.70	£571.01
	Vincristine	£8.99	£394.56
	Prednisolone	£1.93	£0.00
	Rituximab	£1,668.86	£571.01
	Rituximab (maintenance)	£417.22	£142.75
Lenalidomide + rituximab	Lenalidomide	£4,168.50	£0.00
	Rituximab (cycle 1)	£5,006.59	£1,518.35
	Rituximab (cycle 2-5)	£1,251.65	£428.26

Treatment	Treatment component	Drug cost per 28 days	Administration cost per 28 days
R-CHOP	Rituximab	£1,668.86	£571.01
	Cyclophosphamide	£32.70	£571.01
	Doxorubicin	£22.22	£394.56
	Vincristine	£8.99	£394.56
	Prednisolone	£1.93	£0.00
	Rituximab (maintenance)	£417.22	£142.75

Key: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

In the absence of time on treatment (ToT) data reported in SCHOLAR-5, median treatment durations in the current 4L+ care arm were estimated using the reported number of treatment cycles in the relevant SmPC (Table 45). To cost treatment regimens on a per-cycle basis, while appropriately discounting over time, exponential ToT curves were fitted to the estimated treatment durations.

Table 45: Treatment durations (summary of product characteristics)

Treatment	Primary/induction phase (months)	Maintenance phase (months)
Bendamustine plus obinutuzumab	5.52	24
Bendamustine plus rituximab	5.52	N/A
CVP plus rituximab	5.52	24
Lenalidomide plus rituximab	11.04 (lenalidomide) 4.60 (rituximab)	N/A
R-CHOP	5.52	24

Key: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; N/A, not applicable; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Per-cycle drug and administration costs for each treatment in the current 4L+ care blend (Table 44) were applied to the respective estimated ToT curve. Finally, single weighted per-cycle current 4L+ care treatment and administration costs were calculated using the distribution of comparator treatments shown in Table 40.

B.3.5.1.3. Subsequent treatment costs

As discussed in Section B.3.2.3.2, despite the clinical pathway for FL being well established at early treatment lines, there is no established standard of care for adult

patients with r/r FL who are receiving 4L+ care. The distribution of subsequent therapies received in both the axi-cel and current 4L+ care arms of the model are therefore assumed equal to the re-weighted distribution of treatments in the comparator arm of the cost-effectiveness model (Table 40). Table 46 presents the one-off subsequent acquisition and administration costs applied in the model.

Table 46: Subsequent treatment costs

Treatment	Subsequent acquisition costs	Subsequent administration costs
Axi-cel	£45,040.02	£10,131.55
Current 4L+ care	£45,040.02	£10,131.55
Key: 4L+, fourth-line plus; axi-cel, axicabtagene ciloleucel.		

Subsequent treatment costs are applied once at the point of progression as a simplifying assumption. The proportion of patients receiving the cost of subsequent therapies is estimated as the number of patients who leave the pre-progression state in a given cycle, after accounting for the proportion of PFS events that are deaths as observed in ZUMA-5 ([redacted]).

As described in Section B.3.2.2.1, a time point of 5 years is used to determine when patients remaining progression-free are assumed to be long-term survivors and thus no longer experience the cost of subsequent systemic treatment in the axi-cel arm.

B.3.5.2. Health-state unit costs and resource use

Health-state-dependent resource use costs are assumed to be similar to those presented in previous FL NICE submissions and in the European Society for Medical Oncology (ESMO) guidelines.[51, 69] Resource use frequency in the pre-progression health state is further split by induction phase and maintenance phase (Table 47). As current 4L+ care comprises a blend of treatments, the weighted average length of the primary/induction phase was calculated (seven cycles).

In the validation interview with NHS Consultants, it was noted that in the first 6 months following CAR T-cell therapy, monitoring may be more frequent, with monthly blood tests. In the economic model, axi-cel resource use follows the pre-progression (induction) level for six cycles, and the maintenance level thereafter while patients remain progression free until Year 5. As previously discussed, after 5 years patients

who remain alive and free of progression are assumed to be long-term survivors and no longer experience resource use requirements.

Unit costs for haematologist visits and CT scans sourced from NHS reference costs 2019/20 are presented in Table 48.[65] Unit costs comprising diagnostic tests sourced from NICE TA627 are presented in Table 49 and uplifted to the latest cost year using PSSRU inflation indices.[51, 66]

Table 47: Resource use frequency

Frequency	Pre-progression (induction)	Pre-progression (maintenance)	Progressed disease
Haematologist visit	1 every 1 months	1 every 3.5 months	1 every 4 weeks
Diagnostic tests	1 every 1 months	1 every 3.5 months	1 every 4 weeks
CT scans	1 every 6 months	1 every 12 months	0
Key: CT, computerised tomography.			

Table 48: Resource use unit costs (NHS reference costs 2019/20)

Description	Number of cases	Cost	Code / Setting
Haematologist visit	105,221	£95.66	303 clinical haematology consultant led, non-admitted non-face-to-face attendance, follow-up
CT scans	72	£119.90	RD27Z CT scan of more than three areas
Key: CT, computerised tomography; NHS, National Health Service.			

Table 49: Diagnostic test costs

Diagnostic test	Cost	Cost year	Uplifted cost
FBC	£6.28	2017/18	£6.57
Patient history/physical exam	£6.21	2017/18	£6.49
Full profile (U&E, LFT, calcium)	£17.10	2017/18	£17.88
Serum IgG, IgA, IgM and electrophoresis	£25.10	2017/18	£26.25
LDH test	£12.69	2017/18	£13.27
Key: FBC, full blood count; Ig, immunoglobin; LDH, lactate dehydrogenase; LFT, liver function tests; U&E, urea and electrolytes.			

B.3.5.3. Adverse event costs

As discussed in Section B.3.4.4.1, the model attempts to reflect the costs associated with the management of AEs. In line with the approach to utility decrements, as AEs related to the axi-cel arm are expected to occur in the short term after initial treatment, AE management costs are applied as a one-off in the first model cycle (except for hypogammaglobulinaemia). As a simplifying modelling assumption, AE management costs in the current 4L+ arm are also applied as a one-off, despite AEs occurring over the current 4L+ care treatment duration in practice.

B.3.5.3.1. Axi-cel adverse event costs

In line with NICE TA677, TA559 and Hettle et al., it is assumed the cost of managing AEs is captured by the initial infusion and monitoring hospitalisation costs (Section B.3.5.1.1.5) associated with the administration of CAR T-cell therapy, with the following exceptions:

- All patients experiencing an axi-cel-related Grade ≥ 3 AE ([redacted] Table 32) are assumed to incur the cost of an additional bed day (£903.20; Table 38)
- Hypogammaglobulinaemia (B-cell aplasia) is managed with IVIG. Costs for IVIG are included for any patient in ZUMA-5 requiring this treatment ([redacted])
- CRS is managed with tocilizumab. Costs for tocilizumab are included for any patient in ZUMA-5 requiring this treatment ([redacted])
- Patients experiencing Grade 3/4 CRS are assumed to be managed in the intensive care unit ([redacted])

B.3.5.3.1.1. Hypogammaglobulinaemia

Treatment-emergent hypogammaglobulinaemia occurred in [redacted] patients ([redacted] in the 4L+ mITT population of ZUMA-5),[redacted]. [redacted] were treated with IVIG therapy.

Hypogammaglobulinaemia has not been applied as a one-off cost, as it requires ongoing treatment over a relatively long period of time. The cost for administration of a simple parenteral chemotherapy regimen in an outpatient setting was used for IVIG administration, in line with TA677, TA567 and TA559.[45, 53, 54] For the IVIG treatment costs, the immunoglobulin drug costs reported in MIMS were used; specifically, in line with TA677, it was assumed that Gammaplex® 5% solution for infusion would be

used in practice. Table 50 summarises the IVIG unit, measure, pack size and cost per pack.

Table 50: IVIG unit costs (MIMS)[63]

Treatment	Cost per pack	Pack size	Unit (g)
Gammaplex (5% solution for infusion in bottle)	£325.00	1	5
Gammaplex (5% solution for infusion in bottle)	£650.00	1	10
Gammaplex (5% solution for infusion in bottle)	£1,300.00	1	20

In line with the assumptions used in TA677 and TA559 (which were based on Hettle et al.) a dose of 0.5g/kg every 4 weeks was assumed.[45, 52, 54] Furthermore, IVIG was assumed to be administered to pre-progression patients for a duration of 12 months, consistent with the assumption used in TA677 and TA559.[45, 54] In TA677, it was reported that NHS consultants agreed that both the dosing regimen and assumed duration was sensible.[54] The consultants in TA677 added that there is awareness in clinical practice of the cost of IVIG therapy and that, as a result, wastage is likely to be minimised.[54] Despite this, as a conservative approach, wastage is accounted for when costing IVIG (Table 51).

Table 51: Summary of IVIG costs applied in the model

Immunoglobulin parameters	N
Patients treated with immunoglobulins	[redacted]
Percentage of patients treated with immunoglobulins	[redacted]
Treatment duration (months)	12
Dose (g/kg)	0.5
Frequency (every X weeks)	4
Drug cost per dose (including wastage)	£2,782.98
Administration cost per dose	£295.92
Total cost per dose	£3,078.89
Admins per cycle	1.00
Immunoglobulin – cohort cost (per model cycle)	[redacted]
Key: IVIG, intravenous immunoglobulin.	

B.3.5.3.1.2. CRS

As described in Section B.2.10.4.1, [redacted] of patients in the 4L+ mITT analysis set of ZUMA-5 experienced a CRS event. Most of these were Grade 1–2, and, in the full mITT analysis set of ZUMA-5, all CRS events resolved after a median duration of [redacted] days. The method for costing CRS was taken from previous CAR T-cell appraisals and Hettle et al.[45, 52, 54] It is assumed that patients experiencing a Grade 3/4 CRS event ([redacted] of patients) accrue the cost of an intensive care unit (ICU) hospitalisation. The cost of an ICU hospitalisation was calculated based on non-specific, general adult critical care costs from NHS reference costs 2019–2020.[65] A weighted average of the costs for supporting one and two organs was assumed based on feedback from clinicians during validation, equating to an daily ICU cost of £1,508.65. A duration of 4 days was assumed for the ICU stay, based on assumptions in the Final Appraisal Determination for TA559 and in the TA677 company submission.[45, 54] The final ICU cost for all patients with Grade 3/4 CRS is [redacted].

Furthermore, [redacted] patients ([redacted] of patients in ZUMA-5) were treated with a cytokine inhibitor drug – tocilizumab. The modelled cost of cytokine inhibitor drugs is £659.76, taken from NHS reference costs 2019-2020 (currency code PHCD00098 / High Cost Drugs).[65] It is assumed that this cost is the average cost per tocilizumab administration and covers both drug and administration costs. It is further assumed that only one administration of tocilizumab would be required. The total cost for CRS management including hospitalisation and tocilizumab treatment, applied upfront in the model is [redacted].

B.3.5.3.2. Current 4L+ care adverse event costs

AE management costs in the current 4L+ care arm are presented in Table 52.

Table 52: Adverse event management unit costs

Adverse event	Cost	Source (NHS reference costs)[65]
Neutropenia	£3,591.35	NHS reference costs 2019-20, SA08G, NEL
White blood cell count decreased	£4,101.08	Assumed equal cost to leukopenia
Neutrophil count decreased	£3,591.35	Assumed equal cost to neutropenia
Pyrexia	£525.62	NHS reference costs 2019-20, weighted average of WJ07A-D, NES
Hypoxia	£1,122.53	NHS reference costs 2019-20, DZ38Z, NES
Anaemia	£3,577.69	NHS reference costs 2019-20, weighted average of SA03G-H, NEL
Encephalopathy	£1,023.53	NHS reference costs 2019-20, weighted average of AA22C-G, NES
Platelet count decreased	£3,410.88	Assumed equal cost to thrombocytopenia
Confusional state	£898.56	NHS reference costs 2019-20, SA31E, NES, consistent with TA627
Leukopenia	£4,101.08	NHS reference costs 2019-20, SA31E, NEL
Lymphopenia	£4,101.08	Assumed equal cost to leukopenia
Thrombocytopenia	£3,410.88	NHS reference costs 2019-20, weighted average of SA12G-K, NEL
Key: NEL, non-elective long stay; NES, non-elective short stay; TA, Technology Appraisal.		

B.3.5.4. Miscellaneous unit costs and resource use

A patient with end-stage cancer typically incurs costs at the end of life for palliative and hospice care. The publication by Round et al. (2015) is a standard source used for such costs in submissions to NICE.[70] Costs were taken from this publication and inflated to 2019/20 prices using PSSRU inflation indices.[66] As the publication does not specifically report an end-of-life care cost for patients with any form of haematological malignancy, the average cost for all cancer types reported was assumed. End-of-life care costs are applied as a one-off upon death (Table 53).

Table 53: End-of-life care costs (Round et al. [2015])[70]

Description	Cost	Cost year	Uplifted cost
Health care	£4,254.00	2015	£4,641.30
Social care	£1,829.00	2015	£1,995.52
		Total	**£6,636.83**

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 distributions used to reflect uncertainty is provided in Appendix P.

Information on the uncertainty of each parameter, such as standard errors confidence intervals and sample sizes, was taken from the original source where available. Where uncertainty information was not reported, the standard error was assumed to be 10% of the mean value.

A normal distribution was used for costs, resource use frequencies, and durations as per the central limit theorem. A beta distribution was used for probabilities, proportions and utilities, acknowledging that such parameters can never be negative and cannot exceed 1. A log-normal distribution was used for the SMR applied to general population mortality, acknowledging that the SMR cannot be negative and is right-skewed. A multivariate normal distribution (using variance covariance matrices) was used to capture uncertainty in correlated parameters, such as survival parameters and utility regressions, while maintaining the correlation between parameters. In a number of the alternative utility sources used, no indication of covariance was reported in the source to account for correlation between pre-progression and post-progression utility values. Therefore, to ensure that sampled values demonstrated face validity, a pragmatic approach was taken whereby the same random number was used to ensure that pre-progression utility was always greater than post-progression utility.

Inputs not associated with parameter uncertainty, such as the time horizon, discount rates and alternative modelling assumptions, were investigated in the scenario analysis only.

B.3.6.2. Assumptions

The approach to modelling has been designed to make the best use of the available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal. In the absence of key data, key assumptions have been necessary and have been made to minimise potential bias in the analysis

while tending towards conservative assumptions, where assumptions were necessary. Table 54 describes key modelling assumptions with justifications.

Table 54: Key model assumptions

Model input and cross-reference	Source/assumption	Justification
Model structure [B.3.2.2]	The economic model health states capture the elements of the disease and care pathway that are important for patient health outcomes and NHS/PSS costs	The model type and structure is consistent with those accepted for decision-making in the previous appraisals in r/r FL (TA472, TA604, and TA627)[33, 49, 51], and previous appraisals of CAR T-cell therapy in advanced lymphoma (TA559, TA567 and TA677)[45, 53, 54], as well as the mock appraisal of regenerative therapies and cell therapy products published by Hettle et al. (2017)[52]
	Patient utility and health care resource use for patients who are predicted to be progression-free 5 years after axi-cel are expected to be similar to age-matched general population utility estimates for England	This approach is consistent with the decision-making approach in TA559 and TA677, where long-term survivors were assumed to have utility and NHS resources similar to age-matched general population estimates. In line with TA677 (mantle cell lymphoma), 5 years is considered the cut-off for long-term survivorship, as opposed to 2 years for DLBCL in TA599, given the different underlying mechanisms of the diseases.[45, 54]
Survival extrapolation [B.3.3.1.4]	Parametric models were fit separately to ZUMA-5 and propensity score weighted SCHOLAR-5 data to capture lifetime OS and PFS estimates	As per NICE DSU TSD 14, it is generally considered unnecessary to rely on the proportional hazards assumption when patient-level data are available.[58] Furthermore, given the unique mechanism of action for axi-cel and the expectation of long-term survivorship for a proportion of patients treated with axi-cel, it is considered unreasonable to assume proportional hazards between treatment arms
Axi-cel absolute survival estimates [B.3.3]	The expected absolute clinical effectiveness of axi-cel in terms of disease delay and survival is captured by ZUMA-5 mITT PFS and OS KM data captured and extrapolated over a lifetime perspective. Standard parametric models were used for the full cohort until Year 5, after which a proportion of patients are captured as long-term survivors and	This approach captures the relevant pivotal regulatory trial data while reflecting the clinically informed expectation of long-term survivorship following CAR T-cell therapy. Notably this approach was requested by the ERG in prior NICE appraisal for a CAR T-cell therapy in mantle cell lymphoma.[54] Although immaturity of the ZUMA-5 endpoints represents a positive signal for the longer-term benefits of axi-cel treatment for patients with r/r FL, the plateau representing data-driven anticipation of healthy long-term survival for a proportion of patients that has been observed in the broader lymphoma setting has not yet been shown in the FL setting. Formal mixture cure

	experience SMR-adjusted general population mortality	models were therefore ruled out based on the immaturity of the trial data
	The SMR-adjusted general population mortality hazard was applied to 25% of patients treated with axi-cel.	In interviews with clinical experts, it was noted that, although uncertain, it is reasonable to assume that a proportion of patients with r/r FL treated with CAR T-cell therapy (25%) may have mortality hazards that behave more in line with the general population after 5 years.[1] It is acknowledged that this approach is unproven and suffers from limitations inherent to the use of data with a non-optimal follow-up duration. Further study of CAR T-cell therapy in FL will provide more accurate and robust estimates, highlighting that axi-cel is likely to be a candidate for the CDF. Alternative long-term survivor proportions are tested in scenario analysis, including assuming all those that remain alive and free of progression at 5-years are long-term survivors.
	An SMR of 1.09, derived from a publication by Maurer et al. (2014)[56], which assessed the mortality of patients with DLBCL who maintained event-free at 2 years, is used in the model base case to adjust for excess mortality in long-term survivors	In the absence of FL-specific data, the literature-reported SMR derived from patients with DLBCL was assumed applicable to patients with FL. This is consistent with the assumption made in the appraisal of a CAR T-cell therapy in patients with r/r mantle cell lymphoma (TA677). Alternative SMRs are tested in scenario analysis.
Current 4L+ care survival estimates [B.3.3]	The expected absolute clinical effectiveness of current 4L+ care in terms of disease delay and survival is captured by the SCHOLAR-5 PFS and OS KM data, extrapolated over a lifetime perspective using exponential and gamma parametric survival models, respectively.	This approach captures the available PFS and OS data for current 4L+ care patients. SCHOLAR-5, which provides an external control for the ZUMA-5 trial, was aligned to the ZUMA-5 population using propensity score weighting to adjust for known confounders. This enabled comparisons to be drawn by balancing patient characteristics between both data sources. Base case projections for current 4L+ care PFS and OS over time were validated by NHS Consultants[1]
Health state utility values [B.3.4.5]	In the progression-free health state, utility was assumed equal to that of the age-matched general population.	In the absence of HRQL data from ZUMA-5, committee-preferred assumptions from the NICE appraisal of lenalidomide with rituximab for treating FL (TA627) were taken into account when forming the base case analysis.[51]

	In the progressed disease state, utility was assumed equal to the age-matched general population with a relative decrement for progression derived from patients treated with lenalidomide plus rituximab in the AUGMENT study.	In TA627, utility values derived from HRQL data collected in the AUGMENT study were higher than that of the age-matched general population. The Committee therefore agreed that capping the progression-free utility to general population values and using relative decrements from AUGMENT for other health states is appropriate.[60] It is acknowledged that TA627 considered an earlier line of patients and as such HRQL may be higher than that of patients considered in this appraisal, utility values from alternative sources are therefore tested in scenario analysis.
Axi-cel retreatment costs [B.3.5.1.1]	Costs for patients in ZUMA-5 who were retreated with axi-cel were not considered in the analysis	As axi-cel is administered as a one-off infusion, retreatment is not expected to occur in clinical practice in England.
Current 4L+ care treatment distributions [B.3.5.1.2]	Current 4L+ care is modelled as a basket of therapies, as there is no established standard of care for patients with FL who have received three or more prior lines of therapy. SCHOLAR-5 treatment patterns were re-weighted to inform current 4L+ care costs.	SCHOLAR-5 included patients received therapies that are not reimbursed by NHS England for the treatment of FL, experimental treatments, and treatments that were not aligned with real-world NHS England practice. It was therefore necessary to re-weight the SCHOLAR-5 treatment patterns to more accurately capture the cost of current 4L+ care.
Key: 4L+, fourth line or later; CAR, chimeric antigen receptor; CDF, Cancer Drugs Fund; DLBCL, diffuse large B-cell lymphoma; DSU, Decision Support Unit; ERG, Evidence Review Group; FL, follicular lymphoma; HRQL, health-related quality of life; iNHL, indolent non-Hodgkin lymphoma; KM, Kaplan–Meier; mITT, modified intent-to-treat; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; r/r, relapsed or refractory; SMR, standardised mortality ratio; TA, technology appraisal; TSD, Technical Support Document.		

B.3.7. Base case results

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

Table 55 presents the base case incremental cost-effectiveness results for axi-cel (PAS price) versus current 4L+ care. Costs and QALYs are time-preference discounted at 3.5%, in line with the NICE reference case.[48] Markov traces for each arm are presented in Figure 27 and Figure 28.

Based on the outlook for current 4L+ care patients (in the absence of an established standard of care) and the hope and expectation of the transformative effect of CAR

T-cell therapy for patients with advanced lymphomas, axi-cel is expected to offer an incremental health effect of [redacted] undiscounted life years, or [redacted] discounted QALYs, with more time spent in the progression-free state for patients treated with axi-cel.

The estimated deterministic incremental cost-effectiveness model (ICER) of £48,272 for axi-cel (PAS price) versus current 4L+ care falls below the NICE decision-making threshold for treatments given end-of-life weighting.

Disaggregated results and model results compared with the clinical data are presented in Appendix J.

Table 55: Base case results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Current 4L+ care	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,272
Key: 4L, fourth line; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Figure 27: Lifetime Markov trace for axi-cel

Figure 28: Lifetime Markov trace current 4L+ care

Key: 4L+, fourth line plus.

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was undertaken to explore the joint uncertainty of all model parameters based on their distributional information (see Appendix P) and their associated impact on cost-effectiveness results. To ensure convergence, all inputs were varied simultaneously over 2,000 iterations (rolling average incremental costs, life years [LYs] and QALYs were plotted on convergence graphs within the cost-effectiveness model and visually inspected).

All PSA iterations indicated that axi-cel provides an incremental QALY benefit versus current 4L+ care, at an increased total cost. When comparing average PSA results with deterministic results (Table 56), incremental costs are consistent and incremental QALYs slightly lower, leading to a slightly higher mean PSA ICER.

Figure 29 shows the scatter plot for 2,000 PSA iterations (with the axi-cel PAS). Due to the difference between the mean PSA and deterministic ICER, the analysis was re-run, specifically without varying the survival analysis parameters (Figure 30). Comparing Figure 29 and Figure 30 illustrates that the higher PSA ICER is partly due to the asymmetrical uncertainty distributions of interrelated survival analysis parameters resulting in non-normality in the sampled outcomes.

The cost-effectiveness acceptability curve in Figure 31 demonstrates that axi-cel (with PAS) is more likely to be a cost-effective treatment option when compared with current 4L+ care at a willingness-to-pay threshold of approximately £50,000 per QALY gained.

Table 56: Mean results of PSA (2,000 runs) and comparison with deterministic results (with PAS)

Technology	Total costs (£)		Total QALYs		ICER (£/QALY)	
	PSA	Deterministic	PSA	Deterministic	PSA	Deterministic
Current 4L+ care	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	£51,990	£48,272

Key: 4L, fourth line; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 29: Scatter plot of PSA with 2,000 iterations (with PAS)

Key: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 30: Scatter plot of PSA with 2,000 iterations (with PAS; excluding survival analysis parameters)

Key: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.
Note: For comparability, the scale of the axes is equivalent to that of the PSA including the variation of the survival analysis parameters.

Figure 31: Cost-effectiveness acceptability curves for PSA with 2,000 iterations (with PAS)

Key: 4L+, fourth line or later; PAS, patient access scheme; PSA, probabilistic sensitivity analysis.

B.3.8.2. Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to evaluate the sensitivity of the model's ICER to individual inputs, holding all else constant. Inputs with parametric uncertainty were set to the upper and lower limits of their 95% CIs, reported in Appendix P. Where CIs were not reported, upper and lower bounds were calculated from the mean, standard error and assumed distribution of each parameter. Figure 32 and Table 57 present the 10 parameters with the greatest impact on the ICER with descending sensitivity when their values were set to their upper and lower limits of the CIs. The results demonstrate that the model is relatively insensitive to reasonable variation in most parameters. The parameter with the greatest impact on the ICER is the proportion of patients receiving axi-cel that are long-term survivors and thus experience SMR-adjusted general population mortality from 5 years, as described in Section B.3.3.

Figure 32: Tornado diagram showing OWSA results on ICER (with PAS)

Key: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme; R^2, lenalidomide with rituximab.

Table 57: OWSA results for the most influential model parameters on the ICER (with PAS)

Rank of influence	Parameter	Input value			ICER	
		Base case	Lower bound	Upper bound	Lower bound	Upper bound
1	Proportion of patients treated with axi-cel who are long-term survivors	0.25	0.20	0.30	£50,172	£46,163
2	Utility - progression-free - AUGMENT (R^2)	0.847	0.654	0.968	£46,854	£48,902
3	Utility - progressed - AUGMENT (R^2)	0.821	0.639	0.948	£49,395	£48,116
4	Hospital length of stay: malignant neoplasms of lymphoid, haematopoietic & rel. tiss.	8.1	6.5	9.7	£49,268	£47,603
5	Axi-cel - immunoglobulin treatment (%)	[redacted]	[redacted]	[redacted]	£47,392	£49,237
6	Immunoglobulin treatment duration (months)	12	9.648	14.352	£47,689	£48,642
7	Administration cost: intravenous-prolonged	£428.26	£344.32	£512.19	£48,686	£47,859
8	Duration of hospitalisation following axi-cel (days)	[redacted]	[redacted]	[redacted]	£47,945	£48,599
9	Hospitalisation cost: malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 15+	£35,067.13	£28,194.10	£41,940.16	£48,072	£48,472
10	Hospitalisation cost: malignant lymphoma, including Hodgkin and non-Hodgkin, with CC score 6-9	£7,424.34	£5,969.20	£8,879.49	£48,133	£48,411

Key: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme; R^2, lenalidomide with rituximab.

B.3.8.3. Scenario analysis

Table 58 presents the scenario analyses conducted to assess structural and methodological uncertainty in the model. The scenarios that have the largest impact on the ICER relate to the discount rate, survival extrapolations and the long-term survivorship assumptions in the model.

Table 58: Scenario analysis results (with PAS)

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£48,272	N/A
Discount rate for costs and health outcomes	3.5%	0.0%	[redacted]	[redacted]	£31,957	-£16,315
		1.5%	[redacted]	[redacted]	£38,489	-£9,783
		6.0%	[redacted]	[redacted]	£62,073	£13,801
Time horizon	40 years	30 years	[redacted]	[redacted]	£49,161	£889
		20 years	[redacted]	[redacted]	£56,084	£7,812
Half-cycle correction	Yes	No	[redacted]	[redacted]	£48,200	-£72
OS extrapolations	• Current 4L+ care, gamma • Axi-cel, Weibull (25% of treated patients long-term survivors)	Current 4L+ care, exponential	[redacted]	[redacted]	£44,530	-£3,742
		Axi-cel, log-logistic	[redacted]	[redacted]	£39,742	-£8,530
		• Current 4L+ care, exponential • Axi-cel, log-logistic	[redacted]	[redacted]	£37,191	-£11,082
		Axi-cel, log-logistic (no long-term survivorship)	[redacted]	[redacted]	£46,243	-£2,029
Long-term survivorship proportion	25% of treated axi-cel patients are captured as long-term survivors	[redacted] of treated patients (i.e. all in PFS at 5 years)	[redacted]	[redacted]	£45,031	-£3,241
		10% of treated patients	[redacted]	[redacted]	£54,185	£5,913
Long-term survivorship SMR	SMR = 1.09	1.00	[redacted]	[redacted]	£47,955	-£317
		1.20	[redacted]	[redacted]	£48,654	£382
	5 years	2 years	[redacted]	[redacted]	£43,828	-£4,444
		7 years	[redacted]	[redacted]	£50,534	£2,261

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Long-term survivorship time point		10 years	[redacted]	[redacted]	£53,977	£5,705
Current 4L+ care costs, treatment distributions	Exclude idelalisib	Include idelalisib	[redacted]	[redacted]	£48,039	-£233
	Exclude CVP	Include CVP	[redacted]	[redacted]	£50,950	£2,678
Current 4L+ care, treatment duration	Cap at OS (allowing treatment beyond progression)	Cap at PFS (not allowing treatment beyond progression)	[redacted]	[redacted]	£54,163	£5,891
End-of-life costs	Include	Exclude	[redacted]	[redacted]	£48,571	£299
AE disutility	Include	Exclude	[redacted]	[redacted]	£48,265	-£7
Progressed disease general population utility decrement	Relative decrement, AUGMENT, R^2	Absolute decrement, AUGMENT	[redacted]	[redacted]	£48,324	£52
		Relative decrement, AUGMENT, R-mono	[redacted]	[redacted]	£48,280	£7
Health state utility source for progression-free and progressed disease	• Progression-free, general population • Progressed, general population with decrement	Wild et al. (2006)	[redacted]	[redacted]	£49,296	£1,024
		GADOLIN	[redacted]	[redacted]	£48,726	£454
		AUGMENT, R^2	[redacted]	[redacted]	£47,723	-£549
		AUGMENT, R-mono	[redacted]	[redacted]	£47,941	-£331

Key: AE, adverse event; ICER, incremental cost-effectiveness ratio; N/A, not applicable; PAS, patient access scheme; QALY, quality-adjusted life year; R^2, lenalidomide with rituximab; R-mono; rituximab monotherapy; SMR, standardised mortality ratio.

B.3.8.4. Summary of sensitivity analyses results

While there is inherent uncertainty around the precise clinical and cost-effectiveness of axi-cel for patients with r/r FL in the 4L+ setting, the expected incremental benefit of this treatment remains clear across plausible scenarios. The mean probabilistic ICER of £51,990 was marginally above, but close to the deterministic ICER of £48,272, suggesting that the model results are robust to parameter uncertainty. A comparison of the cloud of PSA iterations when included and excluding parametric survival models from the PSA reflects the uncertainty surrounding the magnitude of the long-term clinical benefit of axi-cel, due to the immaturity of the ZUMA-5 time-to-event endpoints at the latest available data cut.

Similarly, OWSA demonstrated that the proportion of patients treated with axi-cel who are captured as long-term survivors at 5 years is the most influential parameter on cost-effectiveness results (it should be noted correlated parameters with joint uncertainty, such as parametric survival models, are not varied in OWSA).

The key areas of uncertainty described above; in particular, uncertainty around expected absolute OS following axi-cel therapy in NHS patients could be plausibly addressed through CDF data collection.

ICERs in the scenario analyses ranged between £31,957 and £62,073, with an equivalent number of the 28 scenarios resulting in a ICER above/below the deterministic base case results, demonstrating that the selected base case provides a balanced view of the structural uncertainty. Scenario analysis results demonstrated that the model was particularly robust to the approach for modelling utility values, with each of the 5 scenarios around the method of deriving or source of resulting in a difference of approximately £1,000 or less to the ICER.

B.3.9. Subgroup analysis

There are no subgroups considered within the analysis.

B.3.10. Validation

B.3.10.1. Validation of cost-effectiveness analysis

Base case deterministic cost-effectiveness results, presented in Section B.3.7, suggest a mean undiscounted life expectancy of [redacted] years following axi-cel infusion. As illustrated in Section B.3.3, median survival has not yet been reached for either PFS or OS in the 4L+ cohort of the ZUMA-5 mITT group; validation of absolute and relative survival estimates associated with axi-cel within the anticipated patient group is therefore intrinsically difficult.

As discussed in Section B.1.3.5, patients with r/r FL who have received three or more lines of systemic therapy represent a difficult-to-treat patient group who often follow an aggressive, chemotherapy-resistant disease course, with poor prognosis and no established standard of care. Although survival expectations depend on several factors, patients are generally not expected to survive beyond approximately 3 years with current 4L+ care options available in England.[1] Base case deterministic cost-effectiveness results presented in Section B.3.7 suggest a mean undiscounted life expectancy of [redacted] years for current 4L+ care patients. This implies the base case modelled survival estimates in the current 4L+ care arm may be higher than that of the anticipated patient group in practice, in turn providing a conservative estimate of the relative benefit of axi-cel. This increased estimate of survival in the current 4L+ care arm may partially be driven by the treatments comprising the SCHOLAR-5 cohort, in which 25% of European patients received experimental treatment and 17% of European patients received a PI3Ki-based therapy, which are not reimbursed for the treatment of r/r FL in England.

Prior to submission (January 2022), the cost-effectiveness model itself was quality-assured by the internal processes of the external economists who built the economic model. In these processes, an economist not involved in model building reviewed the model for coding errors, inconsistencies, and the plausibility of inputs; this was done as a thorough sheet-by-sheet check. The model was also subject to review against a checklist of known modelling errors and questioning of assumptions; the checklist followed was based on publicly available and peer-reviewed checklists.[71-73] Examples of some basic validity checks include the following:

- Extreme-value testing
- Logical relationship testing (e.g. if the intervention drug acquisition costs increase, do the total intervention costs increase accordingly? Does the ICER increase accordingly?)
- Consistency checks (e.g. is an input parameter value in one cell consistently reflected elsewhere?)

The key assumptions of the model were also validated by UK clinical experts. These include:

- There is no established standard of care for patients with 4L+ r/r FL, and as such, treatment options consist of recycled earlier-line treatment options for FL or resorting to generic chemotherapies or experimental/compassionate use treatments. Treatment decisions are made on a case-by-case basis, taking into account factors such as patient fitness, treatment goals and response/durability of response to prior therapy

  - CHOP plus obinutuzumab and CVP plus obinutuzumab were not included in the current 4L+ care blend as neither is used beyond first line in practice
  - CVP alone is unlikely to be used at 4L+ in practice, and is therefore not included in the current 4L+ blend
  - Bendamustine plus rituximab is used more often than bendamustine + obinutuzumab at 4L+

- The exponential and gamma curves provide clinically plausible extrapolations of PFS and OS in the current 4L+ care arm, respectively
- The Weibull curves provide the most suitable parametric models for axi-cel OS and PFS, and it is reasonable to assume that a proportion of patients with r/r FL who were treated with CAR T-cell therapy (25%) may have mortality hazards that behave more in line with the general population after a given time point

B.3.11. Interpretation and conclusions of economic evidence

Patients with r/r FL who have received three prior lines of therapy represent a difficult-to-treat patient group who often follow an aggressive, chemotherapy-resistant disease course and for whom there is no current standard of care.

ZUMA-5 provides promising data supporting the use of axi-cel in this setting. ORR and CR rates were markedly higher with axi-cel compared with current care in SCHOLAR-5, with odds ratios of [redacted] and [redacted], respectively. DOR, PFS and OS analyses showed a clinically meaningful and statistically significant reduction in the risk of relapse post response, as well as the risk of disease progression or death, and of death alone of [redacted]%, [redacted]% and [redacted]%, respectively ([redacted]) with axi-cel compared with current care.

At NHS Consultant review, the ZUMA-5 baseline characteristics of enrolled patients with 4L+ FL were generally considered representative of patients who would be considered for CAR-T treatment. Although it was stated that patients are slightly younger and fitter than the typical UK 4L+ line patient, a notably high proportion of ZUMA-5 patients were classified POD24. It is anticipated that this is a higher proportion of POD24 patients than is expected in current practice, and POD24 outcomes are notably poor.

Although initial ZUMA-5 results outcomes and the immaturity of the ZUMA-5 time-to-event endpoints at latest available database lock represents a positive signal for the longer-term benefits of axi-cel treatment for r/r FL, there is uncertainty around the magnitude of this benefit in clinical practice. This uncertainty provides a significant challenge for the accurate estimation of cost-effectiveness results. However, as described throughout Section B.3 of this evidence submission, the methods and data used to analyse the cost-effectiveness of axi-cel for patients with 4L+ r/r FL have been carefully considered and justified and are believed to be the most appropriate available for decision-making.

Overall, the cost-effectiveness analysis presents a compelling case for axi-cel as a clear candidate for CDF approval; this would both allow access to this transformative therapy to the patient community that so needs it and allow time and further evidence before a final decision.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

Clarification questions

January 2022

File name	Version	Contains confidential information	Date
ID1685-Clarification Qs -Company response v1.0 23022022	V1.0	Yes	23 February 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 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.3. Please clarify how many reviewers conducted risk of bias assessment of the studies identified by the SLR (and further updates) and whether reviewers worked independently**.**

For the SLR, each study that met the criteria for inclusion was critically appraised by a single reviewer and reviewed by a second reviewer using the Cochrane Collaboration's tool for assessing the risk of bias[1], in line with NICE requirements.[2]

Similarly, in the SLR update, quality assessment of the included studies was performed as part of the data extraction process, i.e., each checklist item was extracted from the included full-text articles by one reviewer, and quality checked against the original source by a second reviewer.

1. *Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj. 2019;366*

2. *(2) Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Chichester, England; Hoboken. NJ: Wiley-Blackwell; 2008*

A2. Appendix D, Section D.2.1. The company submission states that 16 studies reporting data for the 4L+ r/r FL setting were identified by the original SLR, and

further studies by the SLR update and grey literature searches. For each identified study (based on the reasons in Section D.5. "*Comparison of SLR evidence with the ZUMA-5 study*") please explain why a comparison with ZUMA-5 was considered unsuitable.

ZUMA-5 was a single-arm study because there is no standard of care (SoC) for this population. As a single-arm study, direct comparison to a comparison arm was not possible.

Patients [with r/r FL] typically receive salvage therapy or potentially allogeneic SCT, but the exact nature and outcome varies greatly depending on patient characteristics including age, disease stage, tumour burden, and the number of prior lines of therapy. This may lead to potential bias when carrying out indirect comparisons of results from published studies. Therefore, to further determine the clinical benefit associated with CAR-T therapy, an accurate detailed description of available treatment options in the relevant patient population and associated outcomes was required.

In the absence of comparable data, Kite Pharma constructed an external cohort of real-world FL (grades 1-3A) patients who would be eligible for ZUMA-5. This real-world cohort was used as an external control for the ZUMA-5 clinical trial.

Description of the technology being assessed

A3. Document B, Section B.1.3.4, Figure 3. Please clarify whether eligibility for axi-cel (as described at the bottom of Figure 3) differs depending on the stage of disease at relapse/refractory.

Eligibility for 4L/4L+ axi-cel is not expected to differ depending on the stage of disease at relapse/refractory. Overall, the ZUMA-5 trial enrolled a majority (85%) of patients with advanced stage (stage III or IV disease) follicular lymphoma and also 15% of patients who had stage I/II disease. It is widely accepted that patients with advanced stage disease will have had multiple prior relapsed on treatment plus it is our understanding (based on clinician elicitation) that by the time patients reach 4L/4L+ treatment (following multiple relapses/refractoriness to treatment), they have exhausted currently available treatment approaches including biologics, chemotherapy and hemopoietic stem cell transplantation. Furthermore, at this stage

of the treatment pathway, therapeutic approaches such as consolidative radiotherapy would not be offered to patients considered fit enough to receive intensive active treatment, such as CAR-T. As such, eligibility for 4L/4L+ axi-cel will not differ, irrespective of the route the patient has taken to reach 4L/4L+ treatment, where the goal treatment is to achieve sustained clinical remission.

Baseline characteristics

A4. Document B, Section B.2.3.1, Table 7, page 29. Some of the values in Table 7 do not add up or make sense. Specifically, the FAS (Full analysis set) columns for the 'age range' do not reflect the upper and lower observations in the other columns. Please clarify if the range reported for 'age' is the interquartile range or the minimum and maximum values.

Unfortunately there were typographical errors in Table 7; a corrected Table 7 for all analysis sets is provided in the Appendix (after Section C in this document).

The median age range for the FAS should be minimum and maximum values (it is currently interquartile range). The corrected range for the FAS is: median (min, max) age, years: [redacted]

A5. Document B, Section B.2.3.1, Table 7, page 29. The FLIPI (Follicular Lymphoma International Prognostic Index) totals and percentages do not make the whole sample. Please check and provide missing values if applicable.

A corrected Table 7 is provided in the Appendix (after Section C in this document). The low risk (0–1) FLIPI total score for the FAS population (two or more lines of prior therapy) should be [redacted] The FLIPI values for the other analysis sets are correct.

A6. Document B, Section B.2.3.1, Table 7, page 29. Please clarify if SAS (safety analysis set) is a sub-cohort of FAS. If it is, the numbers of low risk in the FAS cohort should be equal to or greater than the numbers in the SAS cohort. Please check and clarify these values.

The SAS included all patients who were treated with any dose of axi-cel, whereas the FAS included all enrolled patients (including those who did not receive any dose of axi-cel). As such, you are correct in noting that the number of low-risk patients in the FAS cohort should be equal to or greater than the numbers in the SAS cohort.

We have now corrected this error in the re-submitted Table 7 included in the Appendix (after Section C in this document).

A7. Document B, Section B.2.3.1, Table 7, page 29. As the first part of Table 7 presents data for FL patients with two or more lines of prior therapy, please clarify why in the 'Number of prior lines of therapy' row there are three patients with one prior line of therapy for both the FAS and the SAS populations**.**

Inclusion criterion 102 was amended in Protocol Amend 2 which requires relapse or refractory disease after 2 or more prior lines of therapy. Three subjects (105-003-006, 105-003-007, 105-061-009) who received only one prior line of prior therapy were enrolled and treated under Protocol Amendment 1 when inclusion criteria 102 was not yet implemented, therefore they were included in FAS and SAS populations

A8. Document B, Section B.2.3.1, Table 7, page 29. The last row of Table 7 '*Baseline characteristics of FL patients in ZUMA-5'* shows that patients with no FL present (bone marrow assessment at baseline) have been included. Please explain why.

One subject (105-409-001) had bone marrow assessment result as lymphoma present but not FL at baseline. Subject fulfilled all eligibility criteria at screening (10Sep18) and until after enrolment (leukapheresis) on 18Sep18. On 26Oct18 Kite received information from the site about biopsy results of FL in lymph node and transformed FL in the marrow.

One subject (105-019-022) had bone marrow assessment result as Unknown at baseline. The site confirmed that the unknown result was based on biopsy proven bone marrow assessment, therefore lymphoma presence in bone marrow cannot be confirmed.

A9. Document B, Section B.2.3.1, Table 7, page 29. Some of the values do not seem to be correct. Please, check the numbers presented in Table 7 and provide missing value counts if applicable.

Please refer to the corrected Table 7 in the Appendix (after Section C in this document) with our annotated comments.

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

A10. Document B, Section B.2.4, page 30. The company submission states that "Approximately 160 patients were to be enrolled and treated with axi-cel, including 125 FL patients, with at least 80 patients with FL in the IAS (inferential analysis set)." However, Table 7 and Figure 5 refer to 127 FL patients in the FAS, not 125. Please clarify this inconsistency.

The text is a description of the intended sample size (and considerations) for the SAS analysis set, that is for those patients who were enrolled and treated with any dose of axi-cel. The FAS analysis set included all enrolled patients, including those were not treated with axi-cel. This is why the FAS analysis set includes 127 patients, and the SAS includes 125.

Clinical effectiveness results of the relevant trials

A11. Document B, Section B.2.6, page 35. Please provide a clear definition of the mITT (modified intent-to-treat) FL population and how it differs from the SAS FL population with ≥3 lines of prior therapy.

The mITT population and SAS FL population with ≥3L of prior therapy are the same analysis set; that is, all patients treated with any dose of axi-cel. We have used the terminology 'mITT' to present the efficacy analyses for this analysis set. This is because we intended to align with the anticipated marketing authorisation and target population for reimbursement (FL patients with ≥3L of prior therapy). As the SAS FL population with ≥3L of prior therapy is the closest to the intended reimbursement population (as it is the population which received a dose of axi-cel, as compared to the FAS which included patients who didn't receive axi-cel) we wanted to highlight this by referring to it as the mITT, as it is the key analysis set for efficacy analyses which are relevant to the target population for reimbursement (aligning with NICE's preference for key analyses to be done in the ITT population).

Comparative analysis

A12. PRIORITY. Document B, Section B.2.9.1.1, page 55. Please provide the baseline characteristics of SCHOLAR-5 patients who were included in the

comparative analysis (n=77) for each of the cohorts (A, B and C) separately. Please replicate Table 7.

As requested please see below a table of baseline characteristics of SCHOLAR-5 patients included in the comparative safety analysis, separated by data source. Please note Cohort A (retrospective cohort created from electronic medical records of six sites) and Cohort B (retrospective cohort created from the Vanderbilt University Medical Center's Synthetic Derivative) have been combined under 'real-world cohorts' since only 2 patients in the 4L+ analysis set were derived from Cohort B.

The data presented are pre-weighting only, unfortunately it was not possible to provide the post-weighting data within the available timeframe, however the company will endeavour to provide the post-weighting data during technical engagement.

Table 1: Baseline characteristics of SCHOLAR-5 patients included in the comparative safety analysis, separated by data source

Characteristics	Overall (n = 82)	Real-world cohorts (n = 58)[c]	DELTA (n = 24)[d]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Key: auto-SCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; PI3K, phosphoinositide 3-kinase
Notes: [a] patients with FL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Patients with FL who progressed >6 months of completion of the most recent prior treatment are defined as relapsed. Patients with FL who progressed within 6 months of completion each of the first 2 lines of prior treatment are defined as double refractory. [b] from first anti-CD20-chemotherapy combination. [c] includes 56 patients from cohort A and 2 patients from cohort B. [d] includes patients from cohort C.

A13. PRIORITY. Document B, Section B.2.9.1.3, Table 14, page 52. The propensity score method reference (reference 21, Document B) indicates several methods, including standardised mortality ratio weighting, were applied. Please clarify which method and variables were used for the propensity score matching in Table 14.

Standardised mortality ratio weighting was applied in the "Post-weighting" columns of Table 14 to ensure that baseline characteristics were balanced between SCHOLAR-5 and ZUMA-5. Variables used in this procedure included those listed in Table 14: POD24, number of prior lines of therapy, refractory to prior line, prior SCT, size of prior node ≥7cm, time since last therapy, complete or partial response to prior line of therapy, age 65+ years, and prior anti-CD20 + alkylator combination treatment. The full list of covariates identified by clinicians as prognostic factors can be found in Table 1 of the SCHOLAR-5 SAP. Ranking of the prognostic importance of these covariates can be found in Table 2 of the SCHOLAR-5 SAP. For clarity, these covariates included region, ECOG score, age, FLIPI score, relapsed/refractory status at index date, POD24, sex, race, best response to last line of therapy, time from last treatment, bone marrow involvement, GELF categorization of tumour burden, prior SCT, prior PI3K inhibitor, prior BTK inhibitor, prior alkylating agent, prior anti-CD20 alkylating agent, prior lenalidomide. Propensity score matching was used in a sensitivity analysis.

A14. PRIORITY. Document B, Section B.2.9.1.3, Table 14, page 52. Not all the baseline characteristics in Table 7 have been replicated in Table 14. Please provide pre-and post-weighing for all the characteristics reported in Table 7 for both SCHOLAR-5 and ZUMA-5.

Pre- and post weighting baseline characteristics for SCHOLAR-5 consistent with Table 7 are presented below. Note some ZUMA-5 baseline characteristics were not collected as part of SCHOLAR-5 and therefore cannot be presented. Weighting is

not applied to ZUMA-5, the baseline characteristics are therefore equivalent to those provided in the updated Table 7 presented in the Appendix of these responses.

Table 2: Baseline characteristics of FL patients in SCHOLAR-5

Characteristics	Pre-weighting SCHOLAR-5 (n=82)	Post-weighting SCHOLAR-5 (n=77)
Median age, years (min-max range)	[redacted]	[redacted]
Aged ≥65 years, n (%)	[redacted]	[redacted]
Aged <65 years, n(%)	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]
Female, n(%)	[redacted]	[redacted]
ECOG performance status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Missing	[redacted]	[redacted]
FL histological category at trial entry, n (%)		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3a	[redacted]	[redacted]
Missing	[redacted]	[redacted]
FLIPI total score, n (%)		
Low risk (0–1)	[redacted]	[redacted]
Intermediate risk (2)	[redacted]	[redacted]
High risk (3–5)	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Relapsed/refractory disease[a], n (%)		
Relapsed	[redacted]	[redacted]
Refractory	[redacted]	[redacted]
Double-refractory subgroup[a], n (%)		
Yes	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Median no. of prior therapies (range)	[redacted]	[redacted]
Prior auto-SCT, n (%)	[redacted]	[redacted]
Prior PI3K inhibitor, n (%)	[redacted]	[redacted]
Prior anti-CD20 single agent, n (%)	[redacted]	[redacted]
Prior alkylating single agent, n (%)	[redacted]	[redacted]
Prior anti-CD20 + alkylating agent, n (%)	[redacted]	[redacted]
Time to relapse from first therapy[b], n (%)		
≥24 months	[redacted]	[redacted]
<24 months	[redacted]	[redacted]

Characteristics	Pre-weighting SCHOLAR-5 (n=82)	Post-weighting SCHOLAR-5 (n=77)
Prior lenalidomide, n (%)	[redacted]	[redacted]
Bone marrow involvement n (%)[c]		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Key: auto-SCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; FL, follicular lymphoma; IAS, inferential analysis set; PI3K, phosphoinositide 3-kinase

Notes: [a] Patients with FL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Patients with FL who progressed >6 months of completion of the most recent prior treatment are defined as relapsed. Patients with FL who progressed within 6 months of completion each of the first 2 lines of prior treatment are defined as double-refractory. [b]Time to relapse is defined as the time from initiation of the first line anti-CD20-chemotherapy combination therapy to progression. Number of subjects with time to relapse is based on those who had progressed with date of progression. Percentages are based on the number of subjects who ever received anti-CD20-chemotherapy combination therapy. [c] bone marrow assessment at baseline for lymphoma presence was not reported in SCHOLAR-5 in the same format as in ZUMA-5. Bone marrow involvement (n [%]) is presented here as an alternative.

A15. PRIORITY. Document B, Section B.2.9.1.3, page 51. For the comparative analysis, please provide the list of variables considered to be confounders.

The theoretical advantage of propensity score adjustment methods is to potentially balance unobserved confounders along with observed confounders, leading to improved comparisons between groups. The full list of covariates identified by clinicians as prognostic factors can be found in Table 1 of the SCHOLAR-5 SAP. Ranking of the prognostic importance of these covariates can be found in Table 2 of the SCHOLAR-5 SAP. For clarity, these covariates included region, ECOG score, age, FLIPI score, relapsed/refractory status at index date, POD24, sex, race, best response to last line of therapy, time from last treatment, bone marrow involvement, GELF categorization of tumour burden, prior SCT, prior PI3K inhibitor, prior BTK inhibitor, prior alkylating agent, prior anti-CD20 alkylating agent, prior lenalidomide.

A16. Document B, Section B.2.9.1.3, Table 15, page 55. Please clarify if the patients included in the comparative analysis to model the effectiveness of axi-cel had 3 or more lines of prior therapy or 4 or more lines of prior therapy. The text of the

company submission is not always consistent and, in some cases, refers to 3 or more lines of therapy and in others to 4 lines. Please clarify.

All patients had 3 or more lines of prior therapy in both ZUMA-5 and SCHOLAR-5. That is, the patients in the comparative analysis are aligned with the anticipated marketing authorisation and target population for reimbursement (FL patients with ≥3L of prior therapy; 4L/4L+ position of axi-cel).

A17. PRIORITY. Document B, Section B.2.9.1.3, Figures 14 and 15, pages 56-57. Please provide the time-to-event data (for each individual - not just at summary times) used to plot the Kaplan Meier curves in Figures 14 and 15. For the time-to-event data, please also provide the last treatment each patient received, and all the variables adjusted in the models in Table 15.

Unfortunately, Gilead are not able to share individual patient data.

A18. PRIORITY. Document B, Section B.2.9.1.3, Figures 14 and 15, pages 56-57. Please replicate Figures 14 and 15 with the SCHOLAR-5 data according to whether treatments are reimbursed by NHS England as per Table 40, page 119, Document B.

The SCHOLAR-5 comparator study is based on treatment patterns observed in 4L+ r/r FL patients from medical records and the DELTA clinical trial, and was powered to show comparative results of 4L+ r/r FL treatments vs axi-cel. Observed treatment patterns indicated that a substantial proportion (25%) of 4L+ r/r FL patients receive experimental therapies through enrolment in clinical trials. Excluding all treatments in SCHOLAR-5 that are not included in NHS England routine commissioning would necessitate removal of the “experimental” category, Pi3K inhibitors, and radioimmunotherapy, resulting in a loss of nearly 40% of the study sample. These exclusions would render the analysis underpowered to conduct balanced comparative effectiveness analyses.

However, we expect the outcomes associated with the treatments included within SCHOLAR-5 that are not reimbursed by NHS England, particularly idelalisib, to have favourable outcomes compared to the majority of treatments that are; notably, chemotherapy with/without anti-CD20 monoclonal antibody therapy, which UK clinicians agreed would be expected to have limited benefit in heavily pre-treated

4L+ patients who may likely have relapsed on multiple rituximab-based therapies by this stage.

A19. PRIORITY. Document B, Section B.2.9.1.3, Table 15, pages 55. Please adjust the relative treatment-effect estimates for all the outcomes reported in Table 15 for axi-cel and the treatments reimbursed by NHS England.

Please see response to question A18 above.

A20. Document B, Section B.2.10.1, Table 16, pages 59. [redacted] due to treatment-related TEAE is reported in the '≥Grade 3' column while NA is reported in the 'Any group' column. Please check this is correct.

The NA for any grade versus ≥Grade 3 death events is representative of the fact that all death events have to be ≥Grade 3. For clarity, as of the 18-month analysis data cut-off date, there was [redacted] in ZUMA-5.

Section B: Clarification on cost-effectiveness data

Efficacy inputs and assumptions

B1. Priority. Section B.2.6.1.4 and B.3.5.1.1. It is stated that "[redacted] of the [redacted] treated patients in the ZUMA-5 4L+ mITT analysis set were retreated with axi-cel", but the cost of this retreatment has not been included in the model as retreatment is not expected to occur in clinical practice in England. Please comment on why no corresponding adjustment to the key model efficacy inputs (progression free survival and overall survival) is required.

In ZUMA-5, patients who achieved a partial response or complete response at Month 3 disease assessment, but subsequently experienced progression at a later date may have had the option to receive a second course of axi-cel subject to several eligibility criteria. As such, no corresponding adjustment to progression-free survival was required as patients are not expected to be retreated prior to disease progression.

While censoring patients at the point of retreatment was considered as a potential approach to adjust overall survival for retreatment in the cost-effectiveness analysis; this would have led to informative censoring and thus 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), in response to Question B2 and to align costs in the model with the available clinical effectiveness data, a scenario including the cost of retreatment is provided below.

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. However, it is acknowledged that this information is in regards to a different disease setting than FL.

B2. Priority. Section B.2.6.1.4 and B.3.5.1.1. In the absence of any adjustment to the efficacy inputs please provide a scenario which includes the cost of retreatment for a proportion of patients as observed in ZUMA-5.

As previously described, retreatment is not expected to occur in clinical practice in NHS England and is not requested for reimbursement in this submission. Nonetheless, to align with the available clinical effectiveness data used to inform the model, cost-effectiveness results for axi-cel versus current 4L+ care when including axi-cel retreatment costs are presented in response to this question.

Of the [redacted] patients in the 4L+ mITT cohort 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.3.5.1.1 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 3.

Table 3: 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.	

The cost of retreatment is accounted for in the cost-effectiveness analysis by uplifting the cost of initial treatment which is applied in the first model cycle. This approach, which is applied as simplifying assumption, is likely to overestimate the cost of retreatment, as retreatment costs would not be incurred in the first cycle in practice and would therefore be time-preference discounted at a rate of 3.50% per annum.

Leukapheresis

Accounting for the proportion of retreated patients requiring re-apheresis results in a total leukapheresis cost of [redacted]

Conditioning chemotherapy

Additional conditioning chemotherapy are considered for all patients retreated with axi-cel. This results in an uplifted total conditioning chemotherapy cost of [redacted]

Acquisition costs

Further acquisition costs are not considered for patients re-treated with a cryopreserved 'second bag' of axi-cel that was generated when the product was initially manufactured. The resulting acquisition costs in the model when considering those treated with re-apheresis or PBMCs is [redacted]

Infusion and monitoring hospitalisation costs

Uplifted total infusion and hospitalization cost are [redacted], when accounting for the retreated ZUMA-5 patients.

Table 4 summarizes the axi-cel treatment costs applied in the analysis, in the scenarios without and with retreatment.

Table 4: 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 resulting deterministic cost-effectiveness results are presented in Table 5, with the base case results from the company submission presented in Table 6 for comparison. When compared with the deterministic base case results reported in Section B.3.7.1 of the company submission, the ICER for axi-cel versus current 4L+ care increases from £48,272 to £54,493 when retreatment costs are captured.

Table 5: Deterministic cost-effectiveness results (including retreatment costs)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Current 4L+ care	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£54,493

Key: 4L+, fourth line or later; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 6: Deterministic cost-effectiveness results (company base case)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Current 4L+ care	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,272

Key: 4L+, fourth line or later; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B3. Priority. Section B.2.9.1.3. Figure 14 and Figure 15. It is noted that the effective sample size in SCHOLAR-5 was reduced to 77 patients after applying SMR weights. This is reflected in the number at risk at time zero in figure 15 (OS), but not in figure 14 (PFS) where the number at risk at time zero is [redacted]. Please explain the anomaly and correct the curves if required.

As described in Section B.2.9.1 of the company submission, the SCHOLAR-5 cohort was created from multiple data sources:

- Cohort A – retrospective cohort created from electronic medical records of six sites, including university hospitals and cancer centres with two sites based in the UK and other sites based in France, Spain, Portugal and the US
- Cohort B – retrospective cohort created from the Vanderbilt University Medical Center's Synthetic Derivative: a fully de-identified database derivative of electronic medical records from the university
- Cohort C – prospective cohort created from an open-label Phase II study, DELTA, that enrolled patients with r/r FL who had not responded to or were refractory to rituximab and an alkylating agent and were treated with idelalisib

The SCHOLAR-5 analyses utilized all patients for the assessment of response rates and OS. However, due to the absence of progression assessment dates in the index line of therapy for patients from the DELTA clinical trial (Cohort C), these patients were excluded from PFS analyses. The number at risk post-weighting for the PFS endpoint is correspondingly lower (n = [redacted]) than that for OS (n = [redacted]).

In the primary comparative analysis for ZUMA-5 versus SCHOLAR-5, the ZUMA-5 inferential analysis population was used (n = [redacted]), rather than the ZUMA-5 mITT analysis set (n = [redacted]). The inferential analysis set included ZUMA-5 patients with a minimum of 18-months follow up, whereas the mITT analysis set included all patients who receive axi-cel.

As part of the ZUMA-5 and SCHOLAR-5 comparative analysis, a subgroup was conducted which excluding DELTA patients; however this analysis was performed using the inferential analysis set of ZUMA-5 (n = [redacted]) rather than the mITT population (used to support this submission; n = [redacted]).

Nevertheless, within the inferential population OS results were highly consistent in the analysis which included the DELTA patients ([redacted]) and in the subgroup excluding DELTA patients ([redacted]), suggesting that outcomes for DELTA patients are consistent with the other patient cohorts. Note, within the analysis excluding DELTA patients from SCHOLAR-5, statistically significant differences in baseline characteristics were not observed after SMR weighting.

B4. Section B.2.9.1.3. Figure 15. The OS curve derived from the SCHOLAR-5 data [redacted], and the chosen extrapolation curve (section B.3.3.3.2, Figure 24) appears to provide a poor visual fit to the observed data. Please comment further on the shape of the OS Kaplan Maier curve in relation to the chosen OS extrapolation curve and the shape of the progression free survival curve.

Clinical plausibility of the long-term extrapolation was prioritized during the curve selection process. While it is acknowledged that the selected OS curve in the current 4L+ care arm does not provide the best visual fit to the observed portion of the data; clinicians consulted during submission development stated that it was most aligned to clinical expectations.

During the validation meeting with two NHS Consultants, the generalized gamma and Gompertz curves (which provide the first- and second-best statistical "best-fit" to the SCHOLAR-5 data according to AIC/BIC) were immediately ruled out due to the implausibility of the long-term extrapolation. The generalised gamma and Gompertz models predict [redacted] of current 4L+ care patients are alive at 40 years (aged [redacted]), respectively (prior to any background mortality adjustment), which is not considered clinically plausible. As described in the company submission, during the clinical validation interview, the gamma curve was selected as the preferred OS extrapolation based on the plausibility of the extrapolation, with a median OS of [redacted] years and [redacted] of patients alive at 5 years, and was therefore selected as the base case.

As described above in response to question B3, due to the absence of progression assessment dates in the index line of therapy for patients from the DELTA clinical trial, the SCHOLAR-5 number at risk post-weighting for the PFS endpoint was lower (n = [redacted]) than that for OS (n = [redacted]). As the comparative subgroup analysis excluding DELTA patients from the SCHOLAR-5 cohort was conducted in comparison with the ZUMA-5 inferential analysis set (rather than the mITT set), it is not clear whether the inclusion of DELTA patients in the OS analysis impacts the comparability of the shape of the PFS and OS curves. However, as described in response to question B3, for ZUMA-5 (inferential analysis set) versus SCHOLAR-5, OS results were highly consistent in the analyses without and with DELTA patients excluded.

B5. Section B.3.5.1.2. Table 40 presents the reweighted distribution of SCHOLAR-5 treatments that are costed in the blended comparator. Given the reweighting for costs, please clarify why no corresponding adjustments were made to the efficacy inputs (PFS and OS) from SCHOLAR-5. Please:

a. Comment on the potential for bias (direction and magnitude) arising from the use of efficacy data from SCHOLAR-5 without adjusting for the reweighted treatment distribution in Table 40.

Related to a, is it possible to give an indication of the potential bias by adjusting the Kaplan-Meier data from SCHOLAR-5 to account for the reweighted treatment distribution in Table 40. Alternatively, could the company present the SCHOLAR-5

PFS and OS Kaplan Meier data by the treatments that are used in the NHS in England and those that are not (see A18 above).

As described in response to A18, the sample size in SCHOLAR-5 was not designed to investigate individual treatment comparisons with axi-cel. However, we expect the outcomes associated with the treatments included within SCHOLAR-5 that are not reimbursed by NHS England, particularly idelalisib, to have favourable outcomes compared to the majority of treatments that are; notably, chemotherapy with/without anti-CD20 monoclonal antibody therapy, which UK clinicians agreed would be expected to have limited benefit in heavily pre-treated 4L+ patients who may likely have relapsed on multiple rituximab-based therapies by this stage. This would imply that the outcomes of SCHOLAR-5 are likely to be optimistic compared to current clinical practice in England and therefore the comparison between axi-cel and SCHOLAR-5 is likely a conservative estimation of the expected relative benefits of treatment.

B6. Section B.3.3.2.1. A fraction of those projected to be progression free at 5 years (equating to 25% of the total cohort) are assumed to be longer-term survivors at zero risk of progression from 5 years onwards. The remaining survivors face risks of progression and death based on the chosen extrapolation curves for PFS and OS. However, the extrapolation curves are fitted to observed data for the overall cohort and may not be appropriate for extrapolating outcomes for the subset who are not long-term survivors. Please explore the impact of applying higher risks of progression and death after five years for those not considered to be long-term survivors.

Two scenarios are presented below which explore the impact of capturing a higher risks of progression and death after five years for those not considered to be long-term survivors.

As no long-term FL-specific data were identified to inform the heightened risk of progression or death for the subset of those not considered long-term survivors compared with the full population, a hazard ratio (HR) of 1.09 is applied in the first scenario. This is equivalent to the standardised morality ratio (SMR) applied to general population mortality used to capture the heightened risk of death for those who are considered long-term survivors after five years. In scenario 2, a HR of 1.20

is tested, assuming the hazard of experiencing progression or death is 1.20 times higher for non-long-term survivors compared with that of the overall cohort. It is acknowledged that these values are arbitrary in the absence of data.

Table 7 compares the total LYs gained in the axi-cel arm of the model and the corresponding deterministic ICER for axi-cel versus current 4L+ care in the base case presented in the company submission and the scenarios testing a higher risk of progression and death for those not captured as long-term survivors. The impact on cost-effectiveness results of applying HRs of 1.09 and 1.20 is relatively small, increasing the ICER by £1,815 and £4,054, respectively.

Table 7: Deterministic cost-effectiveness results (heightened risk of progression/death for those not considered long-term survivors)

HR for those not considered long-term survivors after 5 years	Axi-cel total LYs	ICER (axi-cel versus current 4L+ care)
1.00 (no adjustment)	[redacted]	£48,272
1.09	[redacted]	£50,087
1.20	[redacted]	£52,326
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYs, life years.		

B7. Economic model, “OS” Worksheet, column S, row 155 down. The calculation of the weighted average mortality hazard appears to assume long-term survivors are a constant proportion of all survivors over time. Since long-term survivors face a lower hazard of death, this proportion should in theory increase over time. The same issue applies in column S of the “PFS” worksheet, row 155 down. Can the calculations be revised to account for this?

In response to this question, a revised version of the cost-effectiveness model has been submitted with the calculations updated to capture long-term survivors and non-long-term survivors separately. Separating the subsets of patients into individual columns on the “OS” and “PFS” worksheets allows unweighted hazards to be applied to the respective cohorts, before the proportion of patients in each subset are summed together each cycle to ensure the full population is captured. As expected, this approach does not change the overall OS or PFS extrapolations within the first five years of the modelled time horizon. The updated approach allows the time-

varying nature of the proportion of long-term survivors in the model each cycle after five years to be appropriately considered.

The impact on cost-effectiveness results of updating the model to allow the proportion of long-term survivors to increase over time is low (Table 8), with the ICER decreasing by £2,167 compared with the deterministic base case presented in the company submission.

Table 8: Deterministic cost-effectiveness results (long-term survivor proportion calculations revised)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Current 4L+ care	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,105

Key: 4L+, fourth line or later; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B8. Economic model. In addition to a life year gain in the progression free state, the model also projects a life year gain in progressive disease state for axicabtagene. Please comment on why patients treated initially with axicabtagene should be expected to fare better than those treated initially with the blended comparator following disease progression.

As demonstrated by the ZUMA-5 study, there is an observable difference in the PFS and OS data in the 4L+ FL cohort of patients which shows favourable OS outcomes even following disease progression in patients receiving axi-cel.

In addition, following elicited consultation with clinical experts it was determined that the depth of response and subsequent remission that many patients receiving axi-cel were potentially able to gain from treatment meant that, even following disease progression, their survival expectations and prognosis were arguably better than had they received a conventional chemotherapy-based regimen at 4L+ owing to the fact their disease would likely be starting at a more favourable, less bulky disease state following axi-cel infusion.

B9. Section B.2.12. Please provide information on any plans to submit new data and/or model revisions based on the latest data cut from ZUMA-5.

The company plan to submit an additional 6 months of data from ZUMA-5 (24-month data cut) at the technical engagement stage of the NICE STA process. A revised version of the cost-effectiveness model will be provided, with parametric survival analysis conducted using the 24-month data cut of ZUMA-5 for the progression-free survival and overall survival endpoints, this model version will also include updates undertaken as part of these responses.

Health care resource use and costs

B10. Section B.3.5.1.3. It is stated that "The distribution of subsequent therapies received in both the axi-cel and current 4L+ care arms of the model are therefore assumed equal to the re-weighted distribution of treatments in the comparator arm of the cost-effectiveness model (Table 40)". Given the trend for decreasing progression free survival and overall survival with increasing lines of therapy (Figure 13, document B), please comment on the plausibility of the subsequent treatment costs being as high per progressed patient as they are in the initial 4L+ treatment line. Particularly since the base case 4L+ treatment costs are not capped on progression but allow for continuation after progression.

In the absence of robust data it was assumed that further treatment after progression in both arms was equivalent to current 4L+ care. It is acknowledged this is uncertain, therefore scenario analyses are presented testing the impact on cost-effectiveness results of reducing subsequent treatment acquisition and administration costs. Table 9 presents the percentage reduction in subsequent acquisition and administration costs tested in scenario analysis, the corresponding costs applied in each arm of the model, and the resulting deterministic ICER.

Reducing subsequent treatment costs does not have a large impact on cost-effectiveness results, with the ICER for axi-cel versus current 4L+ care increasing by up to £1,809 when costs are reduced by 50%.

Table 9: Deterministic cost-effectiveness results (reducing subsequent treatment costs)

Percentage cost reduction tested	Subsequent acquisition and administration costs	ICER (axi-cel versus current 4L+ care)
0% (base case)	£55,172	£48,272
-25%	£41,379	£49,177
-50%	£27,586	£50,081
Key: 4L+, fourth line or later; ICER, incremental cost-effectiveness ratio.		

B11. Section B.3.5.2. It is stated that "after 5 years patients who remain alive and progression free are assumed to be long-term survivors and no longer experience resource use requirements". However, the ERGs clinical input suggests in practice these patients would continue to receive some limited monitoring. Please explore the impact of long-term survivors requiring limited ongoing follow-up appointments beyond 5 years in the model.

Scenarios which assume patients who are alive and free of progression after 5 years would require some limited monitoring are presented below.

In NICE TA559 (axi-cel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma), it was assumed that patients remaining in progression-free survival beyond the long-term survivorship timepoint no longer incurred the costs of medical resource. However, in TA677 (KTE-X19 for treating relapsed/refractory mantle cell lymphoma), pre-progression patients surviving for longer than 5 years were assumed to incur costs for regular GP appointments. In TA677, the cost of a GP visit was applied every 6 months based on clinical expert opinion.

Here scenarios are presenting assuming 25%, 50%, and 100% (consistent with TA677) of patients alive and free of progression at 5 years and beyond in the axi-cel arm of the model incur the cost of a GP visit every 6 months.

The cost of a GP visit was taken from on the Personal Social Services Research Unit, Unit Costs of Health and Social Care (PSSRU 2020) and is £39.23 per surgery consultation lasting 9.22 minutes (including direct care staff costs, with qualification costs).

Table 10 presents deterministic ICERs for axi-cel versus current 4L+ care. Assuming that all patients alive and free of progression beyond 5 years in the axi-cel arm receive 6-monthly GP visits does not notably impact cost-effectiveness results (deterministic ICER increases by £49).

Table 10: Deterministic cost-effectiveness results (long-term monitoring scenarios)

Resource frequency	Proportion of patients (of those in PFS at 5 years and beyond)	ICER (axi-cel versus current 4L+ care)
None (company submission)	100%	£48,272
GP visit every 6 months	100%	£48,321
GP visit every 6 months	50%	£48,296
GP visit every 6 months	25%	£48,284

Key: 4L+, fourth line or later; GP, General Practitioners; ICER, incremental cost-effectiveness ratio; N/A, not applicable.

B12. Section B.2.10.6. Concomitant medication. For the [redacted] of patients requiring it, it is noted that IVIG (intravenous immunoglobulin) was assumed to be administered to pre-progression patients for a duration of 12 months. Please provide data on time on IVIG from the ZUMA-5 trial to support this assumption. Please also consider the likely frequency and duration of its use in the blended comparator arm.

As hypogammaglobulinemia (B-cell aplasia) is an adverse event of special interest following CAR-T therapy, it is assumed there is no IVIG use in the current 4L+ care arm of the model.

In the 4L+ mITT cohort of ZUMA-5, [redacted] of the [redacted] patients experienced any treatment-emergent hypogammaglobulinemia, [redacted] of which had Grade 2 ([redacted] patients had Grade ≥ 3). [redacted] patients ([redacted]) received concomitant IVIG therapy, the cost of which was considered in the axi-cel arm of the cost-effectiveness analysis.

A limitation of the ZUMA-5 study is that biomarker analysis was not performed, as the Phase II trial was powered only for ORR; no specific data on immune recovery or duration of IVIG therapy are therefore available. As such, the only available data on IVIG usage from ZUMA-5 is the incidence data as described above.

However, King's data in the UK has implied that only 6% of 53 patients treated with CD19-directed CAR-T therapy required regular IVIG replacement after CAR-T and immunoglobulin remained >4g/L despite B-cell aplasia in most patients.

European guidelines only recommend IVIG replacement for ongoing, recurrent infections, and clinical consensus from UK NHS Consultants deemed that although hypogammaglobulinemia is common in 4L+ patients, few would actually require IVIG replacement and the same would be expected after CAR-T therapy (whereby patients are already managed well with prophylactic antibiotics). Furthermore, many patients at 4L+ will have received multiple rituximab-containing regimens, so the introduction of CAR-T would not be expected to increase the requirement or prolongation of subsequent IVIG replacement therapy.

The assumption that IVIG is administered to pre-progression patients for a duration of 12 months is aligned with the consensus for CAR-T therapies in other advanced lymphoma indications in NICE TA677 and TA599. Furthermore, the company submission here considers a more conservative approach to IVIG therapy wastage than that presented in TA677, where it was noted that due to an awareness in clinical practice of the cost of IVIG therapy wastage is likely to be minimized.

Finally, consistent with the known CAR-T peak expansion profile and the AUC of axi-cel, most patients with assessable samples ([redacted]) in the ZUMA-5 study had low levels of detectable CAR gene-marked cells at 12 months after infusion, supporting the hypothesis that CAR persistence beyond 12 months may have limited impact on the recovery of immunoglobulin levels following initial B-cell aplasia. Thus, most patients who require IVIG replacement, would likely do so within the first 12 months post-infusion.

Section C: Textual clarification and additional points

References

C1. If possible, please send the reference package as a RIS file.

As requested, the reference pack has now been sent as a RIS file.

Appendix

Please find below the revised Table 7 (baseline characteristics) to support our responses for questions A4–A9.

Table 11: Baseline characteristics of FL patients in ZUMA-5

Characteristics	FL patients with two or more lines of prior therapy			FL patients with three or more lines of prior therapy		
	FAS (n = 127)	SAS (n = 124)	IAS (n = 86)	FAS (n = 80)	SAS (n = 78)	IAS (n = 60)
Median age, years (min-max range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aged ≥65 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aged <65 years, n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female, n(%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FL histological category at trial entry, n (%)						
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3a	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FLIPI total score, n (%)						
Low risk (0–1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate risk (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
High risk (3–5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapsed/refractory disease[a], n (%)						
Relapsed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Double-refractory subgroup[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median no. of prior therapies (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	FL patients with two or more lines of prior therapy			FL patients with three or more lines of prior therapy		
	FAS (n = 127)	SAS (n = 124)	IAS (n = 86)	FAS (n = 80)	SAS (n = 78)	IAS (n = 60)
Number of prior lines of therapy, n (%)						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior auto-SCT, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior PI3K inhibitor, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-CD20 single agent, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior alkylating single agent, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior anti-CD20 + alkylating agent, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to relapse from first therapy[b], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior lenalidomide, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone marrow assessment at baseline, n (%)[c]						
Lymphoma present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphoma present but not FL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphoma not present	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: auto-SCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; FL, follicular lymphoma; IAS, inferential analysis set; PI3K, phosphoinositide 3-kinase

Notes: [a] Patients with FL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Patients with FL who progressed >6 months of completion of the most recent prior treatment are defined as relapsed. Patients with FL who progressed within 6 months of completion each of the first 2 lines of prior treatment are defined as double-refractory. [b]Time to relapse is defined as the time from initiation of the first line anti-CD20-chemotherapy combination therapy to progression. Number of subjects with time to relapse is based on those who had progressed with date of progression. Percentages are based on the number of subjects who ever received anti-CD20-chemotherapy combination therapy. [c] bone marrow assessment at baseline for lymphoma presence is based on investigator reported Lugano bone marrow assessment/bone marrow assessment using aspirate or core biopsy at screening. If these are not available, lymphoma presence is based on diagnosis history of bone marrow involvement.

Characteristics	FL patients with two or more lines of prior therapy			FL patients with three or more lines of prior therapy		
	FAS (n = 127)	SAS (n = 124)	IAS (n = 86)	FAS (n = 80)	SAS (n = 78)	IAS (n = 60)
Source: ZUMA-5 CSR 18-Month Addendum.						

NICE National Institute for Health and Care Excellence

Patient organisation submission

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

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	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. Lymphoma Action is not a membership organisation. We are funded from a variety of sources predominantly fundraising activity with some limited sponsorship and commercial activity. 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. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and a financial cap of £50,000 of support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees. The policy and approach ensures that under no circumstances will these companies influence our strategic direction, activities or the content of the information we provide to people affected by lymphoma. https://lymphoma-action.org.uk/about-us-how-we-work-policies-and-terms-use/working-healthcare-and-pharmaceutical-companies

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.] If so, please state the name of manufacturer, amount, and purpose of funding.	• Kite/Gilead: £1,000 (support for information and education activities) • Bristol-Myers Squibb Pharmaceuticals: £21,000 (support for information and education activities) • Janssen-Cilag: £8,000 (support for information and education activities) • Roche Products: £22,000 (support for information and education activities)
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	We have used information from UK-respondents to the Lymphoma Coalition's 2020 Global Patient Survey, which seeks to understand patient experience in lymphomas as well as the impact of treatment and care. A total of 679 people from the UK responded to the patient survey, 54% of whom had a low-grade non-Hodgkin lymphoma (follicular lymphoma, marginal zone/MALT lymphoma or lymphoplasmacytic lymphoma). An additional 64 people responded to the caregiver survey, 43% of whom cared for a person with a low-grade non-Hodgkin lymphoma.

carers to include in your submission?	We also sent a survey to our network of patients and carers asking about specifically about their experience of current treatment for relapsed and refractory low-grade non-Hodgkin lymphomas and their opinions on axicabtagene ciloleucel, with particular emphasis on quality of life. We received two responses from patients with relapsed or refractory low-grade non-Hodgkin lymphomas who had had at least two previous treatments, which we have used in this submission. We also included input from a patient who was treated with axicabtagene ciloleucel for a different indication (DLBCL), and information based on our prior experience with patients with low-grade non-Hodgkin lymphomas.
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?	Low-grade non-Hodgkin lymphoma is generally treated with the intention of keeping it under control, rather than curing it. People live with the condition for many years. Some people have few symptoms but others might experience a wide variety of signs and symptoms, including enlarged lymph nodes, weight loss, fevers, night sweats, constant itching or fatigue. If the lymphoma affects the bone marrow, people can develop neutropenia, anaemia and thrombocytopenia. In some cases, low-grade lymphoma can transform into a high-grade lymphoma, which can have serious symptoms requiring urgent treatment. Both the lymphoma and its treatment can significantly affect quality of life. Fatigue is a particularly common – and disabling – symptom reported by the majority of patients. Around 8 in 10 lymphoma patients rate it as the symptom that affects them the most, and stops them doing things that other people their age can do. Patients find it affects all aspects of their life: work, social activities, mood, relationships, exercise and ability to focus or concentrate. Patients report that they are exhausted, tire easily and are unable to do things they used to. They have to manage time very carefully, refusing things they would otherwise have done and resting frequently. People also report struggling with concentration and memory. This affects their working life, social life and ability to do the things they enjoy. One patient said, “I’ve had to give up most of my active hobbies - at my worst I was only able to concentrate / plan / carry out a daytime activity of 2 hours - then I would be asleep the rest of the day. And night.” Many people need to take time off work or studies, or even stop work completely. Over 4 in 10 people with lymphoma report being unable to work or changing their work pattern because of their illness. This can be very difficult financially. Some people who have previously been employed find it frustrating to rely on

	government benefits. One man, who had had two courses of chemotherapy and radiotherapy for low-grade non-Hodgkin lymphoma, told us, “I had to take phased retirement from lecturing (a job I loved) because I no longer had the capacity to prepare and deliver classes to the high standard I’ve always had. So this obviously affected the value of my eventual retirement pension.” The uncertainty of relapse and the need for repeated courses of treatment is also physically and psychologically challenging for patients. Other psychological effects of low-grade lymphoma include isolation, depression, anxiety and loss of self esteem. Many patients find the possibility of relapse frightening. People find it exhausting living with the constant fear. Many examine themselves frequently for signs of relapse, or find themselves thinking about dying. One said, “I was diagnosed at 55, and my wife and I didn’t expect me to make 60.” Caring for someone with low-grade lymphoma is challenging emotionally, practically and financially. Carers often provide transport to-and-from hospital appointments and treatment sessions, requiring time off work. They also provide emotional support, whilst trying to deal with an emotionally difficult situation themselves. Most also take on more chores and household tasks. Over 3 in 4 caregivers report feeling anxious and physically and emotionally worn out. Some carers and family members report needing counselling. Others feel that it puts a serious strain on relationships. Around 3 in 10 patients with lymphoma feel that their illness creates problems with partners, close friends or relatives. A patient who had had three previous courses of treatment for low-grade non-Hodgkin lymphoma told us, “Stays in hospital… put real stress on my wife.”
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	One of the main concerns about current treatments is the lack of a durable response and the need for repeated courses of treatment over the years. Lymphoma patients rate ‘a cure’ as the most important outcome of treatment, but this is rarely the primary aim of treatments for low-grade lymphomas. People worry that there will not be effective treatment available if or when they experience relapse. They are also anxious about having to go through the ordeal of treatment again. Although patients are generally grateful for the treatment they have had, many report significant side effects that have impacted their day-to-day life.

	Fatigue is the most common side effect report by patients treated for lymphoma. It is also the side effect that patients feel is the most difficult to live with. As described in section 6, fatigue can have a significant impact on quality of life. Hair loss, nausea and vomiting, peripheral neuropathy, difficulty concentrating and trouble sleeping are also very common, affecting around half of people treated for lymphoma. Infections are also a common, which can lead to serious complications and hospital stays. Fear of infections, and measures to reduce the risk of developing an infection, can have a massive impact on day-to-day life, particularly during the current pandemic. Just over half of patients treated for lymphoma feel that their side effects have negatively impacted the everyday activities that people their age can do (57%) and their social life (51%). One man, who had had courses of R-CVP, chlorambucil and radiotherapy, said, “The impact of the various treatments cannot be understated. Side effects of nausea, depression, chemo-brain as well as long-term, ever-present exhaustion.” Many people find going through treatment mentally as well as physically challenging.
8. Is there an unmet need for patients with this condition?	There is a clear unmet need for effective treatments that are ideally curative – or at least, provide durable remissions – with fewer side effects and late effects than current options.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The availability of effective treatments for people who have experienced relapse, particularly those who have already had multiple previous courses of treatment, is crucial. Treatments that provide durable remissions, or ideally a cure, are seen as particularly important. The top three features that lymphoma patients feel are most important in a new treatment are improved survival, achieving remission and improved quality of life. The main advantage of axicabtagene ciloleucel is the potential to achieve complete remission of lymphoma, even in patients who have relapsed after multiple previous lines of treatment. This is likely to have a significant impact on quality of life for both the patient and their family and carers. Clinical data so

	far suggests that responses to treatment are durable. Axicabtagene ciloleucel is a potentially curative treatment option. A patient who was treated with axicabtagene ciloleucel for a different type of lymphoma (relapsed DLBCL) said, “The advantages were simply that previous therapies hadn’t worked, yet CAR T-cell therapy did work! My quality of life has been immeasurably improved. CAR T-cell therapy has been a lifesaver for myself.”
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, patients are concerned about the possibility of side effects, which can be serious and significant. However, for patients who otherwise have limited treatment options, these disadvantages may be outweighed by the potential benefits. One patient commented, “It is clearly a demanding form of treatment that can have serious side effects... I would prefer to try other treatments first. Others may benefit – all lymphoma cases are different.” A patient who was treated with axicabtagene ciloleucel for relapsed DLBCL experienced mild-to-moderate cytokine release syndrome, nausea and vomiting, diarrhoea, and profound loss of energy lasting a few weeks. However, he noted that these effects were relatively short-lived compared to the benefit of having a potentially life-saving treatment: “Any disadvantages, such as feeling unwell during the initial stages of the therapy when the cells have been re-infused is a relatively short time (it might not seem so whilst going through it!... Any side effects I have experienced during my treatment… have far been outweighed by the benefit I am experiencing.” The treatment is administered as an inpatient and requires both prolonged hospital admission and that the patient and a carer stay within travelling distance of the treatment centre for several weeks. Some people may have practical concerns over transport, time off work, childcare issues, and travel and parking fees.

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.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	One patient was concerned about the 'postcode lottery phenomenon' if access to treatment varies in different nations of the UK. Another noted that there could be potential equality issues, depending on the specific criteria and selection process to decide which patients are suitable for CAR T-cell therapy.

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

Key messages

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

- Low-grade non-Hodgkin lymphoma is currently considered incurable. Patients live with the disease and its treatment for many years. It has a significant impact on quality of life for both patients and their carers, affecting work and social activities to relationships and mental health.
- Current treatment options may not produce durable responses. Patients typically require repeated courses of treatment and are keen for treatments that give them longer remissions. Patients report that the side effects of current treatments have a significant impact on their day-to-day lives.
- There is an unmet need for an effective treatment that provides durable remissions, or potentially even cure.
- Axicabtagene ciloleucel has the potential to provide complete and durable remissions in patients who have relapsed after multiple previous courses of treatment. As such, it is an important treatment that has the potential to improve outcomes for people who may have limited treatment options left to them.

Thank you for your time.

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

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Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

Produced by Aberdeen HTA Group

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No competing interests to disclose.

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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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Contribution of authors

Moira Cruickshank and Clare Robertson summarised and critiqued the clinical effectiveness evidence; Thenmalar Vadiveloo and Lorna Aucott checked and critiqued the statistical analyses presented in the company submission; Graham Scotland was the health economics lead for the appraisal and with assistance from Corinne Booth and Charlotte Kennedy reviewed and critiqued the cost-effectiveness evidence and the economic model; Paul Manson checked and critiqued the company's search strategies; Gavin Preston provided clinical guidance and comments on the draft report. Miriam Brazzelli was the clinical effectiveness lead for the appraisal and coordinated all its aspects. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

4L+	Fourth-line plus (three or more lines of prior therapy)
AE	Adverse event
BOR	Best overall response
CAR T-cell	Chimeric antigen receptor T-cell
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
DOR	Duration of response
ERG	Evidence review group
FAS	Full analysis set
FL	Follicular lymphoma
HRQoL	health-related quality of life
IAS	Inferential analysis set
iNHL	Indolent non-Hodgkin lymphoma
mITT	Modified intent-to-treat
MZL	marginal zone lymphoma
NHL	Non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PFS	Progression free survival
POD24	Progression of disease within two years of receiving front-line chemoimmunotherapy
PR	Partial response
r/r	Relapsed or refractory
RCT	Randomised controlled trial
SAS	Safety analysis set
SLR	Systematic literature review
TEAE	Treatment-emergent adverse event

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 submitted evidence and ERG's key issues

The focus of the submission received from Kite is axicabtagene ciloleucel (referred to throughout as axi-cel) for treating follicular lymphoma (FL), which is the most common subtype of indolent non-Hodgkin lymphoma, and specifically relapsed or refractory FL.

The clinical evidence submitted by the company consists of an on-going, single-arm, multicentre, open-label phase II trial: ZUMA-5 in which most FL patients had received at least three prior lines of therapy. The overall response rate (ORR; defined as the incidence of complete response [CR] or partial response [PR]) was [redacted] for the inferential analysis set (IAS). CR was achieved by [redacted] of participants. The median duration of response (DOR) was not reached in all responders: [redacted]. The median follow-up for DOR was [redacted]. [redacted] responders had an ongoing response at censoring. At the time of analysis, [redacted] of participants were alive and progression-free. The median PFS [redacted] The median follow-up time for PFS was [redacted]. The median OS was not reached [redacted] The median follow-up time for OS was [redacted] patients had died at the time of analysis. The clinical outcomes used in the economic model are progression-free survival (PFS), overall survival (OS) and adverse event

incidence. The company's literature review identified several studies providing evidence in relevant contexts but did not use any of this evidence in the submission. It is unclear to the ERG if the company's strategy was appropriate as reasons for not including each individual study were not reported by the company, despite being requested at clarification. Instead, the company presented comparative evidence from an external cohort study, SCHOLAR-5. Although there were differences in the distribution of ECOG score between ZUMA 5 and SCHOLAR-5, based on the opinion of their clinical expert, the ERG accepts SCHOLAR-5 as the comparator given the lack of randomised evidence.

The company present a de Novo economic model to determine the cost-effectiveness of axi-cel versus therapies currently available in the NHS in England for [redacted], referred to as the r/r FL 4L+ population throughout. The model takes the form of a partitioned survival model, with efficacy inputs for axi-cel derived from parametric survival analysis of OS and PFS data for the relevant subgroup of ZUMA-5. Efficacy inputs for current 4L+ care are derived from parametric survival analysis of propensity score weighted PFS and OS data from the SCHOLAR-5 study. The company assume that a proportion of patients treated with axi-cel can be considered long-term survivors from a future time point, and thereafter experience zero risk of progression and overall survival in line with the SMR adjusted general population mortality. Non-long-term survivors continue to follow the hazard of progression and death based on the curves fitted to the ZUMA-5 data. The company base case assumes 25% of axi-cel treated patients are long term survivors and applies these extrapolation assumptions from 5 years. Costs and utility values are derived from various sources.

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

Table 1 Summary of key issues identified by the ERG

Issues	Summary of issue	Report sections
Issue 1	Differences between the ZUMA-5 and SCHOLAR-5 cohorts in term of prior treatment received by SCHOLAR-5 patients	Section 3.3 and 3.6
Issue 2	The proportion of patients who can be considered long term survivors following treatment with axi-cel	Section 4.2.6
Issue 3	The PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	Section 4.2.6
Issue 4	Health state utility values applied in the model	Section 4.2.7
Issue 5	The capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Section 4.2.8

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are the modelling of OS for non-long-term survivors, the modelling time on treatment for current 4L+ therapies and subsequent treatment costs, and the source of utility values applied.

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:

- Delaying/preventing progression of disease and increasing overall survival compared to current 4L+ care for patients with r/r FL.

Overall, the technology is modelled to affect costs by:

- Having higher acquisition costs compared to other available treatments
- Delaying or preventing progression of disease which incurs further subsequent treatment costs
- A higher modelled rate of adverse events compared to current care

- Extending expected survival time in the pre- and post-progression health states, which increases health state monitoring costs.

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

- The size of the overall survival benefit, which is determined by:
  - the parametric curve selection for OS in the technology and comparator arm of the model
  - the assumed proportion of patients that can be considered long-term survivors following treatment with axi-cel.
  - The OS extrapolation assumptions applied to axi-cel long-term survivors and non-long-term survivors
- The capping of time on treatment for current comparator therapies on overall survival rather than progression free survival. This assumption also affects the subsequent treatment costs applied in 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 no major issues were identified by the ERG. The CS addresses a more specific population than that specified in the NICE final scope and focuses on follicular lymphoma (FL), a subtype of indolent non-Hodgkin lymphoma, and specifically on FL patients who have received three or more prior lines of therapy (4L+ patients). The ERG in consultation with their clinical expert considers the company's description of the current treatment pathway and treatment options available for people with relapsed or refractory FL (r/r FL) 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 source of clinical effectiveness evidence for axi-cel consists of the ongoing ZUMA-5., single-arm trial. The sample sizes of the analysis cohorts are generally small.

- Data from ZUMA-5 are immature with [redacted] within the current 18-month follow-up analysis.

- Some patients in SCHOLAR-5 received treatments that are not aligned with clinical practice in England, including idelalisib, which is accepted for use within NHS Scotland for the treatment of adults with FL refractory to 2 prior lines of therapy.

Issue 1 Comparability of ZUMA-5 with SCHOLAR-5 data

Report section	Section 3.3 and 3.6
Description of issue and why the ERG has identified it as important	Differences between the ZUMA-5 and SCHOLAR-5 cohorts in terms of prior treatment received by SCHOLAR-5 patients, and generalisability of SCHOLAR-5 to the NHS in England.
What alternative approach has the ERG suggested?	The ERG is not able to suggest an alternative approach, but the lack of randomised evidence leads to uncertainty in the magnitude of progression-free and overall survival benefit that can be expected with axi-cel versus currently available 4L+ treatments. There is also some uncertainty about how applicable the SCHOLAR-5 data are to the NHS in England, as a significant proportion of patients received treatments not routinely available or used in the NHS. However, on balance, the ERG believes this latter issue may bias against axi-cel.
What is the expected effect on the cost-effectiveness estimates?	Uncertainty relating to the magnitude of PFS and OS benefits, driven by the lack of randomised evidence, translates into uncertainty in the economic case.
What additional evidence or analyses might help to resolve this key issue?	The ERG judges this to be unresolvable uncertainty given the available evidence to inform comparative effectiveness.

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

The ERG identifies the following key issues and uncertainties in the company's economic case:

Issue 2 The proportion of patients who can be considered long term survivors following treatment with axi-cel

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	Whilst plausible based on previous experience with CAR T-Cell therapies in haematological cancer, the company's long-term survivor assumptions remain uncertain given the immaturity of the PFS and OS data from ZUMA-5. Whilst the ERG accept that it is plausible to expect a proportion of axi-cel treated patients to achieve long-term survivor status, there are no data available to estimate the proportion to which this assumption should apply. There is further uncertainty around the mortality hazard that long-term survivors might be able to achieve relative to the age and sex-matched general population. A standardised mortality ratio 1.09 is applied in the company base case.
What alternative approach has the ERG suggested?	The company acknowledge the current uncertainties and have conducted a sensitivity analysis to explore the impact of uncertainty around this issue. The ERG accept the company's base case long-term survivor proportion and timing of implementation (5 years) in its own base case but believe that scenario analyses around these inputs should be considered carefully by the committee.
What is the expected effect on the cost-effectiveness estimates?	Reducing the long-term survivor proportion has an upward impact on the ICER substantially, as well as applying it from a later timepoint. Increasing the proportion to which it applies, or applying it from an earlier time point, reduces the ICER.
What additional evidence or analyses might help to resolve this key issue?	The company have indicated that they will update their PFS and OS model inputs using an updated data cut from ZUMA-5 during technical engagement. This may help to better inform the shape of the time to event distributions. However, as the additional follow-up time will be limited, it is likely that the long-term survivor proportion will remain a key area of uncertainty. The company have provided the functionality in their model to address this.

Issue 3 The PFS and OS extrapolation assumptions for axi-cel non-long-term survivors

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	Related to issue 2 above, the company fit parametric curves to the PFS and OS data of the overall subgroup of ZUMA-5 that matches the proposed positioning. However, they assume 25% of these patients achieve a reduced hazard of mortality in line with SMR adjusted general population mortality. From 5 years they use the fitted PFS and OS curves to model the hazard of progression and death only for non-long-term survivors. Since the curves were fitted for the whole patient population, which we assume includes patients achieving long term survivorship, the ERG believes this approach may underestimate the hazard of progression and death for non-long-term survivors. Adding to the uncertainty, the proportion of the surviving model cohort that are considered long-term survivors is fixed over time in the model. In reality, it should be increasing as non-long-term survivors face a higher risk of death. These issues lead to uncertainty with respect to the extrapolated survival gains in the progression-free and progressed model health states.
What alternative approach has the ERG suggested?	The ERG requested scenarios to explore these uncertainties at the clarification stage, which the company provided by applying SMR adjustments (of 1.09 and 1.2) to inflate the hazards of death and progression in non-long-term survivors from 5 years onwards. The ERG has extended the range of SMR adjustments applied in chapter 6 of this report. The company also provided an adjustment to allow the proportional split of the surviving cohort, between long-term and non-long-term survivors, to update over time.
What is the expected effect on the cost-effectiveness estimates?	Inflating the risk of progression and death in non-long-term survivors results in increases in the ICER. Allowing the proportion of survivors who are long-term/non-long-term survivors to update over time, in line with the separate hazards applied, produces reductions in the ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG does not believe it will be possible to resolve this issue through additional evidence or analysis. However, it remains an area of uncertainty that should be considered.

Issue 4 Health state utility values

Report section	4.2.7 Health-related quality of life
Description of issue and why the ERG has identified it as important	There is a lack of robust utility data available in the relevant patient population who would be eligible to receive axi-cel in practice. A literature search identified some potentially relevant studies, but instead, the company used a similar approach to that accepted in TA627 based on utility data collected in the AUGMENT study with values capped at population norms. The ERG is concerned that as the majority of patients in the AUGMENT study are at an earlier stage in the disease pathway, they would be expected to have a higher quality of life than patients receiving treatment at fourth line onward.
What alternative approach has the ERG suggested?	Alternative utility values were identified in a UK study reported by Wild et al., where EQ-5D data were collected in r/r FL patients. While there are also limitations with this study, the utility values are lower than those in AUGMENT and may better reflect the quality of life of patients at this stage of the treatment pathway. These values have also been used in other relevant NICE appraisals of FL treatments (TA604)
What is the expected effect on the cost-effectiveness estimates?	Wild et al. utility values were used in the sensitivity analysis, and this had a small upward impact on the ICER. Using these values increases face validity but does not resolve the uncertainty associated with a lack of robust quality of life data in this patient group.
What additional evidence or analyses might help to resolve this key issue?	The ERG agrees with the company that this remains a key source of uncertainty in the analysis due to the absence of robust data available. A range of alternative utility values, from other sources, were used in sensitivity analysis, all with minimal impact on the results. Further clinical validation of the Wild et al utility values would be useful.

Issue 5 The capping of time on treatment for comparator therapies, and modelling subsequent treatment costs

Report section	Section 4.2.8
Description of issue and why the ERG has identified it as important	For therapies included in the basket of current 4L+ care, the company utilise median numbers of treatment cycles reported in relevant summaries of product characteristics and then fit exponential distributions to estimate time on comparator treatments. However, the time on treatment curves are not necessarily consistent with the derived PFS and OS curves for the comparator arm in this indication (r/r/ FL at 4L+), and in their base case the company cap time on treatment (ToT) so it can't exceed overall survival. This assumes that treatment can continue beyond progression. Furthermore, the company then recycle the mean 4L+ treatment acquisition and administration costs derived for the comparator arm and apply this as a one-off cost of subsequent treatment to the estimated proportion of the cohort that progresses in each cycle of the model. This method would appear to overestimate comparator therapy costs which, based on clinical advice to the ERG, would be stopped upon progression. It may also overestimate subsequent treatment costs. A further uncertainty relates to the assumption that subsequent treatment costs, per progressed patient, are assumed equal between the treatment arms. There may be potential for subsequent treatment costs to be higher in the progressed disease state for those treated with axi-cel, as these patients may have more treatment options left available and may respond for longer.
What alternative approach has the ERG suggested?	In their original submission, the company also provided a scenario analysis whereby they capped time on treatment for comparator therapies to PFS rather than OS. The ERG is of the opinion that the latter assumption is more appropriate based on its clinical advice. It is also more consistent with the assumption that all patients who progress receive subsequent treatment costs in line with the modelled 4L+ comparator costs. The ERG has also assessed the impact of reducing subsequent treatment costs in the current 4L+ care arm relative to those applied in the axi-cel arm.
What is the expected effect on the cost-effectiveness estimates?	The change results in modest increases in the ICER.
What additional evidence or analyses might help to resolve this key issue?	This remains an area of uncertainty for which it is difficult to identify alternative data. The company note that ToT data was not reported for SCHOLAR-5. If such data could be obtained, it could help to resolve the above uncertainty. Alternatively, further clinical opinion could be sought on the suitability of using PFS rather than OS to cap time on treatment for current 4L+ therapies used in NHS England.

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

The company believe the axi-cel may be suitable for consideration on the cancer drug fund. They also argue that it will be used as an end-of-life medicine in this indication. However, both median overall survival and modelled life expectancy in the comparator arm are [redacted] (see chapter 7).

1.7 Summary of ERG's preferred assumptions and resulting ICER

Given the uncertainties outline above, and other issues raised in the report, the ERG prefers to:

1) Apply the company's scenario switch which allows the proportional split of the surviving cohort, between long-term survivors and non-long-term survivors, to be updated on a cycle-by-cycle basis from the time that the long-term survivor assumptions are applied (5 years).
2) Inflate the hazard of progression and death by 1.2 in non-long-term survivors from the time the long-term survivor assumption is applied (5 years).
3) Cap overall survival of non-long-term survivors at SMR adjusted general population mortality, to ensure the risk of death in non-long-term survivors is never lower than that in long-term survivors.
4) Cap the current 4L+ time on treatment to the selected PFS curve for current 4L+ care, rather than the selected OS curve.
5) Apply alternative Wild et al./Pettengell et al. utility values for progression-free and progressive disease states that are available from the literature.
6) Retain the preferred progression-free health state utility for long-term survivors from 5 years, rather than assuming general population utility.

Further scenario analysis around the ERG base case explores the impact of: alternative PFS and OS curve selections; alternative adjustments to the risks of progression or death in non-long-term survivors; relative reductions in the costs of subsequent therapy following progression on current 4L+ care; and changes to the long-term survivor proportion (see section 6.3).

Table 2 Summary of ERG's preferred assumptions and ICER

Preferred assumption	Incremental cost	Incremental QALY	ICER £/QALY	Change from company base case
Company base-case	[redacted]	[redacted]	£48,272	NA
1. Time dependent updating of long-term survivor proportion from 5 years	[redacted]	[redacted]	£46,105	-£2,168
2. Increase progression and mortality risks by 20% after 5 years non-long-term survivors	[redacted]	[redacted]	£52,326	£4,054
3. Cap overall survival of non-long-term survivors at SMR adjusted general population mortality	[redacted]	[redacted]	£48,354	£82
4. Capping the current 4L+ time on treatment to the selected PFS curve for current 4L+ care	[redacted]	[redacted]	£54,163	£5,891
5. Apply Wild et al/Pettengell et al. utility values for progression free and progressive disease states.	[redacted]	[redacted]	£49,296	£1,024
6. Retain PF health state utility from Wilde et al. for long-term survivors (only relevant with 5 above)	[redacted]	[redacted]	£49,993	£1,721
Combined changes (ERG base case)	[redacted]	[redacted]	£56,332	£8,060

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Kite is relapsed or refractory low-grade non-Hodgkin lymphoma in adults. 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 lymphoma (NHL) as diverse group of cancers that originate in the lymphatic system. The CS focuses on follicular lymphoma (FL) as the most common type of indolent (slow-growing) NHL (iNHL).[1] FL mainly affects people aged over 60 years and, while, it is associated with longer survival times, it is less likely to be cured than faster-growing lymphomas and is associated with reduced life expectancy and impaired health-related quality of life (HRQoL) compared to the general population.[2]

FL has an annual incidence of approximately 3.3 per 100,000 people, and it is estimated that around 2,200 people are diagnosed with FL each year in the UK.[3] The 10-year prevalence is 24.7 per 100,000 people, and it is estimated that 16,220 people in the UK will have been diagnosed with FL during the last 10 years.[3] The most common physical symptom of FL is a painless swelling in the neck, armpit, or groin, caused by enlarged lymph nodes.[4] FL is also associated with 'B-symptoms' such as night sweats, erratic fever, weight loss, and unexplained itching.[4] Patients with FL presenting with multiple sites of lymphadenopathy can endure restricted movement, disfigurement, pain, and bone marrow disease that can result in anaemia, leukopenia, and thrombocytopenia.[5, 6] FL is also associated with poorer mental health, with patients experiencing depression and stress, as well as the emotional upset of living with a chronic disease that is incurable and will progress.[7-9] HRQoL is further affected by treatment toxicity effects, and HRQoL is likely to deteriorate with each treatment relapse. Patients with relapsed FL are more likely to experience lower physical, emotional, functional, and social wellbeing HRQoL scores and higher levels of anxiety, depression and activity impairment levels compared with disease-free patients.[5, 10] The burden of illness in patients

with three or more lines of systemic therapy is, therefore, expected to be particularly high. FL is also associated with a high carer burden. In a Canadian cross-sectional cohort of patients with iNHL, including FL, most of the care (74%) was unpaid assistance from a partner or spouse, relative or friend.[11] Carers in the study provided a mean of 9.8 (SD 13.4) days of care in the 30 days prior to data collection and missed a mean of 11.3 (SD 16.2) days of work because of the care they provided.

Treatment decisions for FL are based on several factors, including the stage and grade of the disease, and risk categorisation based on demographic and basic disease characteristics. The company provides a summary of the classifications systems for FL in Table 3, document B of the CS and this is reproduced by the ERG as Table 3.

Table 3 Classification systems for follicular lymphoma

<table>
<tr><th>WHO/REAL</th><th>Cotswolds modified Ann Arbor</th><th>FLIPI score</th></tr>
<tr><td rowspan="2">Grade 1: 0–5 centroblasts
Grade 2: 6–15 centroblasts
Grade 3: >15 centroblasts

Grade 3B: absence of centrocytes</td><td rowspan="2">Stage I: single lymph node group or organ
Stage II: multiple lymph node groups/organ on same side of diaphragm
Stage III: multiple lymph node groups/organ on both sides of diaphragm
Stage IV: bone marrow or distant organ involvement.
Stage X: bulky disease with nodal mass >10 cm
Stage E: extra-nodal extension or single isolated site of extra-nodal disease
Stage A/B: absence or presence of symptoms – B-symptoms include weight loss >10%, fever, drenching night sweats</td><td>Factors (1 point for each variable present):
• Age >60 years
• Ann Arbor Stage III–IV
• Haemoglobin level <12 g/dl
• LDH level >ULN
• ≥4 nodal sites of disease</td></tr>
<tr><td>Risk category (factors):
• Low (0–1)
• Intermediate (2)
• High (3–5)</td></tr>
<tr><td colspan="3">Key: FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; REAL, Revised European-American Lymphoma; ULN, upper limit of normal; WHO, World Health Organization.
Source: Hernandez-Ilizaliturri 2020.[12]</td></tr>
</table>

The aim of treatment is usually to keep the disease in remission for as long as possible.[13] Remission may last for several years, but approximately 10-20% of FL patients will experience multiple relapses. The time spent in remission usually shortens with each successive relapse as the disease becomes more resistant to treatment (known as treatment refractoriness), thus reducing the patient's overall lifespan. High-risk sub-populations include patients who are chemoimmunotherapy resistant and fail to achieve a response within six months of completing initial chemoimmunotherapy and patients who have double-refractory

disease (patients who are refractory to the first two lines of therapy, including both an alkylating agent and an anti-CD20 monoclonal antibody). People who experience progression of disease within two years of receiving front-line chemoimmunotherapy (defined as 'POD24') have a particularly poor prognosis, with only a 50% overall survival (OS) estimate at five years, compared with 90% OS estimate at five years for people without POD24.[14-16] Around 10% of people diagnosed with FL in the UK will receive four or more lines of therapy. This is approximately 220 patients, around 198 of whom will receive their treatment in England or Wales.[10] The survival prognosis of patients with relapsed or refractory FL who have had ≥4 lines of therapy is generally poor.

While there are several guidelines for the treatment of symptomatic advanced-stage FL, there is no consensus on treatment or standard of care for patients beyond the third line of treatment.[17-22] These patients typically follow an aggressive, chemotherapy-resistant disease course, with poor prognosis. By the time patients have received three or more lines of prior therapy (4L+), patients will usually have received multiple rituximab-based regimens and are, therefore, expected to have suboptimal response to further rituximab-based treatment. In the absence of an established standard of care, current 4L+ therapy consists of recycling earlier-line treatment options or resorting to generic haemato-oncology or experimental/compassionate use treatments. Treatment decisions are made on a case-by-case basis, considering factors such as patient fitness, treatment goals, response, and durability of response to prior therapy.

The proposed place of axi-cel in the treatment pathway is presented in Document B, Figure 3 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 August 2021. The company clarified that eligibility for axi-cel is not expected to differ depending on the stage of disease, and will not differ, irrespective of the route the patient has taken to reach 4L/4L+ treatment, where the treatment goal is to achieve sustained clinical remission. 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.

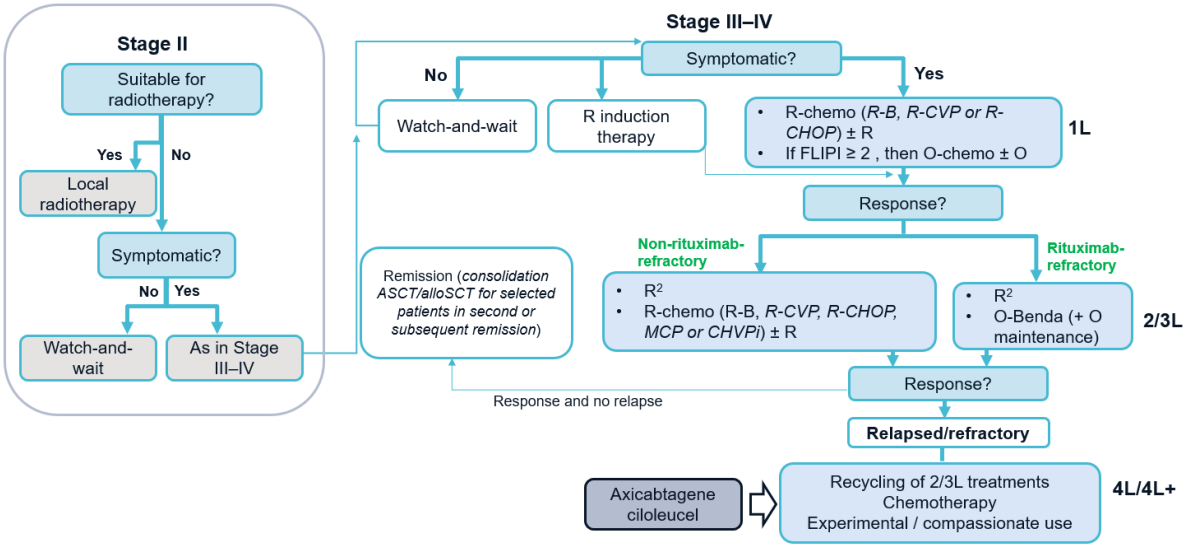

Figure 1 Clinical care pathway for patients with follicular lymphoma and proposed axi-cel positioning

Key: 1L, first-line; 2L, second-line; 4L, fourth-line; alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplant; Benda, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; CHVPi, cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α; CVP, cyclophosphamide, vincristine and prednisolone; FLIPI, Follicular Lymphoma International Prognostic Index; MCP, mitoxantrone, chlorambucil and prednisolone; NICE, National Institute for Health and Care Excellence; O, obinutuzumab; R, rituximab; R-B, rituximab with bendamustine; R^2, lenalidomide with rituximab.
Source: NICE Pathways – Treating follicular lymphoma[23]

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 4 below. A critique of adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 4 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 comment
Population	Adults with relapsed or refractory non-Hodgkin lymphoma	[redacted]	The anticipated marketing authorisation for axicabtagene ciloleucel is for the treatment of '[redacted] As such, this submission is focused on FL, a subtype of indolent non-Hodgkin lymphoma, and specifically on FL patients who have received three or more prior lines of therapy (4L+ patients)	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. A FL variation was submitted to the EMA on 23 July 2021. CHMP opinion is expected in April 2022. The application for GB filing will be submitted in April 2022 for a marketing authorisation extension of axi-cel (Yescarta) to [redacted] The anticipated date of marketing authorisation for this indication is [redacted]

Comparator(s)	• Rituximab monotherapy • Rituximab in combination with chemotherapy • Obinutuzumab with bendamustine • Lenalidomide with rituximab • Clinical management	• Rituximab in combination with chemotherapy • Obinutuzumab with bendamustine • Lenalidomide with rituximab • Clinical management without axicabtagene ciloleucel including chemotherapy (such as cyclophosphamide, fludarabine, bendamustine or chlorambucil)	Rituximab monotherapy is only recommended as an option for the treatment of r/r FL when all alternative treatments have been exhausted (that is, if there is resistance to or intolerance of chemotherapy). If it was being considered for use in patients with r/r FL after three or more lines of systemic therapy, it would be reserved for patients not fit enough to receive intensive active treatment as is the case for best supportive care, thereby constituting a cohort of patients widely considered not suitable or appropriate for consideration of CAR T-cell therapy. Indeed, clinical experts note that by the time patients reach the 4L+ treatment setting, they will have received rituximab monotherapy multiple times and, thereby, additional rituximab monotherapy would most likely be ineffective in this setting.[24] Neither rituximab monotherapy nor best supportive care are therefore relevant comparators for patients being considered for axicabtagene ciloleucel Of the other comparators listed, we would expect obinutuzumab with bendamustine and lenalidomide with rituximab to typically be used earlier in the treatment pathway than the 4L+ treatment setting. In addition, we would expect that chemotherapy (clinical management without axicabtagene ciloleucel) would be used after the 4L+ setting, following approval of axicabtagene ciloleucel.	The ERG clinical expert agrees that the company's choice of comparators is appropriate for this appraisal.

	ent wit hou t axi cab tag ene cilo leu cel incl udi ng che mo the rap y (su ch as cyc lop hos pha mi de, flu dar abi ne, ben da mu stin e or chl ora mb ucil) • Bes t sup por tive car e		However, we have considered these as part of a blended comparator representing current care in the decision problem addressed.	
Out com es	• Ov eral l sur	• Overall survival • Progression-free survival • Response rates	Health-related quality of life data were not collected in ZUMA-5 and are therefore informed by the existing literature base	The outcomes reported in the CS match the NICE final scope. The ERG clinical expert considers the outcomes to be appropriate

	viv al • Pro gre ssi on-fre e sur viv al • Res pon se rate s • Ad ver se eff ect s of trea tme nt • He alth - rela ted qua lity of life	• Adverse effects of treatment • Health-related quality of life		for addressing the topic of this appraisal
Eco nom ic anal ysis	The referen ce case stipula tes that the cost-effecti veness of treatm ents should be expres sed in	Cost-effectiveness is expressed in terms of incremental cost per QALY. The time horizon is set at 40 years; sufficient to capture the plausible maximum life expectancy for the population modelled (who have a mean age of [redacted] years at model entry).	Not applicable	

	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 outcomes between the technologies being compared.	Costs relate to NHS and PSS resources and are valued using the prices relevant to the NHS and PSS. The cost year of the analysis is 2019/20, though the latest available drug prices were used whenever possible using MIMS UK and eMIT databases.		

	Costs will be considered from an NHS and Personal Social Services perspective.			
Subgroups	No subgroups were specified in the NICE final scope			The company presents subgroup analyses for objective and complete response rates for baseline and treatment characteristics in Appendix E of the CS; however, the analyses are for FL patients with ≥2 lines of prior therapy and are, therefore, not the relevant patient population for this appraisal.
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account. Guidance			The ERG agrees with the company that there are no foreseen equality issues with axi-cel. The CS states that there are existing inequalities in current non-immunochemotherapy treatment options available in England compared with Wales and Scotland where idelalisib (a licensed Pi3Kδ inhibitor) is available through routine baseline commissioning to patients who have refractory FL after two prior lines of treatment.

	will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation			

	granted by the regulator			

Key: 4L+, fourth-line plus (three or more lines of prior therapy); CAR T-cell, chimeric antigen receptor T-cell; FL, follicular lymphoma; NICE, National Institute for Health and Care Excellence; r/r, relapsed or refractory.

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 5.

Table 5 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 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 any 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.1.3.1: *"At primary screening, all abstracts were assessed against pre-defined eligibility criteria (**Error! Reference source not found.**) by two reviewers with any uncertainty resolved with a third independent reviewer. At secondary screening (full-text review) publications were independently assessed by two reviewers and discrepancies resolved by consulting a third*

		reviewer and on reaching consensus." Section D.1.3.2: *"The study selection methodology of the SLR update was aligned with the original SLR; screening (both primary and secondary) was performed by two independent reviewers, with discrepancies resolved with a third independent reviewer."*
Was data extraction conducted by two or more reviewers independently?	No	Appendix D, section D.1.3.1: *"Data extraction was performed by one researcher and validated by another independent researcher. Any disagreements were resolved by consulting with the third reviewer."* Section D.1.3.2: *"For data extraction, the template of the original SLR was used, with data extraction conducted by one reviewer, and quality checked against the original source by a second reviewer."*
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	Appendix D, section D.3.1: *"The quality of each RCT identified in the SLR was assessed using the Cochrane Risk of Bias Tool. Each RCT was rated as low risk, unclear risk or high risk of bias. The Downs and Black checklist was used to assess the bias in non-randomised studies."* Section D.3.2: *"In the SLR update, the quality assessment of the included non-RCTs was performed using the Downs and Black checklist including an assessment of the ZUMA-5 study".* The ERG considers the company's assessments to be appropriate
Was the risk of bias assessment conducted by two or more reviewers independently?	No	At clarification: *"For the SLR, each study that met the criteria for inclusion was critically appraised by a single reviewer and reviewed by a second reviewer using the Cochrane Collaboration's tool for*

		assessing the risk of bias, in line with NICE requirements. *Similarly, in the SLR update, quality assessment of the included studies was performed as part of the data extraction process, i.e., each checklist item was extracted from the included full-text articles by one reviewer, and quality checked against the original source by a second reviewer."* The ERG considers the company's strategy to be satisfactory
Was identified evidence synthesised using appropriate methods?	Yes	The company did not conduct a meta-analysis or a NMA but they compared the outcomes of ZUMA-5 with those of SCHOLAR-5 which is an external cohort study. To account for imbalances between the populations in the two studies they used propensity scoring methods, specifically standardised mortality ratio weighting. Although it was not transparent how this was performed, the ERG felt the weighting has improved comparability between the ZUMA-5 and SCHOLAR-5.

The CS reports that 16 studies reporting data for the 4L+r/r FL setting were identified by the original SLR and further studies were also identified in the SLR update. Section D.5 of the CS Appendices states: "*While some data was identified from the SLRs for the 4L+ r/r FL reporting on current treatment options for this setting, the strength of evidence was insufficient to enable robust treatment comparisons of this data with the ZUMA-5 study. There were several reasons for this including:*

- *The low availability of evidence specific for 4L+ r/r FL*
- *The scarcity of RCTs and other types of controlled study designs, which increases the risk of bias in effect estimates and challenges an assessment of comparative effectiveness*

- *The small sample sizes, which increase uncertainty around estimates of the treatment effect*
- *The considerable heterogeneity in patient characteristics and clinical endpoints, making reliable inter-study comparisons difficult*

As such, no literature-based treatment comparisons were conducted for ZUMA-5. Instead, the international, multicentre, external control cohort study, SCHOLAR-5 was used to provide a synthetic control arm for ZUMA-5 and comparative analyses were conducted for r/r FL patients meeting ZUMA-5 eligibility criteria."

At clarification, the ERG requested reasons for each individual study being unsuitable for a comparison with ZUMA-5. The company responded: "*ZUMA-5 was a single-arm study because there is no standard of care (SoC) for this population. As a single-arm study, direct comparison to a comparison arm was not possible. Patients [with r/r FL] typically receive salvage therapy or potentially allogeneic SCT, but the exact nature and outcome varies greatly depending on patient characteristics including age, disease stage, tumour burden, and the number of prior lines of therapy. This may lead to potential bias when carrying out indirect comparisons of results from published studies. Therefore, to further determine the clinical benefit associated with CAR-T therapy, an accurate detailed description of available treatment options in the relevant patient population and associated outcomes was required. In the absence of comparable data, Kite Pharma constructed an external cohort of real-world FL (grades 1-3A) patients who would be eligible for ZUMA-5. This real-world cohort was used as an external control for the ZUMA-5 clinical trial.*"

In addition, the CS states that its SLR identified three studies in the grey literature that reported potentially relevant comparative efficacy data: Batlevi 2020, Link 2019, Fuji 2020.[25-27] The company's justification for not using these studies was that none reported baseline characteristics for the relevant population, and none were conducted in Europe (two in USA: Batlevi 2020, Link 2019; one in Japan: Fuji, 2020). The ERG agrees with these assertions. However, overall, it is unclear to the ERG whether it was appropriate for the company to choose to not use any of the identified evidence in this appraisal. 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.[28] The results are presented in Table 6.

Table 6 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)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are provided in Document B, Section B.2 of the CS. The company presents clinical effectiveness evidence from one on-going, single-arm, multicentre, open-label phase II trial, ZUMA-5. Details of the trial are summarised in Document B, Table 5 of the CS and reproduced in Table 7 below. The methods of ZUMA-5 are reported in Document B, Section 2.3 of the CS and the participant flow is reported in Document B, Section 2.4.1 of the CS. The objective of ZUMA-5 was to evaluate the efficacy of axi-cel, as measured by overall response rate (ORR), in people with relapsed or refractory follicular lymphoma (r/r FL) or marginal zone lymphoma (MZL). The CS states that the focus of the submission is on participants with r/r FL who had already received three or more lines of prior therapy, albeit reporting also baseline and outcome data for participants who had received two or more lines of prior therapy. ZUMA-5 was conducted at 15 sites in the USA and two in France.

The key eligibility criteria for ZUMA-5 are reported in Document B, Section B.2.3, Table 6 of the CS. The study schema for ZUMA-5 is presented in Document B, Section B.2.3, Figure 4 of the CS and is reproduced as Figure 2 below.

Table 7 Summary of clinical effectiveness evidence [reproduced from Table 5, Document B of the CS]

Study (NCT)	ZUMA-5 (NCT03105336)				
Study design	ZUMA-5 is an ongoing Phase II, multicentre, open-label study evaluating the efficacy and safety of axi-cel in r/r iNHL.				
Population	Adult subjects with r/r B-cell iNHL of FL or MZL histological subtypes who have received 2 or more prior lines of therapy. The FL cohort of patients who have received three or more lines of prior therapy is the focus of this submission.				
Intervention(s)	Axi-cel				
Comparator(s)	Not applicable				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	ZUMA-5 presents the pivotal, regulatory, clinical evidence in support of axi-cel in r/r FL				
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life				
All other reported outcomes	• Incidence of anti-CD19 CAR antibodies • Levels of anti-CD19 CAR T-cells in blood • Levels of cytokines in serum				

Key: FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; r/r, relapsed/refractory.
Notes: bolded outcomes are those used in the economic modelling. No outcomes were bolded in Table 5 of the CS. Table 24 of the CS states that clinical parameters of the model were PFS, OS and AE incidence.

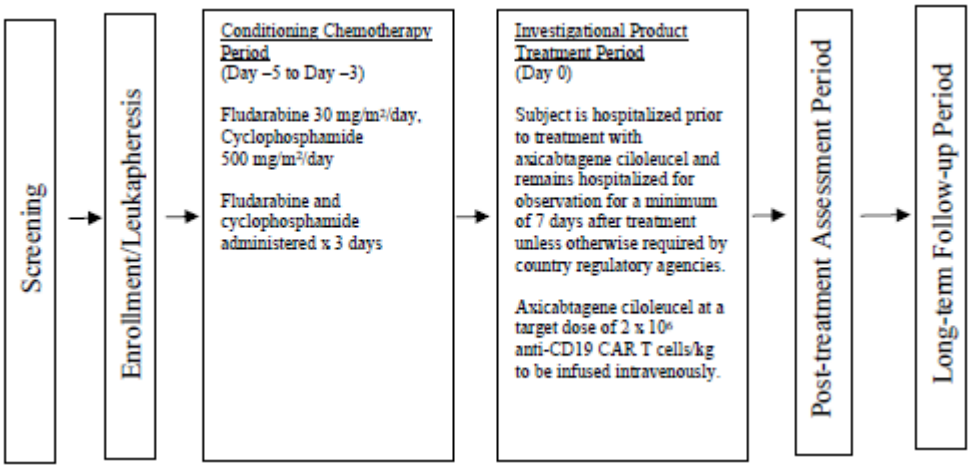

Figure 2 Study scheme for ZUMA-5

Key: CAR, chimeric antigen receptor. **Source:** ZUMA-5 Clinical Study Protocol.

The company assessed risk of bias of ZUMA-5 using the Downs and Black checklist. In general, the ERG agrees with the company's assessment of the study and that the overall risk of bias is low, in the context of a single-arm study, albeit with the bias inherent in non-randomised studies. In addition, ZUMA-5 was funded by Kite, a Gilead company, which declared a role in study design, data collection, data analysis and data interpretation. Details of the baseline characteristics of the full analysis set (FAS), safety analysis set (SAS; also referred to in the CS as the modified ITT [mITT] population for efficacy analyses) and inferential analysis set (IAS) of participants with two or more and three or more lines of prior therapy are presented in Document B, Section B.2.3.1, Table 7 of the CS. The company provided an amended version of the table at clarification, an adapted version of which, is presented as Table 8 below, reporting those participants with three or more lines of prior therapy.

Table 8 Baseline characteristics of participants in ZUMA-5 with ≥3 lines of prior therapy [adapted from Table 7 of company's clarification response]

Characteristics	FL patients with three or more lines of prior therapy		
	FAS (n = 80)	SAS (n = 78)	IAS (n = 60)
Median age, years (min-max range)	[redacted]	[redacted]	[redacted]
Aged ≥65 years, n (%)	[redacted]	[redacted]	[redacted]
Aged <65 years, n (%)	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]
ECOG performance status, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
FL histological category at trial entry, n (%)			
Grade 1	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]
Grade 3a	[redacted]	[redacted]	[redacted]
FLIPI total score, n (%)			
Low risk (0–1)	[redacted]	[redacted]	[redacted]
Intermediate risk (2)	[redacted]	[redacted]	[redacted]
High risk (3–5)	[redacted]	[redacted]	[redacted]

Characteristics	FL patients with three or more lines of prior therapy		
	FAS (n = 80)	SAS (n = 78)	IAS (n = 60)
Relapsed/refractory disease[a], n (%)			
Relapsed	[redacted]	[redacted]	[redacted]
Refractory	[redacted]	[redacted]	[redacted]
Double-refractory subgroup[a], n (%)	[redacted]	[redacted]	[redacted]
Median no. of prior therapies (range)	[redacted]	[redacted]	[redacted]
Number of prior lines of therapy, n (%)			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
≥5	[redacted]	[redacted]	[redacted]
Prior auto-SCT, n (%)	[redacted]	[redacted]	[redacted]
Prior PI3K inhibitor, n (%)	[redacted]	[redacted]	[redacted]
Prior anti-CD20 single agent, n (%)	[redacted]	[redacted]	[redacted]
Prior alkylating single agent, n (%)	[redacted]	[redacted]	[redacted]
Prior anti-CD20 + alkylating agent, n (%)	[redacted]	[redacted]	[redacted]
Time to relapse from first therapy[b], n (%)	[redacted]	[redacted]	[redacted]
≥24 months	[redacted]	[redacted]	[redacted]
<24 months	[redacted]	[redacted]	[redacted]
Prior lenalidomide, n (%)	[redacted]	[redacted]	[redacted]
Bone marrow assessment at baseline, n (%)[c]			
Lymphoma present	[redacted]	[redacted]	[redacted]
Lymphoma present but not FL	[redacted]	[redacted]	[redacted]
Lymphoma not present	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]

Key: auto-SCT, autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; FL, follicular lymphoma; IAS, inferential analysis set; PI3K, phosphoinositide 3-kinase
Notes: [a] Patients with FL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Patients with FL who progressed >6 months of completion of the most recent prior treatment are defined as relapsed. Patients with FL who progressed within 6 months of completion each of the first 2 lines of prior treatment are defined as double-refractory. [b]Time to relapse is defined as the time from initiation of the first line anti-CD20-chemotherapy combination therapy to progression. Number of subjects with time to relapse is based on those who had progressed with date of progression. Percentages are based on the number of subjects who ever received anti-CD20-chemotherapy combination therapy. [c] bone marrow assessment at baseline for lymphoma presence is based on investigator reported Lugano bone marrow assessment/bone marrow assessment using aspirate or core biopsy at screening. If these are not available, lymphoma presence is based on diagnosis history of bone marrow involvement.

Source: ZUMA-5 CSR 18-Month Addendum.[29] *Total is not 100% due to rounding

The median age of participants was [redacted] years ([redacted] years in the IAS) and [redacted] of participants were males. [redacted] participants had ECOG scores of 0 than 1 but the difference was not substantial. [redacted] of the participants had Grade 2 FL, with the remaining participants being split quite evenly between Grades 1 and 3a. [redacted] of the participants were high risk, according to the FLIPI total score, and the [redacted] had refractory disease rather than relapsed. The median number of prior therapies was [redacted] and around [redacted] of participants had [redacted] prior therapies. Time to relapse from first anti-CD20-chemotherapy was [redacted] months in [redacted] of participants. The ERG's clinical expert notes that progression of disease within 24 months of initiating treatment is the strongest predictor of aggressive disease. In general, the ERG's clinical expert is of the opinion that the baseline characteristics of the participants in ZUMA-5 are representative of patients with r/r iNHL 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: OS, progression-free survival (PFS), response rates, adverse effects and HRQoL.

Primary endpoint: ZUMA-5

The primary endpoint of ZUMA-5 was the ORR in patients with r/r FL with two or more lines of therapy who had the opportunity to be followed for at least 18 months from first disease assessment date following axi-cel treatment, defined as the incidence of participants achieving complete response (CR) or partial response (PR), as determined by independent central review per Lugano classification. Thus, the primary endpoint of ZUMA-5 is not relevant to this appraisal, the focus of which is patients with r/r FL with three or more lines of prior therapy.

Secondary endpoints: ZUMA-5

The secondary endpoints reported in the CS and relevant to this appraisal (i.e. for participants with three or more lines of prior therapy) are the following, reported in terms of the IAS (i.e. patients treated with any dose of axi-cel who had the opportunity to be followed up for at

least 18 months from first disease assessment date; [redacted] and post-hoc analyses of the mITT population (i.e. patients treated with any dose of axi-cel; [redacted]):

- **ORR** (defined as incidence of CR or PR by independent central review per Lugano classification in patients who had the opportunity to be followed for at least 18 months from first disease assessment date): ORR was [redacted] of the IAS ([redacted]; exact test for ORR ≤40%: [redacted]). ORR was [redacted] of the mITT population
- **CR** (defined as incidence of CR by independent central review per Lugano classification): [redacted] participants achieved a CR ([redacted]; exact test for CR[redacted]). The CR rate in the mITT population was [redacted]
- **Duration of response** (DOR; defined only for participants who achieved an OR and is the time from first objective response to disease progression or death, by central and investigator assessment): The median DOR was not reached in all responders: [redacted]. Median follow-up for DOR was [redacted]. [redacted] responders had an ongoing response at censoring. In the [redacted] participants with a CR, median DOR was not reached and [redacted] had an ongoing response at data cut-off. In the mITT population, median DOR in the [redacted] responders was [redacted]; the median follow-up time was [redacted]
- **Best objective response** (BOR; defined as incidence of CR, PR, stable disease (SD), progressive disease (PD) or non-evaluable (NE) as best response by the Lugano classification (by central read or investigator read)): in the IAS, CR was achieved by [redacted] PR achieved by [redacted]; stable disease achieved by [redacted]. The remaining [redacted] participants were classified as either "undefined/no disease" or "not done". The CS presents Kaplan-Meier plots for DOR and DOR by best response in Appendix L (IAS) and Document B, Figures 6 and 7 (mITT).

The CS presents summaries of response and duration of response data for the IAS and mITT in Document B, Tables 11 and 12 of the CS, adapted as Table 9 below.

Table 9 Summary of response using central assessment per Lugano classification; FL patients with three or more lines of prior therapy, IAS [adapted from Table 11 and Table 12, Document B, of the CS]

	IAS (N = [redacted]	mITT (N=[redacted])
Objective response rate (CR + PR), n (%) [95% CI]	[redacted]	[redacted]
p-value vs historical control rate	[redacted]	
Best objective response		
Complete response rate, n (%) [95% CI]	[redacted]	[redacted]
Partial response, n (%) [95% CI]	[redacted]	[redacted]
Stable disease, n (%) [95% CI]	[redacted]	[redacted]
Progressive disease, n (%) [95% CI]	[redacted]	[redacted]
Duration of response		
Median duration of response in all responders, months (range)	[redacted]	[redacted]
Median duration of response in CRs, months (range)	[redacted]	

Key: CI, confidence interval; CR, complete response; CSR, clinical study report; IAS, inferential analysis set; NE, not evaluable; PR, partial response.
Source: ZUMA-5 CSR 18-Month Addendum.

The CS reported further outcomes in terms of the IAS and mITT:

- **PFS** (defined as the time from date of axi-cel infusion to date of disease progression per Lugano assessment or death due to any cause): in the IAS, [redacted] had progressed and [redacted] had died at the time of analysis; thus, [redacted] were alive and progression-free. Median PFS [redacted] Median follow-up time for PFS was [redacted]. Estimated PFS rates at months 12 and 18 were [redacted], respectively. In the mITT population, median PFS was [redacted] ([redacted]), with a median follow-up of [redacted] months. A total of [redacted] participants had progressed

or died at the time of analysis. Estimated PFS rates at months 12 and 18 were [redacted] respectively. The CS presents Kaplan-Meier plots for PFS in the IAS (Appendix L) and the mITT (Document B, Figure 8).

- **OS** (defined as time from axi-cel infusion to date of death due to any cause): [redacted] patients had died at the time of analysis and [redacted] were alive. Median OS was not reached [redacted] Median follow-up time for OS was [redacted] Estimated OS rates at months 12 and 18 were [redacted] and [redacted], respectively. In the mITT population, median OS was not reached [redacted], with a median follow-up of [redacted] months. Estimated OS rates at months 12 and 18 were [redacted] and [redacted], respectively. The CS presents Kaplan-Meier plots for OS in the IAS (Appendix L) and mITT (Document B, Figure 10).

A summary of PFS and OS outcomes is presented in Table 10 below.

Table 10 Summary of PFS and OS outcomes for IAS and mITT populations

	IAS (N = [redacted])	mITT (N=[redacted])
Progression free survival		
Median (95%CI) PFS	[redacted]	[redacted]
Median follow-up, months	[redacted]	[redacted]
Progression/death, n (%)	[redacted]	[redacted]
Estimated PFS rate at month 12, % (95%CI)	[redacted]	[redacted]
Estimated PFS at month 18, % (95%CI)	[redacted]	[redacted]
Overall survival		
Median (95%CI) OS	[redacted]	[redacted]
Median follow-up, months	[redacted]	[redacted]
Estimated OS rate at month 12, % (95%CI)	[redacted]	[redacted]
Estimated OS at month 18, % (95%CI)	[redacted]	[redacted]
Key: CI, confidence interval; PFS: progression free survival; OS: overall survival; NE: not evaluable		

3.2.3 Adverse reactions

The company presents an overview of safety outcomes from the 18-month analysis of the ZUMA-5 FL patients in section B.2.10 of the CS. The safety analysis set (SAS) was used for all safety analyses for the study, and comprised all patients treated with any dose of axi-cel. No adverse event (AE) data for SCHOLAR-5 are reported in the CS. SCHOLAR-5 is described by the ERG in section 3.3. It is reported in the SCHOLAR-5 CSR that: "*Given the retrospective, observational design of the study, any reporting of adverse drug events had occurred prior to data collection and no additional reporting of AEs took place during this study*."

Published AE data are available for the SCHOLAR-5 Cohort C participants, the prospective cohort created from an open-label Phase II study, DELTA;[30] however, these data include patients who had received ≥2 or more lines of therapy, who are not part of the scope of this appraisal and were treated with idelalisib, which is currently unavailable to 4L+ FL patients in England. The ERG, therefore, feels that it is inappropriate to consider the AE data for the DELTA study in this appraisal.

The company states in Appendix F of the CS that no further studies reporting additional adverse events were identified. The company's economic model compares the AE frequencies from ZUMA-5 with AE frequencies for comparators as reported in the trials that informed the modelling for NICE appraisal TA627 (lenadlidomide with rituximab for previously treated FL).[21] A critique of the company's economic modelling of AE data is presented in chapter 4.

The company presents a summary of common adverse events in Table 17 of the CS, and a summary of serious adverse events (SAEs) that occurred in ≥2% of patients in Appendix N of the CS. Of the patients with ≥3 lines of prior therapy (n=78), the most common any grade adverse events (AEs) of patients with ≥3 lines of therapy were pyrexia ([redacted] patients [redacted] hypotension ([redacted] patients [redacted]), and headache ([redacted] patients [redacted%]). The most common Grade ≥3 AEs were neutropenia ([redacted] patients [redacted]), anaemia ([redacted] patients [redacted], and pyrexia ([redacted] patients [redacted%]). The most common SAEs experienced by patients with ≥3 lines of therapy were pyrexia ([redacted] patients [redacted]), pneumonia ([redacted] patients [redacted]), confusional state ([redacted]patients [redacted]), and encephalopathy ([redacted] patients [redacted%]).[31] The most common Grade ≥3 SAEs were

encephalopathy ([redacted] patients [redacted]), pneumonia ([redacted] patients [redacted]), and confusional state ([redacted]patients [redacted]).

The company presents details of treatment-emergent adverse events (TEAE) in Table 16 of the CS. A summary of TEAE and treatment-related AEs is presented in Table 11. Of the patients with ≥3 lines of prior therapy, [redacted] patients ([redacted]) experienced at least one serious TEAE, and [redacted] patients ([redacted]) experienced a Grade ≥3 serious TEAEs; [redacted] patients ([redacted]) experienced a serious treatment-related TEAE, and[redacted] patients ([redacted]) experienced a Grade ≥3 serious treatment-related TEAE. At the 18-month analysis data cut-off date, [redacted] Common treatment-related adverse events occurring in ≥20% of patients are presented in Table 18 of the CS. The most common any grade treatment-related AEs of patients with ≥3 lines of therapy were pyrexia ([redacted] patients [redacted]), hypotension [redacted]patients [redacted]) and headache ([redacted] patients [redacted]). The most common Grade ≥3 treatment-related AEs were neutropenia ([redacted] patients [redacted]) pyrexia ([redacted] patients [redacted]), hypoxia ([redacted] patients [redacted]), and encephalopathy ([redacted] patients [redacted]).

Table 11 Safety summary for FL patients in ZUMA-5 with three or more lines of therapy

Type of adverse event	FL patients with three or more lines of prior therapy SAS (n = 78)	
	Number (%) of patients experiencing AE any grade	Number (%) of patients experiencing AE Grade ≥3
TEAE	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
Treatment-related TEAE	[redacted]	[redacted]
Serious treatment-related TEAE	[redacted]	[redacted]
Death due to treatment-related TEAE	[redacted]	[redacted]
Common treatment-related adverse events occurring in ≥ 20% of FL patients in ZUMA-5		
Pyrexia	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Tremor	[redacted]	[redacted]
Chills	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]

Key: AEs, adverse events FL, follicular lymphoma; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
Source: ZUMA-5 CSR 18-Month Addendum[29]

Adverse events of special interest

The company presents adverse events of special interest in section B.2.10.4 of the CS; including cytokine release syndrome (CRS), neurological events, and cytopenia and the ERG presents a summary of these data in Table 12.

- **Cytokine release syndrome** Of the FL patients with ≥3 lines of prior therapy, [redacted] ([redacted]) experienced a CRS event, of which [redacted] had Grade ≥3 CRS, and [redacted] had Grade 5 CRS, who [redacted]

[redacted]. The most common symptoms of CRS Grade ≥3 were hypoxia ([redacted] patients [redacted]), pyrexia ([redacted] patients [redacted]) and hypotension ([redacted] patients [redacted]). The median time to onset of CRS was [redacted] days (range: [redacted]) following axi-cel infusion. At the 18-month analysis data cut-off date, CRS had resolved in [redacted]. For the [redacted] patients with FL whose CRS had resolved, the median duration of CRS was [redacted]days (range: [redacted]).

- **Neurological events** [redacted] ([redacted]) patients with ≥3 lines of prior therapy had at least one neurological event of any grade, and [redacted] ([redacted]) had Grade ≥3 neurological events. [redacted] had a Grade 5 neurological event. The most common Grade ≥3 or higher neurological events were encephalopathy ([redacted] patients [redacted]), and confusional state ([redacted] patients [redacted]). The median time to onset of neurological event was [redacted]days (range: [redacted]); [redacted] had neurological events with an onset >80 days after the axi-cel infusion. The company state that the clinical experts they consulted indicated that the observed delayed/late-onset, low-grade neurological events were not likely to have any considerable impact.[10] [redacted]had unresolved neurological events at the 18-month analysis data cut-off. Of these patients, [redacted]. For the [redacted] patients with FL whose neurological event had resolved, the median duration of the event was [redacted]_days (range: [redacted]).
- **Cytopenia** Of the patients with ≥3 lines of therapy, [redacted]) experienced a cytopenia of any grade, and [redacted] experienced a Grade ≥3 cytopenia. Of the patients with ≥3 lines of therapy, [redacted] experienced Grade ≥3 neutropenia; [redacted] experienced Grade ≥3 thrombocytopenia; and [redacted] experienced Grade ≥3 anaemia. For FL patients whose events had resolved, the mean (standard deviation) and median (range) times to onset of cytopenias were [redacted] ([redacted]) and [redacted] ([redacted]) days after axi-cel infusion. The median duration of cytopenias were [redacted] (range: [redacted]) days.

Table 12 Summary of adverse events of special interest for FL patients in ZUMA-5 with three or more lines of therapy

Type of adverse event of special interest	FL patients with three or more lines of prior therapy SAS (n = 78)		
	Number (%) of patients experiencing AE any grade	Number (%) of patients experiencing AE Grade ≥3	Number (%) of patients experiencing AE Grade 5
Any CRS event[a]	[redacted]	[redacted]	[redacted]
Symptoms of CRS[b]			
Pyrexia	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]
Chills	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Malaise	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]
Any neurological event	[redacted]	[redacted]	[redacted]
Type of neurological event, n (%)			
Tremor	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]

Agitation	[redacted]	[redacted]	[redacted]
Disturbance in attention	[redacted]	[redacted]	[redacted]
Dysarthria	[redacted]	[redacted]	[redacted]
Paraesthesia	[redacted]	[redacted]	[redacted]
Delirium	[redacted]	[redacted]	[redacted]
Hallucination	[redacted]	[redacted]	[redacted]
Patients with any cytopenia	[redacted]	[redacted]	NR
Patients with neutropenia, n (%)	[redacted]	[redacted]	NR
Neutropenia	[redacted]	[redacted]	NR
Neutrophil count decreased	[redacted]	[redacted]	NR
Febrile neutropenia	[redacted]	[redacted]	NR
Patients with thrombocytopenia, n (%)	[redacted]	[redacted]	NR
Thrombocytopenia	[redacted]	[redacted]	NR
Platelet count decreased	[redacted]	[redacted]	NR
Patients with anaemia, n (%)	[redacted]	[redacted]	NR

Key: AE, adverse event; FL, follicular lymphoma; SAS, safety analysis set

Notes: a CRS events are graded according to a modification of the criteria of Lee et al. (2014). Percentages are calculated using the total number of patients in the analysis set as the denominator. b individual CRS symptoms are coded using MedDRA Version 23.0 and graded per CTCAE Version 4.03. Percentages are calculated using the number of patients with any TE CRS of any grade. c. multiple incidences of the same adverse event in one patient are counted once at the worst grade for this patient. Events (neutropenia, thrombocytopenia or anaemia) with onset on or after axicabtagene ciloleucel infusion date are summarised. Thrombocytopenia is identified using the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for haematopoietic thrombocytopenia (narrow search). Neutropenia is identified using MedDRA search terms defined by Kite. Anaemia (including aplastic anaemia) is identified using the SMQ haematopoietic erythropenia (broad search).
Source: ZUMA-5 CSR 18-Month Addendum[29]

Infections

The company presents infection data in section B.2.10.4.3 in the CS. The infection data are not presented by the number of lines of prior therapy received by the FL patients. Infections were experienced by [redacted] patients ([redacted]), of whom [redacted] ([redacted]) had worst Grade 3 infections, and [redacted] ([redacted]) had worst Grade 4 infection. [redacted] Worst Grade 3

events included pneumonia ([redacted] patients [redacted%]) and urinary tract infection ([redacted]patients, [redacted]). The single worst Grade 4 event was sepsis ([redacted] patient, [redacted]). The company states that [redacted] The company reports that [redacted]; however, these data are not reported in the CS or the ZUMA-5 CSR 18-month addendum.

It is the ERG clinical expert's opinion that the AEs reported in the CS are in keeping with the AEs related to the use of axi-cel in diffuse large B cell lymphoma where it is already approved. CAR-T is a single treatment, and most AEs occur within 30 days of treatment, with a far lower risk of AEs beyond that time. This differs from SOC where the risk of AEs remains similar for the duration of treatment, which is often 6 months depending on the regimen used. Like CAR-T, there is still a risk of AEs after treatment, but this is much smaller and gradually declines with time post-treatment.

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

The company did not conduct any formal indirect or mixed treatment comparison but instead presented a comparison with SCHOLAR-5, described in the CS as an international, multicentre, external cohort control study for the purpose of providing comparative evidence for axi-cel in patients fulfilling the eligibility criteria of ZUMA-5. The SCHOLAR-5 CSR (Table 3; ref 21, Doc B) presents a comparison of the inclusion and exclusion criteria of SCHOLAR-5 and ZUMA-5.[32] In general, the criteria are aligned appropriately, and the ERG clinical expert has no concerns. SCHOLAR-5 consisted of three cohorts, described in full in Section B.2.9.1.1 of the CS. In brief, Cohort A and Cohort B were retrospective cohorts created from medical records of a total of seven sites in the UK, France, Spain, Portugal, and the USA. Cohort C consisted of participants of a single-group, open-label, Phase II study, DELTA (Gopal 2014), conducted at 41 sites in the USA and Europe of which the main inclusion criteria were a confirmed diagnosis of B-cell iNHL, including (among others) histological types FL grade 1, 2 or 3a.[30] Inclusion criteria also specified prior treatment with ≥2 prior chemotherapy-based or immunotherapy-based regimens for iNHL, prior treatment with rituximab and an alkylating agent for iNHL and refractoriness to both rituximab and an alkylating agent. The CS states that cohorts were restricted to FL patients with at least three

prior lines of treatment before construction of the analysis set. The ERG noted that SCHOLAR-5 included patients outside of the UK and some of the treatments received by these patients are not in line with clinical practice in England.

Propensity scoring methods - specifically standardised mortality ratio (SMR) weighting - were applied to account for imbalances of confounders between ZUMA-5 and SCHOLAR-5 populations. The ERG felt it was not transparent on how the SMR weighting was applied to the propensity scoring. However, the weighting has improved comparability between the ZUMA-5 and SCHOLAR-5. Baseline characteristics of SCHOLAR-5 and ZUMA-5 patients pre- and post-weighting are presented in Table 14 of the CS and reproduced as Table 13 below. The ERG notes that the abbreviation EES in the table is not defined by the company. However, the abbreviation ESS is defined as estimated sample size, and the ERG believes that incidences of EES should read ESS.

Table 13 Baseline characteristics of patients pre-and post-weighting; FL patients with three or more lines of prior therapy, SCHOLAR-5 ESS, ZUMA-5 mITT [reproduced from Table 14, Document B of the CS]

Characteristics	Pre-weighting			Post-weighting		
	SC-5 (n = 82)	Z-5 (n = 78)	p-value [SMD]	SC-5 (EES = 77)	Z-5 (n = 78)	p-value [SMD]
POD24, n (%)						
Yes						
No						
Missing						
Prior lines of therapy						
Mean (SD)						
Median (range)						
Relapsed/refractory to prior line of therapy						
Relapsed						
Refractory						

Characteristics	Pre-weighting			Post-weighting		
	SC-5 (n = 82)	Z-5 (n = 78)	p-value [SMD]	SC-5 (EES = 77)	Z-5 (n = 78)	p-value [SMD]
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Prior SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]		[redacted]	[redacted]	
No	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Tumour bulk ≥ 7 cm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]		[redacted]	[redacted]	
No	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Time since last treatment, months	[redacted]		[redacted]	[redacted]		[redacted]
Mean (SD)	[redacted]	[redacted]		[redacted]	[redacted]	
Median (range)	[redacted]	[redacted]		[redacted]	[redacted]	
	[redacted]	[redacted]		[redacted]	[redacted]	
CR or PR to prior line of therapy	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
Yes	[redacted]	[redacted]		[redacted]	[redacted]	
No	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Age ≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]		[redacted]	[redacted]	
No	[redacted]	[redacted]		[redacted]	[redacted]	
Missing	[redacted]	[redacted]		[redacted]	[redacted]	
Prior anti-CD20 + alkylator combination	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]		[redacted]	[redacted]	

Characteristics	Pre-weighting			Post-weighting		
	SC-5 (n = 82)	Z-5 (n = 78)	p-value [SMD]	SC-5 (EES = 77)	Z-5 (n = 78)	p-value [SMD]
No Missing	[redacted]	[redacted]		[redacted]	[redacted]	

Key: CR, complete response; ESS, estimated sample size; mITT, modified intent-to-treat; POD24, progressed disease within 24 months after initiation of first-line anti-CD20 chemo combination therapy; PR, partial response; SC-5, SCHOLAR-5; SCT, stem cell transplant; SD, standard deviation; SMD, standardised mean difference; Z-5, ZUMA-5.
Note: Percentages may not add up to 100% due to rounding.
Source: SCHOLAR-5 Technical Report.[32]

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

Indirect or multiple treatment comparisons were not conducted by the company for this appraisal.

3.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG requested the time to event data for progression-free survival and overall survival, but the company explained that they do not have permission to share their patient-level data (i.e., the time to event raw data underpinning the Kaplan Meier curves).

3.6 Conclusions of the clinical effectiveness section

The company decision problem is appropriate for addressing the NICE final scope for this appraisal. The company did not conduct any formal indirect or mixed treatment comparison. The key clinical effectiveness evidence for axi-cel for treating relapsed or refractory follicular lymphoma was based on a comparison with SCHOLAR-5 cohorts which were created from three data sources. Two of the data sources were retrospective cohort (real-world analysis set) which contained 58 patients and the third data source was a prospective cohort created from an open-label Phase II study, DELTA which contained 24 patients. The ERG noted that there were differences in the distribution of ECOG performance score (0 and 1) between ZUMA 5 and SCHOLAR 5. Another possible source of bias is that some patients in SCHOLAR 5, received treatments not approved for routine use by NHS England (e.g., idelalisib as part of the DELTA study). It is, therefore, plausible that the results from SCHOLAR-5 may overestimate OS for the current 4L+ treatments used in NHS England, which potentially acts against axi-cel; however, we do not have data to verify this. It would have been preferable to have comparator cohorts more in line with current NHS practice in England.

With regards to propensity scoring methods, specifically SMR weighting, the ERG felt the weighting has improved comparability between the ZUMA-5 and SCHOLAR-5; however, it is not transparent how this was performed.

After reviewing the analysis of the outcomes presented in the CS, the ERG agrees with the company that there is a beneficial effect on OS, PFS and RR rate from axi-cel. The Kaplan Meier plots show a reduction in the risk of disease progression and death, however, the ERG noted that the median PFS and OS were not reached for ZUMA-5. Although the confidence intervals around the effect sizes were wide, the large effect sizes on the ORR and CR show the difference between the two cohorts.

The ERG has inspected the adverse events being reported in ZUMA-5 in section B.2.10 of the CS. The ERG is not concerned with the proportions of serious adverse events or rates of adverse events. No adverse event (AE) data for SCHOLAR-5 are reported in the CS.

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. Details were provided in appendix G of their submission. Comprehensive searches were originally undertaken to May 2020, and then later updated to May 2021. The review aimed to include all economic evaluations, and resource use and costing studies, of any interventions in adults with relapsed or refractory indolent non-Hodgkin lymphoma - grade 1-3a follicular lymphoma, or nodal or extra nodal marginal zone lymphoma.

The review identified a total of 33 studies, of which 19 were full economic evaluations. Details of the included study designs, modelling approaches, modelling inputs and findings were all tabulated from comparison in appendix G of the company submission. In their main submission document, the company have focused on three economic modelling studies that have informed previous NICE appraisals in r/r/ FL: TA604 (idelalisib), TA627 (lenalidomide with rituximab) and TA629 (obinutuzumab with bendamustine [TA472 CDF review]).[21, 22, 33, 34] The company notes that insights were drawn from these appraisals throughout their own submission. They further note that in addition to those studies identified in their review, they drew insights from three previous NICE appraisals of CAR T-cell therapies in advanced previously treated lymphoma indications, and a published mock appraisal of regenerative and cell therapy products.[35-38]

The ERG is satisfied that the company have undertaken a thorough review of the published economic evidence of relevance to this appraisal. Rather than using the existing economic evidence base to draw conclusions about the cost-effectiveness of axi-cel for r/r FL, the focus of their review was on gaining insights on methodological approaches, inputs and assumptions of relevance to the current appraisal.

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 reference case
Perspective on costs	NHS and PSS	Aligns with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with reference case
Synthesis of evidence on health effects	Based on systematic review	Aligns with reference case, but limited evidence available to inform comparative effectiveness.
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.	Aligns with reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligns with reference case, but no data available that applies specifically to the lines of therapy specified in the company's proposed population.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with 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 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	Aligns with reference case, although some uncertainty around some of the values applied.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with 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

The company describe their de novo cost-effectiveness model in section B.3.2.2 of their submission document. It takes the form of a three-state partitioned survival model: pre-progression, progressed and dead. The structure, they note, is consistent with those used in all previous NICE appraisals in relapsed or refractory follicular lymphoma.

The PFS and OS data to inform the model comes from the relevant subgroup (treatment line 4L+) of the ZUMA-5 trial for axi-cel and from the propensity score weighted SCHOLAR-5 data for the blended comparator (section 3.3 above). Based on experience from the use of CAR-T therapies in other haematological cancers, and precedence set by previous NICE appraisals, a proportion of those alive and progression free at 5 years are assumed be long-term survivors. This proportion face no further risk of progression but do face an elevated mortality rate relative to the age/sex matched general population. An SMR of 1.09 is applied in the base case in line with appraisals of CAR-T therapies in diffuse large B-cell lymphoma (DLBCL) (TA559, TA567).[35, 36]

Model settings are in line with the NICE reference case with respect to perspective on costs and outcomes, time horizon, and discounting. A cycle length of 28 days was chosen, and a half-cycle correction appropriately applied.

The ERG is broadly supportive of the model structure but note a few structural uncertainties related to the Part SA approach and the company's long-term survivorship assumptions.

- *A fraction of those projected to be progression free at 5 years (equating to 25% of the total cohort) are assumed to be longer-term survivors at zero risk of progression from 5 years onwards. The remaining survivors face risks of progression and death based on the chosen extrapolation curves for PFS and OS. However, the extrapolation curves are fitted to observed data for the overall mITT cohort and so may not be appropriate for extrapolating*

outcomes for the subset who are not long-term survivors. The ERG asked the company to consider this at the clarification stage and explore the impact of applying higher risks of progression and death beyond five years to those not considered to be long-term survivors.

- *The fractional weighting of long-term survivors versus those who remain at risk of progression in the model is assumed to be constant over time from 5 years. In reality, the fraction of the surviving cohort that are long-term survivors should increase over time as those who are not continuing to progress and face a higher risk of mortality. The company were also asked to consider an adjustment for this in the model at the clarification stage.*
- *The Part-SA approach creates challenges with respect to validating the time spent in the progressed disease state by treatment arm of the model, and also the expected costs of subsequent lines of treatment. For example, all progressed patients, irrespective of treatment arm, are assumed to incur subsequent therapy costs equal to those incurred in the comparator arm in the first treatment line of the model. This is despite an expectation that increasing lines of therapy are associated with poorer response rates and reduced PFS and OS. Further, the selected PFS and OS curves in the model infer that patients who progress on axi-cel can expect to survive for longer following progression compared to those who progress on the comparator. The clinical plausibility of this is unclear, but if valid it might also suggest that higher subsequent therapy costs could be expected per progressed patient on axi-cel. This is not the case in the model. There is a post progression survival benefit for axi-cel without any increase in subsequent therapy costs.*

4.2.3 Population

In line with the proposed marketing authorisation and the data from ZUMA-5 used to inform the model inputs, the population considered in the model is those with [redacted] (referred to as the 4L+ population in the company submission). The starting age of the cohort is [redacted] in line with the mean age at baseline of 4L+ patients in ZUMA-5.

The ERG has no major concerns regarding the proposed population, but note it is a subset of the overall population of relapsed or refractory non-Hodgkin lymphoma as set out in the final scope for the appraisal. Correspondingly, it is a subgroup from the ZUMA-5 trial which is used to inform the model inputs. ZUMA-5 also included patients with marginal zone lymphoma and patients with relapsed or refractory disease after fewer prior lines of therapy.

4.2.4 Interventions and comparators

The intervention is axi-cel, as described in section B.3.2.3.1 of the company submission.

The company argue that there is no true standard of care for the 4L+ r/r FL population, and so consider the comparator to be a basket of treatments (blended comparator). Whist rituximab monotherapy and best supportive care (BSC) were listed as comparators in the scope, the company argue that both would be reserved for patients considered not fit enough to receive intensive active therapy, a group considered not suitable for CAR-T therapy. Therefore, both rituximab monotherapy and BSC are excluded from the blended comparator. The data used to inform the comparative efficacy of the blended comparator come from the SCHOLAR-5 study. Further discussion of the blended comparator is provided in the following sections.

The ERG's clinical expert was broadly in agreement with the company's blended comparator, and that rituximab and BSC should not be considered comparators.

4.2.5 Perspective, time horizon and discounting

The perspective on cost and outcomes is in line with the NICE reference case. The time horizon is 40 years, with a starting age of [redacted] for the modelled cohort. Given the potential for long-term survivorship for a fraction of the cohort, this seems reasonable. Shorter time horizons are explored by the company in scenario analyses.

4.2.6 Treatment effectiveness and extrapolation

Clinical inputs for axi-cel were derived from the analysis of PFS and OS data of the modified intention-to-treat population of ZUMA-5, comprising [redacted] patients with r/r FL with three or more lines of prior therapy. All analyses were based on the September

2020 data cut at the time of the main company submission, providing a median follow-up of [redacted] for PFS and [redacted] for OS. The company plans to update these analyses and utilise later data with 6 more months of follow-up during technical engagement.

Clinical inputs for the comparator arm, current 4L+ care, were derived using propensity score weighted data from the SCHOLAR-5 study discussed in section 3.3 above.[32] This external control included [redacted] patients with FL at 4L+ for comparison with the ZUMA-5 mITT population. The company noted that following propensity weighting of the SCHOLAR-5 data the effective sample size was reduced to 77 patients. However, they further clarified that due to an absence of progression dates for the index therapy in DELTA study, a sub-cohort of SHOLAR-5, these patients were excluded from the PFS analysis. Thus, there were fewer patients (n=51) to inform PFS post-weighting.

Given the unique mechanism of action of axi-cel compared to other available 4L+ treatments, the company considered it unreasonable to expect proportional hazards between treatment arms to hold, and so independently fitted parametric curves to PFS and OS data for each treatment arm (see company submission, section B.3.3.1.4). Seven standard parametric survival models were fitted for each outcome. Following NICE DSU TSD guidance, the company considered visual fit, statistical fit, and plausibility of long-term extrapolation, based on clinical opinion, to select a parametric curve for each outcome.

Axi-cel PFS

Based on consideration of visual and statistical fit, and clinical expert opinion, the company selected the most conservative Weibull curve for extrapolation of PFS. However, the company note that from interviews with clinical experts, it is reasonable to expect a proportion of r/r FL patients treated with axi-cel to have mortality hazards that are more in line with the general population after 5 years. The company base case assumes this applies to 25% of the cohort, which is approximately [redacted] of those alive and progression free at 5 years ([redacted]) in the model. They assume that this 25% face zero risk of progression from 5 years, and a risk of death which is held at 9% (SMR=1.09) above general population mortality. The remainder, who are not

considered to be long-term survivors, continue to follow the extrapolated hazard of progression or death based on the chosen Weibull PFS curve.

Axi-cel OS

With respect to OS, the company fitted the same seven standard parametric curves to the data from ZUMA-5 (see Figure 22 of the company submission, document B), and selected the Weibull curve for their base case. The company highlight the immaturity of the OS data and note that the AIC and BIC were within five points across all models with the exception of the BIC for the generalised gamma and log normal models. The more pessimistic extrapolations produced by the generalised gamma and Gompertz models were ruled out based on advice of clinical experts on the clinical plausibility of the long-term extrapolations, as was the log-normal which produced unrealistically high long-term survival. Of the remaining options, the Weibull was chosen for the company base case. This is the third most pessimistic (after the Gompertz and generalised gamma), projecting survival of [redacted] at 5 years, [redacted] at 10 years, [redacted] at 20 years, [redacted] at 30 years, and [redacted] at 40 years. However, as noted above for PFS, the company base case assumes that 25% of those treated with axi-cel are long-term survivors who face and SMR adjusted general population mortality from 5 years onwards. Therefore after 5 years, the chosen Weibull is only used to extrapolate survival of those assumed not considered to be long-term survivors. It should be further noted that there is an override in the model which ensures the extrapolated mortality never falls below the mortality hazard for the age/sex matched general population. This applies to the chosen Weibull curve from [redacted] years when it projects [redacted] survival. This is somewhat counterintuitive, as it assumes a lower mortality rate for the non-long-term survivors compared to long-term survivors from [redacted] years onwards.

ERG critique

There are clearly challenges related to the extrapolation of PFS and OS given the immaturity of the data. Further uncertainties relate to company's long-term survivor assumptions, with currently no data available to validate this in the r/r FL, 4L+ population. In addition, their approach to applying different hazards of progression and death for long-term survivors creates some inconsistencies in the model:

1. *The extrapolation curves were fitted to data for the whole mITT ZUMA-5 cohort, but from 5 years are only applied to those assumed not to be long-term survivors. There is scope for these fitted curves to overestimate the survival for this fraction of the cohort; had it been possible to fit curves separately for non-long-term survivors, more pessimistic extrapolations may have been obtained.*
2. *Related to (1) above, it is not clear if the clinical experts who validated the chosen PFS and OS extrapolation curves were aware that they were intended for projecting expected survival for only a fraction of the cohort from 5 years onwards, rather than the whole cohort.*
3. *The company's original approach to separating the hazards (from 5 years) assumed a constant proportional split between long-term and non-long-term survivors, which didn't account for the differing hazards of progression and death moving forwards. The company implemented a correction for this at the clarification stage, which had a modest downward impact on the ICER (see company response to the clarification letter, QB7).*
4. *The override to ensure the mortality hazard for non-long-term survivors doesn't fall below general population mortality, whilst assuming long-term survivors face SMR adjusted general population mortality, results in non-long-term survivors facing a lower hazard of death than long-term survivors from [redacted] years in the model.*

The above issues may contribute to the extrapolated post-progression life-year gain for axi-icel versus current 4L+ care in the company base case. Whilst there are plausible reasons why axi-cel treated patients might experience better post-progression survival than those treated with current 4L+ therapies (see company response to clarification letter, QB8), overestimating OS for the non-long-term survivor fraction could also contribute to the modelled post-progression survival benefit. Given the above, the ERG requested scenarios from the company to explore the impact of increasing the risk of progression and death for the non-long-term survivor fraction from 5 years. The company provided this by applying hazard ratios of 1.09 and 1.2 to the chosen axi-cel PFS and OS curves from five years, which had a modest upward impact on the ICER years (see response to clarification letter, QB6).

The company noted the arbitrary nature of the HR values applied given the lack of data.

A further potential issue related to the modelling of OS for axi-cel treated patients, is the acknowledgement that a number of patients in ZUMA-5 who achieved a complete or partial response at month three, but subsequently experienced disease progression, were allowed retreatment with axi-cel. This is noted to have occurred in [redacted] of the 4L+ mITT cohort. The company noted that retreatment would not be expected to occur in routine clinical practice in England and so have not accounted for these costs in the model. However, they have not made any corresponding adjustment to the Kaplan-Maier OS data. Nevertheless, the OS data is very immature, and it may be too early for any potential bias to have materialised in the observed OS data. But it perhaps should be considered when choosing extrapolation curves for OS. In the absence of providing an adjustment to OS to account for the removal of post-progression axi-cel from the ZUMA-5 data, the company have provided a scenario analysis in response to the clarification letter which includes these retreatment costs. This has a moderate upward impact on the ICER (see response to clarification letter, QB2.)

Standard 4L+ PFS

Parametric survival models were fitted to the propensity score weighted data from the SCHOLAR-5 study. As indicated above, the company noted that the timing of progression could not be determined for cohort C of SCHOLAR-5, so these patients were excluded from the analysis of PFS to inform the comparator arm. This results in substantially fewer patients (n=51) informing the PFS curve compared to the number informing the OS curve (n=77) for the blended comparator. Cohort C of SCHOLAR-5 came from the open label phase II DELTA study of patients with r/r FL treated with idelalisib.

The available PFS data was mature, with the Kaplan-Maier curve reaching [redacted] by approximately 31 months. This results in less uncertainty related to the choice of parametric curve in the comparator arm, and the company note that clinical experts they consulted suggested all the parametric curves provided plausible extrapolations.

Therefore, the company selected the exponential curve for their base case based on statistical fit (lowest AIC and BIC).

Standard 4L+ OS

OS for the comparator arm was informed by analysis of the propensity weighted data from all sub-cohorts of SCHOLAR-5. Based on AIC and BIC, the generalised gamma provided the best statistical fit to the observed OS data. However, the company note that it, along with the Gompertz, provides implausibly high long-term survival projections. The company note that based on the clinical validation interviews, the gamma curve was selected for the base case based on plausibility of the extrapolation. This provides the second most pessimistic extrapolation of OS of the available curves for the comparator arm (see Figure 24 of the company submission, document B)

ERG critique

There are several uncertainties relating to the company's approach to estimating efficacy inputs for the comparator arm of the economic model. The uncertainties inherent in constructing an external control group for the single arm ZUMA-5 trial were discussed in section 3.3 above. Accepting that the company are limited by the availability of data and the non-randomised design of ZUMA-5, the ERG identifies some further issues related to the company's approach:

- *It is potentially problematic that cohort C of SCHOLAR-5 (data from the DELTA trial) was excluded from the analysis of PFS but included for the analysis of OS. The result is that PFS in the model is informed by* [redacted] *fewer patients than OS, which may invalidate the use of the chosen curves for partitioning the standard care cohort. The ERG sought clarity on this issue at the clarification stage. The company noted in their response that a subgroup analysis had been conducted as part of the SCHOLAR-5/ZUMA-5 comparative analysis, in which the DELTA sub-cohort of SCHOLAR-5 had been excluded from the comparison of OS using the smaller inferential analysis set of ZUMA-5 (n=60). They note that this produced an estimated hazard ratio for OS that was very similar to the main analysis which included DELTA patients (see company response to clarification letter, QB3). However, this does not fully address the concern because: 1) the model does*

not rely on hazard ratios, but independently fitted survival curves; and 2) the model outcomes for axi-cel are based on the mITT population rather than the inferential analysis set. Given the above, the ERG believe it might have been preferable to conduct an analysis that excluded the DELTA patients from the OS curve fitting for the comparator arm. This could be further justified by the potential lack of generalisability of the DELTA cohort (treated with idelalisib) to the NHS in England, where idelalisib is not available.

- *As things stand, with the DELTA patients included in the OS curves for the comparator arm, there appears to be* [redacted]*, which may not be consistent with the PFS curve which excludes the DELTA patients. Further, the parametric curves that provide the best statistical and visual fit to the observed OS data result in implausibly high projections of long-term OS, whilst the curves that provide more plausible long-term projections of OS, according to clinical experts, provide poorer statistical and visual fit to the observed data. The company acknowledge this issue and note that they prioritised the plausibility of extrapolation during the curve selection process. The ERG acknowledges that the better fitting curves lack plausibility with respect to long-term survival but are concerned that the chosen OS curve provides a poor fit to the observed data which undermines confidence in its suitability for extrapolation.*
- *A further issue with the comparator data from SCHOLAR-5 is that it includes patients who received treatments that are not available in the NHS in England (including idelalisib). Therefore, the company reweighted the distribution of SCHOLAR-5 treatments for the purpose of calculating the blended comparator costs in the model (Table 15). However, no corresponding adjustment to efficacy was possible. The company were asked to comment on the expected direction and magnitude of any bias that this may introduce. The company response focussed on the more favourable outcomes that idelalisib would be expected to have over treatments that are used at fourth line or above in the NHS in England. Thus, they suggest that the SCHOLAR-5 curves are optimistic compared to current clinical practice in England. However, the ERG notes that those patients (19%) who received CVP alone in SCHOLAR-5*

and were redistributed to other treatments for the purpose of costing, may have experienced poorer outcomes than would be expected in the NHS. It is not clear how the 26% of patients who received experimental treatments in SCHOLAR-5 would have fared on the other treatments available in routine practice in England. Therefore, it is difficult to predict the overall direction and magnitude of bias caused by the mismatch between the SCHOLAR-5 treatment distribution and the treatment distribution used in the NHS in England. Assuming that those treated with idelalisib or experimental treatments in SCHOLAR-5 would tend to have experienced better outcomes than they otherwise would, the ERG believes that the mismatch is more likely to biases in favour of the comparator (against axi-cel). However, it remains uncertain.

Table 15: Distribution of current 4L+ care therapies [source: Table 40, Document B of the CS].

Treatment	SCHOLAR-5 distribution	Include as comparator?	Re-weighted distribution
Idelalisib	12.0%	No	**0.0%**
Bendamustine + obinutuzumab	5.3%	Yes	**13.3%**
Bendamustine + rituximab	10.7%	Yes	**26.7%**
CVP + rituximab	6.0%	Yes	**15.0%**
Radioimmunotherapy	3.0%	No	**0.0%**
Lenalidomide + rituximab	9.0%	Yes	**22.5%**
R-CHOP	9.0%	Yes	**22.5%**
CVP	19.0%	No	**0.0%**
Experimental	26.0%	No	**0.0%**
Total	100.0%	**Re-weighted total**	**100.0%**

Key: 4L+, fourth-line plus; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SCT, stem cell transplant.

4.2.7 Health related quality of life

Quality of life was captured in the model by applying utility weights to pre-progression and progressed health states, with adverse event disutilities applied separately. In the company base case, no distinction was made for patients classified as long-term survivors with the chosen pre-progression utility value assumed to apply.

As quality-of-life data were not collected in the ZUMA-5 or SCHOLAR-5 studies, a systematic literature search was conducted to identify relevant utility values for use in the model. The search identified 7 studies reporting health state utility values in the r/r FL population but none of the identified studies were used in the model base case. Instead, assumptions from the NICE appraisal of lenalidomide with rituximab for previously treated FL (TA627) were used.[21] In TA627, utility values were derived from quality of life data collected in the AUGMENT study but capped to ensure the progression-free utility value remained below age-adjusted general population values. Relative utility decrements were then applied to the progressed health states. The company adopts the same approach here on the basis that these utility values were accepted by NICE in a similar patient population. The utility values used are reported in table 16 below.

Many of the studies identified in the literature search reported the same set of utility values from Wild et al 2006/Pettengell at al 2007 and these values were used in sensitivity analysis.[5, 39] As only the abstract was available for the Wild et al study, this was not included in the literature review but information from the study is reported in other published papers and relevant NICE appraisals (TA627, TA604).[21, 33] The study reported in Wild et al and Pettengell et al is from 222 patients in the UK with histologically confirmed FL. Patients completed several patient-reported outcome measures and were analysed according to five disease states: ‘active disease-newly diagnosed’, ‘active disease-relapsed’, ‘partial response’, ‘complete response’ and ‘disease free’. These health states were then grouped to form two broad health states of progression-free (partial response, complete response and disease free) and progressed disease (active disease-newly diagnosed and active disease-relapsed). Quality of life was assessed using the EQ-5D, Functional Assessment of Cancer Therapy –Lymphoma (FACT-Lym) measure and the Hospital Anxiety and

Depression Scale. The EQ-5D data were used to derive utility values for progression-free and progressed disease health states.

The CS notes that in TA604 utility values from Pettengell et al/ Wild et al were used in the model, whereas in TA627 these values were used in a scenario analysis due to the availability of EQ-5D data from the AUGMENT study. Given the lack of relevant quality of life data from the trial, the company acknowledge the chosen utility values are uncertain and explore the impact of using alternative data sources. A summary of the utility values identified in the literature and relevant NICE appraisals which were used in scenario analyses are presented in Table 16.

Table 16: Summary of relevant utility values used in the company base case and sensitivity analysis [adapted from Table 31, Document B of the CS]

Health state	**Base case and TA627 FAD[21]**	**AUGMENT (TA627)[21]**		**Wild et al. (2006)[39] /Pettengell et al. (2008)[5] (TA604)[33]**	**GADOLIN (TA629; as reported in TA627)[21]**
		R^2	**R-mono**		
Pre-progression	Age-matched general population 0.829 at baseline ([redacted] years)	0.847	0.840	0.805 (0.018)	On-treatment: 0.822 (0.010) Off-treatment: 0.807 (0.012)
Progressed disease	Age-matched general population (with relative decrement) 0.803 at baseline ([redacted] years)	Off-treatment: 0.821 On-treatment: 0.791	Off-treatment: 0.813 On-treatment: 0.784	0.736 (aggregated) 0.62 (0.06 – relapsed disease)	0.758 (0.024)

Key: FAD, Final Appraisal Determination; R-mono, rituximab monotherapy; R^2, lenalidomide with rituximab; TA, technology appraisal.

The ERG agrees there is uncertainty in the utility values due to a lack of quality-of-life data available in the patient population who would be eligible to receive axi-cel in clinical practice. A literature search identified a number of potentially relevant studies, but the company provided limited justification for deciding to adopt a similar approach to that used in TA627 in preference to other studies identified in the literature. While the patients in the AUGMENT study had r/r FL (or marginal zone lymphoma), the majority were enrolled at second-line (54%) with only 24% fourth-line or greater who would be comparable to the patients who would be eligible for axi-cel. As patients in the AUGMENT study are at an earlier stage in the disease pathway, clinical expert advice to the ERG indicates these patients would be expected to have a higher quality of life than patients receiving treatment at fourth line and beyond. Although it is not clear what line of treatment patients were receiving in the Wild et al/Pettengell et al study, the utility values are lower than those in AUGMENT and may better reflect the quality of life of patients at this later stage of the r/r FL treatment pathway. The values from Wild et al/Pettengell et al have been used in other appraisals in either the base case (TA604)[33] or sensitivity analysis (TA627)[21] but are also associated with some limitations. The study dates back to 2006 and is not published with only the poster abstract available. The utility values from the study are widely quoted in NICE appraisals but the ERG has been unable to verify them in a published paper. Despite these limitations, the ERG prefers the increased face validity of the Wild et al study utility values in the base case but conclude the lack of relevant quality of life data in fourth line r/r FL patients remains a key uncertainty.

Adverse events

The quality-of-life impact of adverse events was captured in the model as a one-off utility decrement. The impact of grade ≥3 treatment-related adverse events in 5% or more patients in ZUMA-5 were included. In addition, all grades of adverse events were included for those considered to be clinically important for CAR T-cell therapies. The CS notes this approach is consistent with previous NICE CAR T-cell therapy appraisals. The following adverse events were modelled for axi-cel:

- Grade ≥3 axi-cel related adverse events occurring in 5% or more of subjects in ZUMA-5 (see CS table 32 for adverse events included)

- Grade ≥3 treatment-emergent CRS occurring in ZUMA-5 ([redacted]) and any grade CRS requiring treatments with tocilizumab ([redacted])
- Patients who received immunoglobulin treatment ([redacted])

For current 4L+ care, adverse event frequencies were sourced from clinical trial data reported in TA627 for the treatments included in the basket of current care. Only grade ≥3 adverse events that occurred in 5% or more of ZUMA-5 patients were included in the model, which the CS states is a conservative assumption.

In terms of utility decrements, a one-off QALY decrement of 0.15 was applied in the first model cycle for most grade ≥3 adverse events occurring in more than 5% of patients based on a study by Guadagnolo et al in patients with Hodgkin lymphoma.[40] For grade ≥3 CRS a quality of life of 0 was applied for the duration of the event ([redacted]) and for hypogammaglobulinaemia it was assumed there would be no impact on quality of life. The approach taken is consistent with that used in NICE appraisals of CAR T-cell treatment in advanced lymphoma (TA559 and TA677).[35, 37]

The approach to adverse event disutilities is generally consistent with other relevant NICE appraisals of CAR T-cell treatments. Some simplifying assumptions have been made but in general the ERG considers these assumptions are reasonable. One potential area of uncertainty is the adverse event durations were taken from ZUMA-1 and ZUMA-2 as reported in TA677/TA559 rather than ZUMA-5. No explanation was provided for this other than maintaining consistency with other relevant NICE appraisals. This is unlikely to be a key source of uncertainty.

4.2.8 Resources and costs

The costs and resource use included in the model can be categorised as follows: axi-cel treatment-related costs, current 4L+ costs and administration, costs of subsequent treatments, health state resource use, adverse event and end-of-life costs.

Axi-cel treatment-related costs

In addition to drug acquisition and monitoring costs for axi-cel, other treatment-related costs are incurred due to axi-cel production involving patient T-cells. These include:

- Leukapheresis to extract patient T-cells
- Bridging therapy for some patients to remain stable prior to the CAR T-cell infusion
- Conditioning chemotherapy

A summary of the axi-cel costs included in the model is provided in table 17 below.

Table 17: Summary of axi-cel treatment costs (adapted from Table 39, Document B of the CS)

Axi-cel cost category	Cost	Source and assumptions
Leukapheresis	[redacted]	• Same approach as used in previous NICE appraisals for CAR T-cell therapies (TA677 and TA559).[35, 37] • Cost uses weighted average of stem cell and bone marrow harvest from NHS reference costs (2019/2020).[41] • The weighted average cost (£1,953.38) was adjusted to account for patients ([redacted]) who underwent leukapheresis but did not receive axi-cel
Bridging therapy	[redacted]	• Bridging therapy cost consisted of 1 dose of rituximab based on the ZUMA-5 trial where [redacted] required bridging therapy.
Conditioning chemotherapy	£2,880.65	Drug cost: • IV cyclophosphamide and IV fludarabine on 5th, 4th and 3rd day prior to axi-cel infusion • Drug wastage was included • Resulting costs were £17.50 and £39.51 per dose for cyclophosphamide and fludarabine respectively Hospitalisations: • Assumed administered in hospital over 3 days in elective inpatient setting, consistent with other CAR-T therapies • Cost based on weighted average malignant lymphoma, including Hodgkin lymphoma and non-Hodgkin lymphoma from NHS reference costs 2019/2020 (£7,301.52).[41] • Mean cost per day of £903.20 per day based on mean length of stay of 8.1 days for malignant neoplasms of lymphoid, haematopoeietic and related tissues
Drug acquisition	[redacted]	• The drug acquisition cost of axi-cel is [redacted] at list price.

		• A patient access scheme (PAS) of [redacted] has been agreed with NHS England reducing the acquisition cost to [redacted]. • [redacted] of the [redacted] treated patients in ZUMA-5 received re-treatment with axi-cel, but the costs are not included as thisdoes not form part of the expected marketing authorisation and is not expected to occur in practice.
Infusion and monitoring	[redacted]	Following infusion, patients are monitored in an elective inpatient setting consistent with assumptions applied in other CAR T-cell appraisals • Cost of hospitalisation based on weighted average cost for malignant lymphoma, including Hodgkin lymphoma and non-Hodgkin lymphoma from NHS reference costs.[41] • ZUMA-5 mean duration of hospitalisation is [redacted] days. Hospitalisation cost based on mean cost per day of £903.30 for [redacted] days.
Total	[redacted]	

The ERG considers the costs associated with axi-cel treatment in general have been implemented appropriately in the model and are largely consistent with the approach used in other relevant NICE appraisals for CAR T-cell therapies (TA559 and TA677).[35, 37] *One area of uncertainty relates to axi-cel retreatment. Although [redacted] of patients required retreatment in the ZUMA-5 trial, the costs of this were not included in the model on the basis that retreatment would not occur in practice. Following clarification, the company provided an analysis including retreatment costs to align with the clinical effectiveness data used in the model. This analysis included the costs associated with the elements of retreatment received by the patients in the ZUMA-5 trial and increased the total axi-cel cost to [redacted] (see response to clarification letter QB2) resulting in a moderate increase to the ICER. The ERG notes that if the marketing authorisation specifies that retreatment is not permitted then the relevant costs for the model are those treatment patients would receive in practice, ie subsequent treatment costs, rather than axi-cel drug acquisition costs and therefore this sensitivity analysis may be considered conservative from a cost perspective.*

Clinical expert advice to the ERG confirmed that retreatment was unlikely to happen in practice at least in the short term.

Current 4L+ care costs

There is no single established treatment for patients who have received 3 or more lines of treatment for r/r FL. To estimate the cost of current treatment a weighted average basket of treatments was included based on the treatments patients received in SCHOLAR-5 adjusted to reflect treatments approved for routine use in England (see Table 15 above). Wastage was included for treatments administered intravenously. For oral treatments (lenalidomide and prednisolone) the most efficient pack size was included based on the dosing schedule. Administration costs were costed using NHS reference costs according to the complexity of the procedure with oral administration assumed to incur no costs (see CS, document B tables 43 and 44). No time on treatment data are available from SCHOLAR-5 to estimate treatment durations in the model and as such treatment durations were based on the median treatment durations reported in relevant SmPCs and assumed exponential time on treatment curves were assumed to the estimated treatment durations.

Clinical expert advice to the ERG confirmed the range and proportions of treatments included for current 4L+ are broadly reasonable and likely to reflect the treatments patients receive in practice. Stem cell transplant is not included as a treatment option, and this was considered appropriate. However, the adjustments made to better reflect treatment proportions used in practice may impact on the clinical effectiveness estimates of current 4L+ care as described in section 4.2.6. The adjustment to exclude idelalisib may work in favour of the comparator arm with an arguably more effective treatment efficacy being included without the cost. Conversely, the re-weighted proportions result in higher proportions of higher cost drugs obinutuzumab and lenalidomide being included in the costings but without any corresponding adjustment for efficacy. The direction of any bias as a result of these adjustments is unclear but on balance the ERG consider any bias to be in favour of current 4L+care. Another source of uncertainty is the use of the median time on treatment from the SmPCs which results in patients receiving current 4L+ treatments beyond progression. Clinical expert advice to the ERG indicates this would not occur in practice, as

patients would stop treatment upon progression. The ERG's preferred base case, therefore, assumes patients on current 4L+ treatments receive treatment until progression, reducing the cost of the comparator arm.

Subsequent treatment costs

The approach taken to model subsequent treatment costs is similar to that outlined above for current 4L+ care. On the basis that there is no established standard of care at this stage of the treatment pathway, it was assumed that the distribution of subsequent therapies is equal in both the axi-cel and current 4L+ care arms of the model. This is applied using a one-off subsequent treatment cost at the point of progression of £45,040.02 and administration cost of £10,131.55.

The ERG notes the simplifying assumption made that subsequent therapy costs are equal in both arms of the model and considered this may not be appropriate particularly as the model estimates post-progression survival benefit with axi-cel. Furthermore, since the comparator 4L+ care costs are recycled to approximate the costs of subsequent therapy, and the company's approach to modelling current 4L+ care costs allow for treatment beyond progression, this approach will likely overestimate subsequent treatments costs. However, if time on current 4L+ treatment is capped at PFS, then the approximated cost of subsequent treatment drops accordingly. While the exact cost of subsequent therapy is uncertain, the clinical expert advice to the ERG suggested that it is not unreasonable to assume equal subsequent costs between the arms.

Health-state unit costs and resource use

Health-state resource use was applied in the model to be consistent with previous FL NICE submissions and relevant clinical guidelines. Costs were applied to the pre-progression and progressed disease health states, with pre-progression further split into induction and maintenance phases. Resources included haematologist vists, diagnostic tests and CT scans. For axi-cel, the duration of the induction phase is 6 cycles followed by maintenance until year 5. Beyond year 5, patients who are alive and progression-free in the axi-cel arm (long-term survivors) are assumed to require no further resource use. For current 4L+ care, the duration of the induction phase was

7 cycles based on a weighted average of the treatments included. The health state resource use costs applied in the model are summarised in table 18.

Table 18: Summary of health state resource use assumptions (adapted from Table 47, Document B of the CS)

Resource use	Pre-progression (induction)	Pre-progression (maintenance)	Progressed disease
Haematologist visit	1 every 1 months	1 every 3.5 months	1 every 4 weeks
Diagnostic tests	1 every 1 months	1 every 3.5 months	1 every 4 weeks
CT scans	1 every 6 months	1 every 12 months	0
Total cost/cycle	**£171.20**	**£52.85**	**£152.82**
Key:CT, computerised tomography Cost source: NHS reference costs 2019/20[41]			

The resource use costs appear low but are largely consistent with those accepted in TA627 and have been validated by the ERG clinical expert. One source of uncertainty relates to the assumption that long-term survivors require no further monitoring beyond year 5. Clinical advice to the ERG suggests practice is variable with respect to long-term follow up, and at clarification the company included the cost of a GP visit every 6 months, which had minimal impact on the ICER. However, this remains a source of uncertainty as it may be that ongoing consultant visits are more realistic which would incur a higher cost. It was also noted that haematologist visits were costed assuming non-face-to-face attendance (£95.66), whereas TA627 used the cost of a face-to-face attendance (£171.18).[21] It is likely the non-face-to-face cost was applied on the assumption that virtual appointments are more likely during the COVID-19 pandemic, but clinical advice confirmed it is more appropriate to assume in person attendance in the model, particularly for progressed patients who would be receiving ongoing treatment.

Adverse event and end-of-life care costs

Most adverse event costs were applied as one-off costs in the first model cycle as a simplifying assumption. For axi-cel treated patients, it was assumed that the treatment-related monitoring and hospitalisation costs included the cost of managing most adverse events. An additional bed day cost was included for all patients experiencing grade ≥3 AE ([redacted]). Additional costs were also included for managing hyopgammaglobulinaemia and CRS.

The cost of intravenous immunoglobulin (IVIG) to treat hypogammaglobulinaemia was included for a proportion of patients ([redacted]). As treatment for this adverse event is ongoing, costs were applied to pre-progression patients for a duration of 12 months. This is consistent with the assumptions applied in TA677 and TA559. The weighted average cost applied was [redacted] per model cycle.

In ZUMA-5 [redacted] of patients required tocilizumab to manage CRS and this cost is included in the model [redacted]). In addition, patients experiencing grade 3/4 CRS ([redacted]) are assumed to be managed in intensive care, which is consistent with the costing approach taken in TA559 and TA677. A daily ICU cost of £1,508.65 was used based on a weighted average of the costs for supporting one or two organs. Length of stay was assumed to be 4 days to be consistent with TA559 and TA677 resulting in a grade 3/4 CRS cost of [redacted]. The total cost of CRS management included in the model is [redacted]. For current 4L+ care adverse events only those experienced by 5% or more of ZUMA-5 patients were included using rates reported in TA627 weighted by the treatments received in current practice. This was considered a conservative assumption.

Finally, the cost of end-of-life care was included as a one-off cost of £6,636.83 applied upon death. This was estimated from an average cost from the Round et al (2015) study which has been used in a number of submissions to NICE.[42]

The ERG considers the approach to modelling adverse events is generally appropriate and consistent with that used in other NICE appraisals.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's base case ICER at the time of the main submission is outlined in Table 19. With the PAS price applied for axi-cel, and publicly available prices applied for the comparator therapies, the ICER is £48,272. axi-cel is associated with an incremental cost of [redacted] for an incremental QALY gain of [redacted] over current 4L+ therapies. A confidential appendix will be provided for the committee, which includes confidential price discounts available for comparator and subsequent treatments.

Figure 27 and Figure 28 of the company submission provide graphical representations of the Markov trace for axi-cel and current 4L+ care respectively. The Excel model provides further breakdowns of the incremental cost and QALYs. The majority of the QALY gain results from increased time spent in the progression free state. However, there is also a substantial modelled life-year gain for axi-cel in the progressive disease state, inferring that those treated with axi-cel can be expected to survive for longer following progression compared to those who progress on current 4L+ therapies. With respect to the incremental cost, this is driven primarily by the additional drug acquisition costs for the index line of therapy in the model. axi-cel is associated with a saving in subsequent treatment costs (due to delayed/averted progression), a modest increase in adverse event costs and other HCRU costs, and slightly lower discounted end of life costs.

Table 19 Company base case deterministic results (with PAS for axi-cel), adapted from Table 55, Document B of the CS)

Technologies	Total costs (£)	Total LYG*	Total QALYs	Δ costs (£)	Δ LYG*	Δ QALYs	ICER (£/QALY)
Current 4L+ care	[redacted]	[redacted]	[redacted]	-	-	-	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,272
Key: 4L, fourth line; Δ, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year. *Life-years undiscounted.							

5.2 Company's sensitivity analyses

The company provided the results of probabilistic sensitivity analysis in Table 56 of their submission document B. The results are reproduced in Table 20 below. The incremental cost is very similar to the deterministic result, but the incremental QALY is slightly lower, resulting in a modest increase in the ICER. The company provide some further analysis which indicates that this difference is attributable to the asymmetric uncertainty surrounding correlated survival analysis parameters.

Table 20 Company base case probabilistic results (with PAS for axi-cel), adapted from Table 56, Document B of the CS)

Technologies	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£/QALY)
Current 4L+ care	[redacted]	[redacted]	[redacted]	[redacted]	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	£51,990

Key: 4L, fourth line; Δ, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year. *Life-years undiscounted.

The company provide results of one-way sensitivity analysis in Figure 32 and Table 57 of their submission. Their base case ICER was most sensitive to variation in the proportion of the axi-cel treated patients considered long-term survivors, followed by the utility value for the progression free state and the utility value for the progressive disease state. Hospital length of stay for axi-cel treatment, and the percentage requiring immunoglobulin, were also both relatively important.

With respect to scenario analyses conducted by the company, covering structural uncertainties and assumptions, these are provided in Table 58 of the company submission (document B). The ICER was relatively sensitive to assumptions around long-term survivorship; both the assumed proportion it applies to and the timepoint from which it applies. Capping the time on comparator 4L+ treatments to progression free survival, rather than overall survival, also had a modest upward impact on the ICER. *The ERG is of the opinion that the latter assumption is more appropriate based on its clinical advice. It is also more consistent with the assumption that all patients who are assumed to progress receive a one-off subsequent treatment costs in line with the modelled 4L+ comparator costs*.

The company provided limited exploration of alternative OS curve extrapolations for axi-cel and current 4L+ care. This focussed on the log-logistic as a more optimistic alternative for axi-cel, and the exponential as a more pessimistic alternative for current 4L+ care. Since curves for axi-cel were fitted to the whole mITT population of ZUMA-5 but used only for the extrapolation of OS of non-long-term survivors beyond 5 years, the ERG requested some further scenarios that applied higher risks of progression and death after five years for those not considered to be long-term survivors. The company provided this by applying SMRs of 1.09 and 1.2 to their preferred PFS and OS curves for axi-cel after 5 years, which had a modest upward impact on the ICER for axi-cel. They also provided a further scenario whereby they allowed the proportion of long-term survivors to update over time based on the split progression/survival assumptions. This resulted in a modest reduction in the ICER. Finally, the company also provided additional scenarios that applied axi-cel re-treatment costs as observed in ZUMA-5, reduced subsequent treatment costs by set percentages, and included some ongoing monitoring costs for long-term survivors beyond 5 years. The results of all the additional scenarios provided by the company in response to the clarification letter are replicated in Table 21 below.

Table 21 Further deterministic cost-effectiveness scenario results provided by the company's clarification response [source: Tables 3, 5, 6, 7 and 8 of the company's clarification response].

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£48,272	N/A
Increase risks of progression and death from 5 years for non-long-term survivors	Use PFS and OS curves fitted to whole mITT population of ZUMA-5.	Apply SMR of 1.09 to selected PFS and OS curve	[redacted]	[redacted]	£50,087	£1,814
		Apply SMR of 1.2 to selected PFS and OS curve	[redacted]	[redacted]	£52,326	£4,054
Dynamic updating of surviving proportion that are long-term survivors	Apply a static/fixed proportion of long-term survivors	Allow the proportion that are long-term survivors (in progression free and progressive disease states) to increase over time.	[redacted]	[redacted]	£46,105	-£2,168
Reduce subsequent treatment costs given lower expectations for PFS and OS in subsequent lines of therapy	Recycle total expected 4L+ care costs as one-off cost applied to progressed patients	Reduce subsequent treatment costs by 25%	[redacted]	[redacted]	£49,177	£905
		Reduce subsequent treatment costs by 50%	[redacted]	[redacted]	£50,081	£1,809
Regular 6 monthly GP visit applied to	No follow-up of long-term survivors from 5 years.	100%	[redacted]	[redacted]	£48,321	£48
		50%	[redacted]	[redacted]	£48,296	£24

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
percentage of long-term survivors		25%	[redacted]	[redacted]	£48,284	£12

5.3 Model validation and face validity check

In section B.3.10.1 of their submission document, the company describe quality assurance checks conducted on the model prior to submission. The ERG has similarly conducted its own consistency checks, using a combination of formula checking and black box tests suggested by Tappenden and Chilcott.[43] The results of the black-box tests are summarised in Table 22. No major issues were identified. Issues relating to structural inconsistencies and other uncertainties have been covered in the preceding sections.

A greater challenge is validating the survival projections produced by the model. The company acknowledge the immaturity of the PFS and OS data for the ZUMA-5 mITT population, which makes it challenging to extrapolate and validate the absolute and relative survival gains for axi-cel. There is further uncertainty regarding the long-term survivor assumptions applied in the model, and the use of the parametric PFS and OS curves (fitted to the whole mITT cohort of ZUMA-5) to model outcomes for only the non-long-term survivors from 5 years. There is potential with these assumptions to overestimate survival for axi-cel treated patients, particularly the non-long-term survivor proportion. It is worth further noting that the company base case does in fact project a substantial post progression survival gain for axi-cel, which could in part be down to unrealistic survival assumptions being applied to non-long-term survivors. However, there are plausible reasons why the introduction of axi-cel could confer a post progression survival benefit, including ongoing benefits of the CAR T-cells after progression, and the fact that it represents an additional treatment in the pathway, meaning that patients will have more of the current options available to them following progression than those in the comparator arm. On the latter point, however, it should be noted that patients in the axi-cel arm are not assumed to incur any increase in subsequent treatment costs compared to those who progress following treatment with current 4L+ therapies.

With the respect to the current 4L+ comparator, the company acknowledge the limitations of SCHOLAR-5 data for informing expected OS and PFS due to the substantial proportions that received idelalisib or experimental treatments that are not available routinely in England. The company also note that based on clinical feedback, patients with r/r FL are generally not expected to survive beyond 3 years

when treated with available 4L+ options in England. The modelling based on extrapolation of the survival data for SCHOLAR-5 does not appear to support this, despite fairly pessimistic parametric curves being selected, which suggests it may be overestimating OS compared what might be expected in the NHS in England. The ERG broadly agrees that there is potential for SCHOLAR-5 data to overestimate survival for the current 4L+ care arm, but it is difficult to verify this without actual data that is more applicable the NHS setting.

Given the above, there is considerable uncertainty surrounding the magnitude of the projected survival gain for axi-cel versus current 4L+ care.

Table 22 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	Equalised the survival curve parameters on the 'PSM inputs' sheet, switched all survival curves to the exponential distribution, removed the long term survivorship assumption and equalized the QALY decrement for adverse events. This led to equal QALY and LYG for the treatment arms.
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	No issues found.
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. Incremental costs behave as expected.

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
	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	Minimal effect on the axi-cel arm as drug acquisition costs are applied in the first cycle.
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	Not possible as several cost inputs are calculated as a one-off cost in the first cycle. Given the first test of clinical trajectory found no issues there is no concern.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a number of further scenario analyses to address uncertainties it believes the company had not fully explored. These are outlined below, with results provided in Table 23.

Given the uncertainty surrounding the long-term extrapolations of PFS, and in particular OS (section 4.2.6 above), the ERG undertook further scenario analysis around the choice of parametric survival curves for axi-cel and current 4L+ care (scenarios 1-4).

Further, due to the uncertainty arising from using curves fitted to PFS and OS data from the whole mITT cohort of ZUMA-5, to extrapolate only for non-long-term survivor from 5 years (section 4.2.6 above), the ERG extended the company's scenarios that inflate the hazard of the extrapolated progression and mortality from 5 years (Scenario 5 below).

Noting a possible anomaly in the model with respect to the long-term mortality risk of non-long-term survivors falling below that of long-term survivors (section 4.6), the ERG implemented a fix to cap OS for non-long-term survivors to that of long-term survivors (i.e. the SMR adjusted general population mortality) – Scenario 6 below.

To further explore the possibility of longer-term secondary care-based follow-up of long-term survivors (Section 4.8), the ERG explored the impact of applying the cost of haematology follow-up every 12 months beyond year 5 (Scenario 7).

To explore the possibility of patients treated with axi-cel having more untried treatment options available to them following recurrence, and surviving for longer in the progressive disease state, the ERG assessed the impact on reducing subsequent treatment costs following progression on current 4L+ care by set percentages relative to subsequent treatment costs following axi-cel (scenario 8).

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

The results of the additional scenario analyses outlined in section 6.1 are presented in Table 23 below. The greatest upward uncertainty in the ICER for axi-cel arises form more optimistic extrapolations of OS for current 4L+ care (scenario 3); more pessimistic extrapolation of OS for non-long-term axi-cel survivors (scenario 5); and relative increases in the cost of subsequent treatment for those who progress on axi-cel versus those who progress on current 4L+ care (scenario 8). The ICER for axi-cel is reduced somewhat with the selection of the more pessimistic exponential extrapolation of OS for current 4L+ care (scenario 3), and more optimistic extrapolation of PFS for axi-cel (scenario 2).

Table 23 Results of the ERG's further scenario analysis around the company base case

Setting	Company base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£48,272	N/A
1. PFS extrapolation (4L+)	Exponential	Generalised gamma	[redacted]	[redacted]	£48,357	£84
		Lognormal	[redacted]	[redacted]	£48,385	£113
2. PFS extrapolation (axi-cel)	Weibull	Generalised gamma	[redacted]	[redacted]	£46,698	-£1,574
3. OS extrapolation (4L+)	Gamma	Lognormal	[redacted]	[redacted]	£58,745	£10,473
		Weibull	[redacted]	[redacted]	£50,898	£2,626
		Exponential	[redacted]	[redacted]	£44,530	-£3,742
4. OS extrapolation (4L+)	Weibull	No plausible less optimistic alternative available when non-long term survivors modelled as a fixed proportion.				
5. Increase risks of progression or death in non-long-term survivors	SMR = 1	SMR = 1.09	[redacted]	[redacted]	£50,087	£1,814
		SMR = 1.2	[redacted]	[redacted]	£52,326	£4,054
		SMR = 1.5	[redacted]	[redacted]	£58,552	£10,280
		SMR = 2	[redacted]	[redacted]	£69,258	£20,986

Setting	Company base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
6. OS cap for non-long-term survivors	General population survival	General population SMR adjusted survival	[redacted]	[redacted]	£48,354	£82
7. Follow up of long term survivors.	No follow-up of long-term survivors from 5 years.	Assume annual haematologist visit for all	[redacted]	[redacted]	£48,331	£59
8. Costs of subsequent therapy following progression (Axi-cel)	Costs equal between arms upon progression	Costs in 4L+ arm reduced by 10%	[redacted]	[redacted]	£49,283	£1,011
		Costs in 4L+ arm reduced by 25%	[redacted]	[redacted]	£50,799	£2,527
		Costs in 4L+ arm reduced by 50%	[redacted]	[redacted]	£53,327	£5,055

6.3 ERG's preferred assumptions

Based on the critique providing the preceding sections of this report, the ERGs preferred assumptions for its base case analysis are as follows**:**

1. Given the company's approach to assuming different risks of progression and death for long-term and non-long-term survivors from 5 years, the ERG prefers the company's amendment that allows for the OS and PFS survival to be extrapolated separately from 5 years for the two groups. This allows time dependent updating of the proportion of survivors that are long-term survivors/non-long-term survivors, so that the weighted average hazard of death or progression can be accurately calculated.
2. Because the OS and PFS curves for axi-cel were fitted for the whole mITT population of ZUMA-5, but then from 5 years only used to extrapolate outcomes for non-long-term survivors, there is a risk the chosen curves will result in upward bias of PFS and OS for this group. The ERG, therefore, believes that a downward adjustment should be applied to the PFS and OS extrapolation curves from 5 years when the modelled hazards are a split by long-term survival status. The ERG, therefore, applies an SMR of 1.2 to the chosen curves from 5 years. Accepting that the chosen SMR is arbitrary, further scenario analysis is conducted around this parameter from the ERG preferred base case.
3. Capping of overall survival of non-long-term survivors at SMR adjusted general population mortality, to avoid the risk of death in non-long-term survivors dropping below that of long-term survivors.
4. Capping current 4L+ care time on treatment to the selected PFS curve for current 4L+ care. This assumes that treatment can continue up to the point of progression but not beyond as assumed in the company base case. This is justified by clinical advice to the ERG and the company's approach to modelling subsequent treatment costs upon progression.
5. Lower utility values reported by *Wild et al and Pettengell et al* for the progression free and progressive disease state, to account for the fact the current population is more heavily treated and at a later stage in the disease pathway than the population considered in TA627.[5, 21, 39]

6. Retain PF health state utility from Wild et al. for long-term survivors from 5 years.[39] The company scenario using Wild et al assumes general population utility from 5 years for long-term survivors.

The cumulative effect of these changes on the ICER are illustrated in Table 24 below. Combined, they result in a modest increase in the ICER, to £56,332 per QALY gained. The results of probabilistic analysis from this alternative base case are provided in Table 25 and Figure 3 and 4.

Given remaining uncertainties related to the economic case for axi-cel, the ERG also conducted further scenario analysis around its revised base case (Table 26), including: alternative curve selections for PFS and OS (scenarios 1-4); an increased risk of mortality and progression in non-long-term survivors, above those projected by the curves fitted to the axi-cel cohort as a whole (scenario 5); relative reductions in the cost of subsequent treatment following progression on current 4L+ care compared to progression on axi-cel (scenario 6); changes to the assumed long-term survivor fraction (scenario 7); and increasing the SMR used to adjust the survival of long-term survivors relative of general population survival (scenario 8).

Table 24 ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Incremental cost	Incremental QALY	Cumulative ICER £/QALY	Change from company base case
Company base-case		[redacted]	[redacted]	£48,272	
1. Time dependent updating of long-term survivor proportion from 5 years	*4.2.6*	[redacted]	[redacted]	£46,105	-£2,168
2. Increase progression and mortality risks by 20% after 5 years non-long-term survivors	*4.2.6*	[redacted]	[redacted]	£48,709	£437
3. Cap overall survival of non-long-term survivors at SMR adjusted general population mortality	*4.2.6*	[redacted]	[redacted]	£48,749	£477
4. Capping the current 4L+ time on treatment to the selected PFS curve for current 4L+ care	*4.2.8*	[redacted]	[redacted]	£54,736	£6,464
5. Apply Wild et al/Pettengell et al. utility values for progression free and progressive disease states.	*4.2.7*	[redacted]	[redacted]	£55,383	£7,111
6. Retain PF health state utility from Wilde et al. for long-term survival from 5 years	*4.2.7*	[redacted]	[redacted]	£56,332	£8,060

Table 25 ERG base case (probabilistic)

Technology	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALYs)
Current 4L+ care	[redacted]	[redacted]			
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	£58,773

Figure 3 Cost-effectiveness scatter-plot (ERG base case)

Figure 4 Cost-effectiveness acceptability curve (ERG base case)

Table 26 Additional scenario analysis around the ERG preferred base case

Setting	ERG Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£56,332	N/A
1. PFS extrapolation (4L+)	Exponential	Generalised gamma	[redacted]	[redacted]	£56,541	£209
		Lognormal	[redacted]	[redacted]	£56,550	£218
2. PFS extrapolation (axi-cel)	Weibull	Generalised gamma	[redacted]	[redacted]	£54,950	-£1,382
3. OS extrapolation (4L+)	Gamma	Lognormal	[redacted]	[redacted]	£67,765	£11,433
		Weibull	[redacted]	[redacted]	£59,171	£2,839
		Exponential	[redacted]	[redacted]	£52,383	-£3,949
4. OS extrapolation (4L+)	Weibull	Generalised gamma	[redacted]	[redacted]	£73,034	£16,702
5. Increase risks of progression or death in non-long-term survivors	SMR = 1.2 over selected PFS and OS curves	SMR = 1	[redacted]	[redacted]	£53,470	-£2,862
		SMR = 1.09	[redacted]	[redacted]	£54,797	-£1,535
		SMR = 1.5	[redacted]	[redacted]	£60,084	£3,752
		SMR = 2	[redacted]	[redacted]	£65,190	£8,858
6. Costs of subsequent therapy following progression (4L+)	Costs equal between arms upon progression	Costs in 4L+ arm reduced by 10%	[redacted]	[redacted]	£56,887	£555
		Costs in 4L+ arm reduced by 25%	[redacted]	[redacted]	£57,721	£1,389

Setting	ERG Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
		Costs in 4L+ arm reduced by 50%	[redacted]	[redacted]	£59,109	£2,777
7. Long term survivor proportion	25%	10%	[redacted]	[redacted]	£66,840	£10,508
		All who are alive and progression free at 5 years	[redacted]	[redacted]	£52,130	-£4,202
8. SMR applied to long term susrvivors	SMR = 1.09	SMR = 1.2	[redacted]	[redacted]	£57,142	£810

6.4 Conclusions of the cost effectiveness section

The company have provided robust and flexible model to assess the cost-effectiveness of axi-cel versus current 4L+ care for patients with r/r FL. The case is broadly in line with the final scope for the appraisal, although it focusses a sub-group of wider population defined. The cost-effectiveness case is inherently uncertain given the lack of a randomized comparator in the clinical data, and the immaturity of the PFS and OS data for axi-cel from the ZUMA-5 trial. The company acknowledge the uncertainty and consider that axi-cel would be a suitable candidate for cancer drug fund approval, so that current uncertainties can be addressed.

The ERG believe that company have provided a reasonable estimate of the ICER given the data available but suggest a number of changes may be justified which result in a modest increase in the ICER. The ERG believes that a number of uncertainties were not identified or fully explored in the original company submission. However, these issues have been addressed in further scenario analysis provided by the company in response to clarification letter and further scenario analysis undertaken by the ERG. The remaining areas of uncertainty that result in the greatest uncertainty in the ICER are:

1. the proportion of patients that can be considered long-term survivors following treatment with axi-cel, and the time point from which this applies.
2. the assumptions around overall survival extrapolation for those considered to be long-term survivors and those who considered to be non-long-term survivors.
3. The OS for patients treated with current 4L+ therapies available in the NHS
4. The costs of current 4L+ treatment based on time on treatment assumed, and whether this should be capped using the PFS curve from SCHOLAR-5 or allowed to continue beyond progression.
5. Related to point 4, the cost of subsequent treatment that is assumed to apply in the model, and whether it is reasonable to assume this is equal between treatment arms or that it could potentially be higher following progression on axi-cel.

7 End of life

The company make a case for axi-cel being considered an end-of-life drug for the current indication (see section B.2.13.14 of the company submission). The company claim that life expectancy in this cohort is usually approximately three years and refer to their SCHOLAR-5 data and clinical expert opinion. They acknowledge that this is longer than the 24 months stated in the NICE end of life criteria, but they also note that they believe clinicians would adopt axi-cel as an end-of-life treatment in NHS England - perhaps suggesting that clinicians would use it more judiciously in those with lower life expectancy at its 4L+ positioning. It is not in doubt that axi-cel can be expected to deliver gains in overall survival of more than three months.

The ERG acknowledges the company's case but would note that it is median overall survival in SCHOLAR-5 that is close to 3 years, rather than average life expectancy (which is unobserved). The extrapolation modelling for the company base case suggests a mean undiscounted life expectancy of [redacted] *years in the current 4L+ care arm. Given this, the end-of-life criteria is not strictly met.*

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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 low-grade non-Hodgkin lymphoma [ID1685]

'*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 Friday 25 March 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 <u>confidential information</u>, 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

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table: List of Abbreviations 1. Definition of BOR is 'Best Objective Response' 2. Definition of ORR is 'Overall response rate'	1. Please define BOR as 'Best Overall Response' in the table and subsequent text 2. Please define ORR as 'Objective response rate' in the table and subsequent text	The amendments will make the definitions consistent with the Company Submission for BOR and ORR	Accepted. Changes made.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive Summary; Page X and Page 20 The description of DOR is not clear, and the 95% CI are not reproduced in full	Please could you amend the sentence to read 'the median duration of response (DOR) was not reached in all responders: [redacted]	The amendment will clarify that what the full range of the 95% CI is	Accepted. Change made.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Executive Summary: Page xi The description of	Please could you remove the word 'prior' from the population wording such that it reads '[redacted]	This amendment will bring the wording of the anticipated	Accepted. Change made

the population of interest incudes the word ‘prior’		population in line with the Company Submission	

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 19 There is a typo in the description of the patient population of interest	Please could you remove the word ‘of’ from the population wording and replace with ‘or’ such that it reads “Thus, the primary endpoint of ZUMA-5 is not relevant to this appraisal, the focus of which is patients with r/r FL with three or more lines of prior therapy”	This amendment will remove the typo in the description of the population of interest to the submission	Accepted. Change made

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21 The reported values for PFS rates at months 12 and 18 are incorrect	Please could you replace the current 12 and 18 estimated PFS rates in the mITT population from: “In the mITT population, median PFS was not reached ([redacted]), with a median follow-up of [redacted] months. A total of [redacted] participants had progressed or died at the time of analysis. Estimated PFS rates at months 12 and 18 were [redacted] respectively” To	This amendment will correct the data for the 12 and 18 month PFS rates for the mITT population, and will also add in the AIC marking for the ‘not reached’ data	Accepted. Change made.

	"In the mITT population, median PFS was [redacted] ([redacted]), with a median follow-up of [redacted] months. A total of [redacted] participants had progressed or died at the time of analysis. Estimated PFS rates at months 12 and 18 were [redacted] respectively"		

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 10 1. The reported values for PFS progression/death for IAS are incorrect 2. The reported values for estimated 12 and 18-month PFS rates for mITT are incorrect	1. Please could you replace the current progression / death value for PFS of [redacted] 2. Please could you replace the current estimated PFS rates at month 12 and month 18 in the mITT rows as follows a. Estimated PFS rate at month 12, %(95%CI): [redacted] **to** [redacted] b. Estimated PFS rate at month 18, %(95%CI): [redacted] **to** [redacted]	This amendment will correct the typos in Table 10	Accepted. Changes made

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 The values for Grade ≥3 sinus tachycardia and neutropenia are incorrect and the resulting statement is incorrect as sinus tachycardia is not a common Grade ≥3 AEs	1. Please correct the value for sinus tachycardia from [redacted] patients ([redacted] to [redacted] patient ([redacted] 2. Please correct the value for neutropenia from [redacted] patients ([redacted] to [redacted] patients ([redacted]%) 3. Please revise the sentence to: "The most common Grade ≥3 AEs were neutropenia ([redacted] patients [[redacted] anaemia ([redacted] patients [[redacted]%]) and pyrexia ([redacted] patients [[redacted]%])	This amendment will correct the statement describing the most common Grade ≥3 AEs in ZUMA-5	Accepted. Changes made and we have deleted sinus tachycardia from the sentence.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33 and Page 35, and Page 36 The population is described as remitting or relapsed follicular lymphoma	The population should be described as "relapsed or refractory", rather than "remitting or relapsed"	Consistent with population addressed in the decision problem and anticipated marketing authorisation, and consistent with terminology in prior NICE appraisals	Accepted. Corrections made.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 54 The end-of-life care one-off cost is	The end of life care one-off cost applied in the model in the company submission was £6,636.83	Typographical error	Accepted. Correction made.

reported as £6,361.77.			

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69 – Table 25, Column 1 The labels for technology are inaccurate (currently read "Company base-case" and "1. Time dependent updating of long-term survivor proportion from 5 years"	These labels should read "Current 4L+ care" and "Axi-cel"	Typographical error	Thank you. Correction made.

(please cut and paste further tables as necessary)

Errors in AIC/CIC Markings

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.	
ERG report – Executive summary (page x)	The number of patients alive and progression-free at the time of analysis should be marked as AIC "At the time of analysis, 40/60 (66.7%) of participants were alive and progression-free"	At the time of analysis, [redacted] of participants were alive and progression-free	Accepted. Change made.

ERG report – Executive summary (page xiii)	The immature DOR, PFS and OS statement should be marked as AIC "Data from ZUMA-5 are immature with median DOR, PFS and OS yet to be reached within the current 18-month follow-up analysis"	Data from ZUMA-5 are immature with [redacted] within the current 18-month follow-up analysis	Accepted. Change made.
ERG report – Executive summary (page xix)	The end-of-life median overall survival and modelled life expectancy should be marked as AIC "However, both median overall survival and modelled life expectancy in the comparator arm are greater than 24 months (see chapter 7)"	However, both median overall survival and modelled life expectancy in the comparator arm are [redacted] (see chapter 7).	Accepted. Change made.
ERG report – Page 18	The description of patient characteristics in ZUMA-5 should be marked as AIC "The median age of participants was 60.5 years (62.0 years in the IAS) and more than half of participants were males. More participants had ECOG scores of 0 than 1 but the difference was not substantial. Around half of the participants had Grade 2 FL, with the remaining participants being split quite evenly between Grades 1 and 3a. Around half of the participants were high risk, according to the FLIPI total score, and the majority had refractory disease rather than relapsed. The median number of prior therapies was four and around one-third of participants had five or more prior therapies. Time to relapse from first anti-CD20-chemotherapy was <24 months in over half of participants"	"The median age of participants was [redacted] years ([redacted] years in the IAS) and [redacted] of participants were males. [redacted] participants had ECOG scores of 0 than 1 but the difference was not substantial. [redacted] of the participants had Grade 2 FL, with the remaining participants being split quite evenly between Grades 1 and 3a. [redacted] of the participants were high risk, according to the FLIPI total score, and the [redacted] had refractory disease rather than relapsed. The median number of prior therapies was [redacted] and around [redacted] of participants had [redacted] prior therapies. Time to relapse from first anti-CD20-chemotherapy was [redacted] months in [redacted] of participants"	Accepted. Change made.

ERG report – Page 19	The prespecified value for CR should be marked as AIC "[redacted] participants achieved a CR ([redacted]; exact test for CR≤15%: [redacted])"	"[redacted] participants achieved a CR ([redacted]; exact test for CR [redacted])"	Accepted. Change made.
ERG report – Page 20	The median DOR result should be marked as AIC "In the mITT population, median DOR in the [redacted] responders was not reached; the median follow-up time was [redacted] months"	In the mITT population, median DOR in the [redacted] responders was [redacted]; the median follow-up time was [redacted] months"	Accepted. Change made.
ERG report – Page 25	The reporting of CRS should be marked as AIC "Of the FL patients with ≥3 lines of prior therapy, [redacted] experienced a CRS event, of which [redacted] had Grade ≥3 CRS, and one (1%) had Grade 5 CRS"	Of the FL patients with ≥3 lines of prior therapy, [redacted] experienced a CRS event, of which [redacted] had Grade ≥3 CRS, and [redacted] had Grade 5 CRS	The numerical text in this sentence is already marked as AIC. For precision, we have also highlighted those % symbols, which were left out.
ERG report – Page 26	The word 'three' has incomplete AIC marking "T[redacted] had unresolved neurological events at the 18-month analysis data cut-off"	"[redacted] had unresolved neurological events at the 18-month analysis data cut-off"	Accepted. Change made.
ERG report – Page 26	The value for cytopenia should be marked as AIC "Of the patients with ≥3 lines of therapy, 60 (77%) experienced a cytopenia of any grade"	Of the patients with ≥3 lines of therapy, [redacted] experienced a cytopenia of any grade	Accepted. Change made.
ERG report – Page 28	The value for infections (number 18) should be marked as AIC in full "Infections were experienced by [redacted] patients ([redacted]%), of whom [redacted] ([redacted] had worst Grade 3 infections"	Infections were experienced by [redacted] patients ([redacted]%), of whom [redacted] ([redacted] had worst Grade 3 infections	Accepted. Change made.

ERG report – Table 16 (page 46)	Baseline age in ZUMA-5 should be marked as AIC "Age-matched general population 0.829 at baseline (60 years)"	Age-matched general population 0.829 at baseline ([redacted] years)	Accepted. Change made
ERG report – Table 16 (page 46)	Baseline age in ZUMA-5 should be marked as AIC "Age-matched general population (with relative decrement) 0.803 at baseline (60 years)"	Age-matched general population (with relative decrement) 0.803 at baseline ([redacted] years)	Accepted. Change made
ERG report – Section 4.2.7 (page 48)	Duration of CRS events should be marked AIC "For grade ≥3 CRS a quality of life of 0 was applied for the duration of the event (6 days) and for hypogammaglobulinaemia it was assumed there would be no impact on quality of life."	For grade ≥3 CRS a quality of life of 0 was applied for the duration of the event ([redacted]) and for hypogammaglobulinaemia it was assumed there would be no impact on quality of life."	Accepted. Change made

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Technical engagement response form

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm on 11th May 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Kite, a Gilead company
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2: Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Differences between the ZUMA-5 and SCHOLAR-5 cohorts in term of prior treatment received by SCHOLAR-5 patients.	Yes	SCHOLAR-5 was used as an external control for ZUMA-5, after alignment to the ZUMA-5 population using propensity score weighting to adjust for known confounders. As described in the original submission, the SCHOLAR-5 cohort comprised patients from multiple data sources: • Cohort A – retrospective cohort created from electronic medical records of six sites, including university hospitals and cancer centres with two sites based in the UK and other sites based in France, Spain, Portugal and the US • Cohort B – retrospective cohort created from the Vanderbilt University Medical Center's Synthetic Derivative: a fully de-identified database derivative of electronic medical records from the university • Cohort C – prospective cohort created from an open-label Phase II study, DELTA, that enrolled patients with r/r FL who had not responded to or were refractory to rituximab and an alkylating agent and were treated with idelalisib Although the index line of treatment used in SCHOLAR-5 for patients from the DELTA clinical trial (Cohort C) was for the line of therapy received after completion of idelalisib, this group of patients could

		be considered less generalisable to England, as idelalisib was not recommended by NICE for treating FL that has not responded to two prior lines of treatments in adults. In the original submission, the SCHOLAR-5 analyses utilized all included patients (Cohorts A–C) for the assessment of OS; however, due to the absence of progression assessment dates in the index line of therapy for patients from DELTA (Cohort C), these patients could not be included in the PFS analyses, and were excluded post propensity score weighting. The number at risk post-weighting for the PFS endpoint in the submission was consequently lower (n = [redacted]) than the number at risk for OS (n = [redacted]). As such, there was a discrepancy between the populations informing time-to-event data across endpoints in the current 4L+ care arm of the cost-effectiveness analysis. In response to key issue 1, and as requested by the ERG, we have updated the SCHOLAR-5 analyses such that DELTA patients (Cohort C) are removed from the OS and PFS analyses prior to propensity score weighting to match to ZUMA-5. We acknowledge that the removal of DELTA patients from SCHOLAR-5 may not fully resolve all the uncertainty relating to (i) differences between the ZUMA-5 and SCHOLAR-5 cohorts in terms of prior treatment received, and (ii) generalisability of SCHOLAR-5 to the NHS in England. However, we agree with the ERG that this analysis improves comparability, generalisability, and consistency (across OS and PFS analyses), and we have therefore used the updated analysis in our revised economic base case following technical engagement. The impact of excluding DELTA patients from SCHOLAR-5 prior to propensity score weighting on cost-effectiveness results is presented in Table 6. Figure 1 compares current 4L+ care (SCHOLAR-5) Kaplan-Meier data and extrapolations for OS when (i) including DELTA patients in SCHOLAR-5 (per the original submission) and (ii) excluding DELTA from SCHOLAR-5 before propensity score weighting (revised analysis). Table 3 presents landmark OS

		estimates for each parametric survival model for SCHOLAR-5 when excluding DELTA patients prior to propensity score weighting to match to ZUMA-5. As reported in the original submission, although survival expectations depend on several factors, including previous treatment regimens received and response to previous treatment, patients are generally not expected to survive beyond approximately three years with current 4L+ care options that are currently available in England. The three parametric models which produce mean survival estimates of less than 5 years were tested in the revised analysis (gamma, exponential, and Weibull), based on the plausibility of the long-term extrapolations. The gamma curve is selected in the revised base case, which is consistent with the original analysis including DELTA. **Figure 1: Current 4L+ care (SCHOLAR-5) – OS, original submission (left) and revised analysis excluding DELTA before weighting (right)** 

Table 3: Current 4L+ care - OS landmarks - SCHOLAR-5, excluding DELTA before propensity score weighting

Model	Mean (months)	Median (months)	6 months	12 months	24 months	60 months
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 2 compares current 4L+ care (SCHOLAR-5) Kaplan-Meier data and extrapolations for PFS when (i) excluding DELTA patients from SCHOLAR-5 PFS analysis after propensity score weighting (per the original submission) and (ii) excluding DELTA from SCHOLAR-5 before propensity score weighting (revised analysis). Table 4 presents landmark PFS estimates for each parametric survival model for SCHOLAR-5 when excluding DELTA patients prior to propensity score weighting to match to ZUMA-5.

The impact of excluding DELTA patients before propensity score weighting (rather than after weighting per the original submission) on SCHOLAR-5 PFS outcomes is minimal. In line with the original submission, the exponential curve was selected in the revised base case. As is also consistent with the original submission, the choice of survival extrapolation does not have a large impact on the long-term PFS estimate given the maturity of the SCHOLAR-5 PFS data.

Figure 2: Current 4L+ care (SCHOLAR-5) – PFS, original submission (left) and revised analysis excluding DELTA before weighting (right)

Table 4: Current 4L+ care - PFS landmarks - SCHOLAR-5, excluding DELTA before propensity score weighting

Model	Mean (months)	Median (months)	6 months	12 months	24 months	60 months
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gen. Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The proportion of patients who can be considered long term survivors following treatment with axicabtagene ciloleucel	No	We agree with the ERG that the precise proportion of patients treated with axi-cel achieving long-term survivorship, and SMR for long-term survivors compared with the general population, remains uncertain in the absence of longer-term follow up data. Given this inherent uncertainty, we believe axi-cel is a suitable candidate for the CDF. In the CDF, axi-cel would offer clinicians a much-needed effective treatment option for 4L+ patients with r/r FL, while allowing time for further data collection, as needed to more robustly assess the cost effectiveness before a final decision on routine reimbursement is made. [redacted]
The PFS and OS extrapolation assumptions for axicabtagene ciloleucel non-long-term survivors.	No	We agree with the ERG that the proportion of long-term survivors comprising the cohort over time should be dynamic, rather than a fixed proportion applied at each model cycle. As such, the base case has been revised (Table 6) in line with the ERG preferred assumptions. Furthermore, we acknowledge that parametric survival curves were fitted for the overall subgroup of ZUMA-5 that matches the proposed positioning of axi-cel (4L+ patients with FL), which includes patients assumed to achieve long-term survivorship. As such, the hazard for non-long-term survivors beyond 5 years could be underestimated when extrapolating using data for the overall subgroup. Although the value of 1.20 used in the ERG base case to inflate the risk of progression and death in non-long-term survivors beyond 5 years is arbitrary, we accept this assumption in the absence of longer-term follow-up data and as such the base case has been updated (Table 6).
Health state utility values applied in the model	No	In the absence of HRQL data from ZUMA-5, committee-preferred assumptions reported in the NICE FAD for lenalidomide with rituximab for treated FL (TA627) were considered in the original base case at the time of this submission. As such, general population utility values were used in the progression-free state, with relative decrements from AUGMENT used in the progressed state.

		However, we acknowledge the ERG's concern that as most (>75%) of the population considered in TA627 (AUGMENT) were treated at an earlier line of therapy and therefore may be expected to have a higher health-related quality of life than the 4L+ patients considered in this appraisal. As such, we have adopted the source of utility values used in the ERG base case (Wild et al.) in our revised base case (Table 6). In the ERG's preferred base case, it is assumed the utility value reported by Wild et al. for the progression-free health state would be retained for those who are alive and free of progression beyond 5 years, i.e. long-term survivors suffer a utility decrement compared with the general population for rest of life. We note that this approach is inconsistent with prior appraisals of CAR-T cell therapies in advanced lymphoma indications. In TA559, age-equivalent general population utility was assumed for those with relapse-free disease at 2 years and beyond. Similarly in TA677, general population utility was assumed for patients whose disease had not progressed after 5 years. Therefore, in line with previous appraisals, in our revised base case it is assumed that the health-related quality of life for those patients who are alive and free of progression at 5 years and beyond returns to that of the general population. The impact of using the utility values reported by Wild et al. and assuming general population health-related quality of life for those patients who are alive and free of progression at 5 years and beyond on cost-effectiveness results is presented in the revised base case (Table 6). Given that long-term survivors experience a heightened risk of mortality compared with the general population (captured through the SMR in the economic analysis), it is acknowledged that the health-related quality of life of those who are alive and free of progression after 5 years is uncertain and may not fully return to that of the general population. As such, in the absence of longer-term health-related quality of life data, we have provided an additional scenario assuming the utility of patients who are alive and progression-free after 5 years falls between the ERG base case (sustained Wild et al. utility) and our revised base case (return to general population utility). In this scenario (Table 8), the health-related

		quality of life of those patients alive and progression-free beyond 5 years is reduced by a multiplier equal to half the relative decrement of Wild et al. (0.805) versus general population at baseline (0.829) (this results in a general population utility multiplier of 98.6%, since 0.986 is halfway between 0.971 [0.805/0.829] and 1). This scenario has a minimal impact on the ICER.
The capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	No	We acknowledge the ERG's concern that allowing treatment beyond progression, whilst applying subsequent treatment costs at the point of progression may, in some cases, overestimate costs in the current 4L+ care arm of the model. Given the uncertainty in overall time on treatment for current 4L+ care, we adopt the ERG's preferred base case assumption of capping comparator time on treatment at progression-free survival in the revised base case (Table 6).
Key: 4L+, fourth-line plus; CDF, Cancer Drugs Fund; ERG, Evidence Review Group; FAD, Final Appraisal Determination; FL, follicular lymphoma; HRQL, health-related quality of life; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; r/r, relapsed or refractory; SMR, standardized mortality ratio; TA, technology 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 5: 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: End of life	Section 7	Yes	As reported in the original submission, we believe axi-cel would be adopted by clinicians as an end-of-life therapy in NHS England. In the revised SCHOLAR-5 analyses that better aligns to the ZUMA-5 population and expected real-world population, the estimated median life expectancy with current 4L + care is shown to be [redacted] months (Table 3). While this is still slightly longer than the "normally less than 24 month" criteria applied to an assessment of short life expectancy within end of life assessments by NICE, it does reflect short life expectancy in real terms to patients and their carers. Considered alongside the significant unmet need (with no established clinical care), and the physical and emotional burden of experiencing a third relapse within a chronic and progressive disease cycle, this is a severe disease setting for which patients, clinicians and wider society are likely to highly value effective treatment options. Further, this is a setting where we would expect the committee to be able to apply a greater weight to QALYs if the severity decision modifier was applicable, rather than the end-of-life modifier.
Key: 4L+, fourth-line plus; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; QALY, quality adjusted life year.			

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 6: 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 base-case (reported in submission); axi-cel versus current 4L+ care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £48,272
Issue 1: Comparability of ZUMA-5 with SCHOLAR-5 data	• Included DELTA patients in the SCHOLAR-5 cohort before propensity score weighting, despite idelalisib not being recommended by NICE for patients with FL • Excluded DELTA patients from PFS post-weighting, as DELTA did not collect progression data for subsequent lines of therapy	Excluded DELTA patients (Cohort C) from the SCHOLAR-5 cohort before performing propensity score weighting to align with the ZUMA-5 cohort	ICER: £41,213 ICER change from base case: -£7,059

Issue 3: The PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	• No mortality adjustment for non-long-term survivors beyond 5 years • Apply a fixed proportion of long-term survivors over time • Cap the hazard of death for non-long-term survivors at the unadjusted general population mortality hazard	• Inflate the mortality of non-long-term survivors beyond 5 years by 1.20 (in line with ERG base case) • Allow the proportion of long-term survivors to change over time (in line with ERG base case) • Cap the hazard of death for non-long-term survivors at the SMR-adjusted general population mortality hazard (in line with ERG base case)	ICER: £48,749 ICER change from base case: +£477
Issue 4: Health state utility values	• Progression-free utility source: TA627 (general population) • Progressed disease utility source: TA627 (general population with decrement from AUGMENT)	• Progression-free utility source: Wild et al. (in line with ERG base case) • Progressed disease utility source: Wild et al. (in line with ERG base case) • Assume health-related quality of life returns the that of the general population for those patients alive and free of progression at 5 years and beyond (in line with prior appraisals TA559 and TA677)	ICER: £49,296 ICER change from base case: +£1,024

Issue 5: The capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Cap current 4L+ care time on treatment at overall survival	Cap current 4L+ care time on treatment at progression-free survival (in line with ERG base case)	ICER: £54,163 ICER change from base case: +£5,891
ERG base case (reported in ERG report); axi-cel versus current 4L+ care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £56,332
ERG preferred assumptions (with updated SCHOLAR-5 analysis excluding DELTA in response to key issue 1); axi-cel versus current 4L+ care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £48,606
Gilead base case following technical engagement; axi-cel versus current 4L+ care			Incremental costs: [redacted] Incremental QALYs: [redacted] ICER: £47,905
Key: 4L+, fourth-line plus; ERG, Evidence Review Group; FL, follicular lymphoma; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; SMR, standardized mortality ratio; TA, technology appraisal.			

Sensitivity analyses around revised base case

Probabilistic sensitivity analysis (PSA) was conducted around the revised company base case. To ensure convergence, all inputs were varied simultaneously over 2,000 iterations (rolling average incremental costs, LYs and QALYs were plotted on convergence graphs within the cost-effectiveness model and visually inspected). All PSA iterations indicate that axi-cel provides an incremental QALY benefit versus current 4L+ care, at an increased total cost (Figure 3). When comparing average PSA results with deterministic results (Table 7), incremental costs are consistent and incremental QALYs marginally lower, leading to a marginally higher mean PSA ICER (£49,906 versus £47,905). The cost-effectiveness acceptability curve (Figure 3) demonstrates that axi-cel (with PAS) is more likely to be a cost-effective treatment option when compared with current 4L+ care at a willingness-to-pay threshold of approximately £50,000 per QALY gained.

Revised OWSA results (Figure 4) were consistent with the original submission, with the proportion of patients receiving axi-cel that are long-term survivors identified as the parameter with the greatest influence on results.

Scenario analyses around the revised base case are presented in Table 8. Results were generally consistent with the original scenario analysis presented in the submission; with non-reference case discounts rates having the largest impact on the ICER for axi-cel versus current 4L+ care. Reducing the proportion of patients treated with axi-cel considered long term survivors to 10% increased the ICER by £7,738, while increasing the proportion to all patients alive and progression free at 5 years improved the ICER by -£3,188. Testing alternative plausible current 4L+ care OS extrapolations had a small impact on the ICER (exponential +£238, and Weibull +£731). Similarly, selecting a more optimistic OS extrapolation for axi-cel (log-logistic) while simultaneously assuming no patients are captured as long-term survivors and receive SMR-adjusted general population mortality had a small

impact on the ICER of -£998. All scenarios around the source of utility values for the progression-free and progressed health states improved cost-effectiveness results for axi-cel versus current 4L+ care (change in ICER between -£551 and -£1,589), suggesting the most conservative source (Wild et al.) is selected in the revised base case.

Table 7: Revised mean PSA results versus deterministic results (with PAS)

Technology	Total costs (£)		Total QALYs		ICER (£/QALY)	
	Revised PSA	Revised deterministic	Revised PSA	Revised deterministic	Revised PSA	Revised deterministic
Current 4L+ care	[redacted]	[redacted]	[redacted]	[redacted]		
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]		
Incremental	[redacted]	[redacted]	[redacted]	[redacted]	£49,906	£47,905

Key: 4L, fourth line; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Figure 3: Revised cost-effectiveness plane and cost-effectiveness acceptability cure (with PAS)

Key: 4L+, fourth-line plus; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Figure 4: Tornado diagram showing revised OWSA results on ICER (with PAS)

Key: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; PAS, patient access scheme.

Table 8: Revised scenario analysis (with PAS)

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£47,905	N/A
Discount rate for costs and health outcomes	3.5%	0.0%	[redacted]	[redacted]	£32,296	-£15,609
		1.5%	[redacted]	[redacted]	£38,588	-£9,317
		6.0%	[redacted]	[redacted]	£60,904	£12,999
Time horizon	40 years	30 years	[redacted]	[redacted]	£48,628	£723
		20 years	[redacted]	[redacted]	£54,916	£7,011
OS extrapolations	• Current 4L+ care, gamma • Axi-cel, Weibull (25% of treated patients long-term survivors)	• Current 4L+ care, exponential • Axi-cel, Weibull	[redacted]	[redacted]	£48,143	£238
		• Current 4L+ care, Weibull • Axi-cel, Weibull	[redacted]	[redacted]	£48,636	£731
		• Current 4L+ care, gamma • Axi-cel, log-logistic	[redacted]	[redacted]	£41,898	-£6,007
		• Current 4L+ care, exponential • Axi-cel, log-logistic	[redacted]	[redacted]	£42,076	-£5,828
		• Current 4L+ care, Weibull • Axi-cel, log-logistic	[redacted]	[redacted]	£42,447	-£5,458
		Axi-cel, log-logistic (no long-term survivorship)	[redacted]	[redacted]	£46,906	-£998
Long-term survivorship proportion	25% of treated axi-cel patients are captured as long-term survivors	[redacted] of treated patients (i.e. all in PFS at 5 years)	[redacted]	[redacted]	£44,717	-£3,188
		10% of treated patients	[redacted]	[redacted]	£55,643	£7,738

Setting	Base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Long-term survivorship SMR	SMR = 1.09	1.00	[redacted]	[redacted]	£47,394	-£511
		1.20	[redacted]	[redacted]	£48,502	£597
Long-term survivorship time point	5 years	2 years	[redacted]	[redacted]	£44,769	-£3,136
		7 years	[redacted]	[redacted]	£50,025	£2,121
		10 years	[redacted]	[redacted]	£53,050	£5,145
Health state utility source for progression-free and progressed disease	Wild et al. (with general population utility for those alive and free of progression beyond 5 years)	• Progression-free, general population (TA627) • Progressed, general population with AUGMENT decrement (TA627)	[redacted]	[redacted]	£46,833	-£1,072
		GADOLIN	[redacted]	[redacted]	£47,354	-£551
		AUGMENT, R^2	[redacted]	[redacted]	£46,316	-£1,589
		AUGMENT, R-mono	[redacted]	[redacted]	£46,524	-£1,381
Utility value for those alive and progression-free beyond 5 years	General population	Adjust general population utility (98.6%)	[redacted]	[redacted]	£48,253	£348

Key: ICER, incremental cost-effectiveness ratio; N/A, not applicable; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year; R^2, lenalidomide with rituximab; R-mono; rituximab monotherapy; SMR, standardised mortality ratio; TA, technology appraisal.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

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.

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A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Clinical expert statement

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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.

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Deadline for comments by **5pm on 11 May 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed or refractory low-grade non-Hodgkin 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 Graham Collins
2. Name of organisation	Oxford University Hospital NHS Foundation Trust
3. Job title or position	Consultant Haematologist and lymphoma lead clinician
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 non-Hodgkin lymphoma? ☐ A specialist in the clinical evidence base for non-Hodgkin lymphoma or axicabtagene ciloleucel? ☐ 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 low-grade non-Hodgkin lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	There are 2 main aims: 1. To induce a durable remission 2. To maintain good quality of life Most treatments are not considered curative (with the exception of allogeneic stem cell transplant which is not performed commonly in this condition)
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount)	Ideally a complete response on CT or PET scan as this is usually associated with a longer remission duration. However a partial response is also of value. I would also want to see a progression free survival of treated patients of at least 12 months (which would compare favourably with other agents in the 3rd or 4th line setting).
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory low-grade non-Hodgkin lymphoma?	Yes. The natural history of low-grade NHL is that subsequent remission generally get shorter. Whilst many patients have very long first remissions, this is not the case for a significant number. Patients with a short 1st remission (often defined as within 24 months of diagnosis but there is no good rationale for such a hard cut off) are at high risk of dying of their disease. A particularly difficult group of patients to treat are those who become refractory to alkylating agents and / or anti-CD20 antibody therapy.
11. How is relapsed or refractory low-grade non-Hodgkin 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 axicabtagene ciloleucel have on the current pathway of care?	1st line: R-chemo (R-bendamustine, R-CHOP or R-CVP) 2nd line: R-chemo (one of the other regimens above) or ritux + lenalidomide 3rd line: ritux + lenalidomide (if not already used) or alternative R-chemo 4th line: no current standard Note: autologous stem cell transplant is sometimes performed after usually 2nd line treatment to prolong remission. Allogeneic stem cell transplant is used in a small minority in an attempt to cure the condition in young, fit patients with a good donor (e.g. matched sibling). Usually to consolidate 2nd or 3rd line treatment.

	The BCSH guidelines (first author McNamara) BJHaem is used. Or local MDT pathway guidelines.
12. Will axicabtagene ciloleucel 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 axicabtagene ciloleucel and current care? • In what clinical setting should axicabtagene ciloleucel be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce axicabtagene ciloleucel? (For example, for facilities, equipment, or training)	Axi-Cel is a CAR-T product associated with significant rates of cytokine release syndrome and neurotoxicity. Its use is limited to approved CAR-T infusion centres which have had JACIE accreditation for immune effector cell therapy and been commissioned specifically by NHS England. Axi-Cel is currently licensed and funded (on the CDF) for relapsed / refractory DLBCL, primary mediastinal B-cell lymphoma and transformed follicular lymphoma in the 3rd line setting. No further investment would be needed for facilities, equipment or training. However approval in FL would increase the number of patients being treated and therefore may need an expansion of infrastructure in CAR-T infusion centres.
13. Do you expect axicabtagene ciloleucel to provide clinically meaningful benefits compared with current care? • Do you expect axicabtagene ciloleucel to increase length of life more than current care? • Do you expect axicabtagene ciloleucel to increase health-related quality of life more than current care?	Length of life: The current Zuma-5 suggests a PFS of over 3 years which is significantly longer than I would expect in this patient group. This was also true for high-risk patients such as 'POD24'. I would regard a 'promising' PFS as 12 months in this higher risk group. So yes I do expect Axi-Cel to increase length of life in this setting. Axi-Cel is a one off treatment and for many patients quality of life is very good afterwards. A subset of patients do have prolonged cytopenias and recurrent infections which can be problematic and require frequent hospital visits. The use of prophylactic intravenous immunoglobulin is needed in a fairly small minority of patients.
14. Are there any groups of people for whom axicabtagene ciloleucel would be more or less effective (or appropriate) than the general population?	I am not aware of any subgroups in whom this would be expected to be more or less effective. There are however groups of patients who would be expected to do less well with CURRENT treatments and therefore they may benefit relatively more from a cellular therapy approach with Axi-Cel. These are: - POD24 (progression of disease within 24 months of diagnosis) patients

	- Patients refractory to rituximab or an alkylating agent - Patients double refractory to both alkylating agents and rituximab - Patients needing later lines of treatment (3rd or higher for example)
15. Will axicabtagene ciloleucel 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)	Axi-Cel is very different from other treatments. However it is being used for relapsed diffuse large B-cell lymphoma and the process is very similar for follicular lymphoma. Frequent supportive medications required are: - Tocilizumab (for cytokine release syndrome) - Dexamethasone (for cytokine release syndrome and neurotoxicity) - MRI head is needed if neurotoxicity occurs - Ready access to ITU and neurological input is mandatory - IV antibiotics are frequently required In some ways for the patient the treatment is easier than others as the treatment is one off. However there are frequent visits before infusion (e.g. for apheresis) and close follow up is needed after as patients may be left cytopenic. Some may also require antibody replacement if left with hypogammaglobulinaemia with recurrent infections (this is a minority though).
16. Will any rules (informal or formal) be used to start or stop treatment with axicabtagene ciloleucel? Do these include any additional testing?	The key decision points are: 1. Prior to apheresis. Currently eligibility is checked by the national panel. Patients need to be performance status 0-1, have histological confirmation that the disease being treated is appropriate, have adequate organ function. Some testing or organ function is required usually: an echo to assess the heart, creatinine clearance for those with borderline renal function, possibly lung function testing. 2. Prior to re-infusion. Patients should not have an active infection and should have a performance status of at the very most 2. This requires clinical assessment but beyond simple blood tests should not require additional testing.

17. Do you consider that the use of axicabtagene ciloleucel 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 axicabtagene ciloleucel 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	A single infusion maybe of considerably benefit to some patients (although as above, the caveat is that multiple follow up visits are needed before infusion and for follow up).
18. Do you consider axicabtagene ciloleucel 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? • Axicabtagene ciloleucel a 'step-change' in the management of the condition? • Does the use of axicabtagene ciloleucel address any particular unmet need of the patient population?	Yes. CAR-T in general is revolutionising lymphoma medicine and is soon to impact other haematological and solid tumour cancer types. 3rd and 4th line treatment is currently poor for follicular lymphoma and although only tested so far in single arm phase 2 studies, the results have deeply impressed the lymphoma treating community.
19. How do any side effects or adverse effects of axicabtagene ciloleucel affect the management of the condition and the patient's quality of life?	There are short term and longer-term side effects. Short term: - Cytokine release syndrome. This is treated with dexamethasone and tocilizumab. About 10% of patients require ITU admission for this. - Neurotoxicity. This is severe in about 20%. It is treated with dexamethasone and investigations are required to rule out other causes (e.g. infectious encephalitis) - Infections. Longer term: As patients may have prolonged neutropenia, lymphopenia and hypogammaglobulinaemia, recurrent infections is a problem for some. This may

	need multiply rounds of antibiotics, prophylactic antibiotics and in a minority, prophylactic antibody infusions. This can affect the quality of life for some patients.
20. Do the clinical trials on axicabtagene ciloleucel reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The trial was a single arm phase II so there is no comparator. The primary endpoint (overall response rate) is not a particularly valuable endpoint but secondary endpoints of progression free survival, duration of response and overall survival are very relevant. I am not aware of quality of life data being collected. In my view PFS is the most relevant outcome. Overall survival can take too long to mature and in general, PFS appears a reasonably surrogate for OS. The only caveat to that, is that for indolent lymphomas progression events are not necessarily treated straight away, so may not be immediately relevant. Time to next treatment is often thought to be a helpful endpoint in this respect although has inherent subjectivity. I am not aware of any adverse outcomes coming to light later.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA137, TA627 and T629]?	For 4th line treatment I would argue there is no standard and therefore there is very little data on relevant comparators. I would highlight the following publications in addition to Scholar 5 which seek to look at the population more broadly: Casulo et al, Lancet hematology (2022) reports on a fairly large cohort of multiply relapsed follicular patients and identifies refractoriness to alkylating agents as of particularly poor prognosis.

	Batlevi et al, Blood Cancer Journal (2020) gives fairly up to date analysis of outcomes for patients at different stages in their follicular lymphma journey. It is from a single large US institution however.
23. How do data on real-world experience compare with the trial data?	I am not aware of real world CAR-T data in follicular lymphoma. In diffuse large B-cell lymphoma the real-world data has been surprisingly similar to the trial data.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering 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.	As people get older, they may tolerate CAR-T therapy less well but this is true of all of our cancer interventions. There is no (and should not be) a specific age cut off for CAR-T however. It is currently based on fitness and comorbidities reflecting the ability to tolerate the procedure. There are no other equality issues I'm aware of.

Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

PART 2 – Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Differences between the ZUMA-5 and SCHOLAR-5 cohorts in term of prior treatment received by SCHOLAR-5 people - Generalisability of SCHOLAR-5 to ZUMA-5 and the NHS in England.	Zuma-5 was not randomised and comparison has been made with Scholar-5. Scholar-5 does contain patients treated with agents not available in the NHS, e.g. idelalisib (some patients from the idelalisib licensing Delta study were included in Scholar-5). However, patient in the Delta were refractory to both rituximab and an alkylating agent. Including these patients would if anything be expected to make the outcomes from Scholar-5 to be better than similar NHS treated patients who do not have access to this agent. Furthermore, in recent years I would argue that there has been no major step forward in licensed treatments for multiply relapsed follicular lymphoma in any country. I would therefore see the outcomes for patients included in Scholar-5 to be similar to those for patients treated in the NHS.

Clinical expert statement

Key issue 2: The proportion of patients who can be considered long term survivors following treatment with axicabtagene ciloleucel – Uncertainty around company's long-term survivor assumptions**.** No long-term survivor status data available to estimate the proportion of relapsed/refractory follicular lymphoma people treated with axicabtagene ciloleucel.	The issue of long-term survivors is very difficult as follow up is so short. The only treatment I am aware of which can lead to long-term disease-free survivorship (and therefore likely cure) in relapsed follicular lymphoma is allogeneic stem cell transplantation. This is not performed much in follicular lymphoma due to the risk of the procedure. However, when it is performed, approximately 30-40% of patients survive long term and are likely cured. This establishes a proof of principle. Both CAR-T cell therapy and allogeneic stem cell transplantation are forms of immunotherapy, relying on the activity of T-cells (in CAR-T cell therapy it is the genetically modified T-cell; in allogeneic stem cell transplantation it is the donor-derived T-cells). It is therefore plausible that there may be some long-term relapse-free survivors following CAR-T cell therapy. 25% seems a reasonable estimate but it is very much an estimate and further follow up is the only way of verifying this.
Key issue 3: The progression-free survival and overall survival extrapolation assumptions for axicabtagene ciloleucel	As discussed above, the 25% estimate of long-term survivors is a reasonable guess based on the other main cellular immunotherapy (allogeneic stem cell transplant) used in this group but it's impossible currently to know how accurate this is. For the 25% of long-term survivors, even if they are cured I would not expect mortality to be exactly that of the general population as they will be 4th line or beyond and the late effects from heavy pre-treatment will have some effect although it's hard to say how much.

non-long-term survivors – extrapolation curves fitted to data for the whole ZUMA-5 cohort and assume 25% people achieve reduced hazard of mortality. From 5 years the company fitted progression-free survival and overall survival curves to model the hazard of progression and death only for non-long-term survivors.	
Key issue 4: Health state utility values applied in the model - a lack of quality-of-life data available in people who would be eligible to	I don't have much to add on this. I agree there is poor quality of data on which to base utility values in follicular lymphoma patients. Whilst 4th line patients may have a slightly worse quality of life than 2nd line (most frequent group in the Augment study) my experience would suggest it is not a very big difference and I don't think it would impact much on utility values. I agree that the CAR-T assumptions for utility decrements seem sensible.

receive axicabtagene ciloleucel in clinical practice.	
Key issue 5: The capping of time on treatment for comparator therapies, and modelling subsequent treatment costs – uncertainty in the use of median time on treatment from the SmPCs which results in patients receiving current 4th line treatments and beyond progression. The distribution of subsequent treatment is equal in both the axicabtagene ciloleucel and	As stated in the ERG report there if no current standard of 4th line treatment. Outside of a clinical trial, some sort of conventional chemotherapy with or without an anti-CD20 antibody is likely. Stem cell transplantation is NOT usually used at this line of treatment as it is more effective at earlier lines. These treatments would be stopped at progression. Treatment beyond progression is not a standard approach currently. In terms of types of treatment. Axi-Cel can cause prolonged cytopenias which may limit options in a small proportion of patients progressing after this treatment. Otherwise the treatments would be similar.

current 4th line and beyond care arms of the model.	

Part 3: Key messages

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

Axi-Cel is a very active treatment in relapsed follicular lymphoma

Progression free survival of > 12 months is very good in this setting; over 3 year is very impressive

Treatment is a one-off infusion but some patients may need frequent and sometimes long tern follow up due to cytopenias

There is no current standard of care in 4th line.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see 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 low-grade non-Hodgkin lymphoma [ID1685]

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Clinical expert statement

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Part 1: Treating relapsed or refractory low-grade non-Hodgkin 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 Tobias Menne
2. Name of organisation	The Newcastle upon Tyne Hospitals
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 non-Hodgkin lymphoma? ☒ A specialist in the clinical evidence base for non-Hodgkin lymphoma or axicabtagene ciloleucel? ☐ 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 low-grade non-Hodgkin lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To achieve a long-term remission and to stop progression
9. What do you consider a clinically significant treatment response? (For example, a reduction in disease activity by a certain amount)	At least a 50% reduction in tumour volume but ideally 80% reduction in tumour volume
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory low-grade non-Hodgkin lymphoma?	Yes especially once patient have failed three lines of therapy as treatment options available become quite limited
11. How is relapsed or refractory low-grade non-Hodgkin 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 axicabtagene ciloleucel have on the current pathway of care?	BCSH guidelines Guideline on the investigation and management of follicular lymphoma from 25/6/2020 Mc Namara C et l https:// doi.org/10.111/bjh.16872 In April 20 NICE approved Revlimide/Rituximab (R^2) combination for relapsed follicular lymphoma. Since then centres use it either as 2nd or 3rd line therapy. There is variation in the sequencing of initial chemoimmunotherapies and (R^2) but ultimately most patients who have failed three lines of therapy will have been exposed to bendamustine, anthracyclines, alkylating agents rituximab, revlimide and obinutuzumab. The sequence might be different but after 3 lines of therapy most patients will be refractory or have relapsed to all these compounds and treatment options afterwards are very few available Axicabtagene ciloleucel as 4th line treatment would provide the clinicians with a good treatment option in this cohort of patients where no good therapy arms are available. CAR-T cells are promising in this setting with high response rates and durable remissions with an acceptable toxicity profile considering the line of therapy.

12. Will axicabtagene ciloleucel 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 axicabtagene ciloleucel and current care? • In what clinical setting should axicabtagene ciloleucel be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce axicabtagene ciloleucel? (For example, for facilities, equipment, or training)	Axicabtagene ciloleucel is extensively used in the management of DLBCL in England. Several hundred patients have been treated over the last 3 years. Hence there is good clinical experience available especially in managing the initial inpatient stay and managing the expected CRS and ICANS toxicity. Axicabtagene ciloleucel can only be used in approved CAR-T centres. Currently there are 10 centres in England but it is expected that all allograft transplant centres will receive JACIE accreditation in the next 18 months and that the total number of CAR-T centres will go up to approximately 20. The 10 centres who are already approved CAR-T centres should have appropriate facilities available and capacity to provide the care for relapsed follicular lymphoma cases for their regions. New CAR-T centres might require additional training and need to build capacities to deliver the service (mainly ITU, apheresis, bed capacity and employ CAR-T nurses and coordinators)
13. Do you expect axicabtagene ciloleucel to provide clinically meaningful benefits compared with current care? • Do you expect axicabtagene ciloleucel to increase length of life more than current care? • Do you expect axicabtagene ciloleucel to increase health-related quality of life more than current care?	Yes the updated ZUMA-5 data presented at ASH21 for 86 FL patients treated with axicel (median FU of 30.9 months) showed a CR rate of 79% and a PR rate of 15% with a median PFS of 39.6 and a 24 month PFS rate of 63.4%. The Median OS rate has not been reached and the 2 year OS rate is 81.2 %. These data were presented for a mixture of 3 and 4th + lines. 26 cases were 3rd line. The majority of cases were 4th line or later. Compared to historical Scholar-5 data presented at EHA 21 there appears to be a significant difference in OS and PFS. More recently a retrospective study of eight academic US centres looked at outcome of FL patients receiving three or more lines of systemic therapy. Casulo C et al Lancet haematol 2022 e289-e300) With a median follow up of 71 months and 441 FL patients meeting the criteria the 5 year OS rate was 75% and the median progression free survival was 17 months and the ORR rate 70%. The authors concluded that high response rates with short duration were observed with contemporary therapies.

	Yes but it difficult to quantify the health-related quality of life. In the initial 1-2 months post CAR-T cells the quality of life will be impaired as patients are inpatient and will have to deal with the initial side-effects of therapy but as time passes the quality of life will improve and in a good proportion it will be close to normal
14. Are there any groups of people for whom axicabtagene ciloleucel would be more or less effective (or appropriate) than the general population?	No specific subgroup and subanalysis showed similar benefits for all patients
15. Will axicabtagene ciloleucel 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)	Axicabtagene ciloleucel will be only available in dedicated CAR-T centres and cannot be given in district general hospital. Patients require a 2-3 week admission often far away from home. It is more difficult to deliver than other chemotherapy options.
16. Will any rules (informal or formal) be used to start or stop treatment with axicabtagene ciloleucel? Do these include any additional testing?	Patients will need to fulfil the criteria as outlined by CDF. No additional testing is required
17. Do you consider that the use of axicabtagene ciloleucel 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 axicabtagene ciloleucel or	No the health related benefits are clearly outlined in the quality adjusted life year calculations

have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider axicabtagene ciloleucel 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? • Axicabtagene ciloleucel a 'step-change' in the management of the condition? • Does the use of axicabtagene ciloleucel address any particular unmet need of the patient population?	Yes the genetic modification of the patient's own immune system is an important step forward in the management of lymphoma patients and has been significant progress as it overcomes some of the hurdles encountered by continuing with chemoimmunotherapy As already outlined FL patients who have failed three lines of therapy have limited treatment options and the availability of axicabtagene ciloleucel has the potential of providing a good treatment option in an otherwise difficult treatment scenario where typically only short responses to standard therapy are achieved.
19. How do any side effects or adverse effects of axicabtagene ciloleucel affect the management of the condition and the patient's quality of life?	Cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS) are significant side effects of therapy in the first 2-3 weeks after administration of Axicel. A proportion of patients will have to go to ITU and the TRM rate is between 3-5 % based on RWD. The initial CRS and ICANS is manageable with the administration of toculizumab and dexamethasone and as centres have gained more experience in the management of these conditions outcomes have improved. After the initial inpatient stay a proportion of patient have cytopenias and some patients require blood products for few months afterwards. The risk of infections is increased in the first few months but gradually gets better as immune system recovers.
20. Do the clinical trials on axicabtagene ciloleucel 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?	The trial did not allow bridging therapy and CAR-T manufacturing from apheresis to delivery was significantly shorter in the trial setting then what is expected in the UK. A higher proportion of older patients will be selected in real world setting compared to the trial setting.

• 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?	PFS and OS are the most important markers and they have been presented in the trial. A proportion of ZUMA-5 patients had only 2 lines of therapy and might have better outcomes than patients who have already failed 3 lines. Acute COVID infections post CAR-T cell therapy have a high mortality rate and vaccinations are not as effective in this setting
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA137, TA627 and T629]?	No new evidence has emerged since the publications the NICE TAs, except the SCHOLAR-5 study and the Lanc Haem paper already mentioned in question 13.
23. How do data on real-world experience compare with the trial data?	Not yet available for FL. As comparison for DLBCL the data for Axicel are relatively comparable to the ZUMA-1 study data in large French (DESCART), American (CIBMTR) and English RWD sets
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering 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	No

belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

PART 2 – Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Differences between the ZUMA-5 and SCHOLAR-5 cohorts in term of prior treatment received by SCHOLAR-5 people - Generalisability of SCHOLAR-5 to ZUMA-5 and the NHS in England.	In general the prior treatment lines given in Zuma-5 and Scholar-5 are similar to what is used in England. Most patients have received anthracyclines, alkylating agents and rituximab or obinutuzumab and a proportion of patients had undergone autograft and some had received R^2 therapy. Some patients included in the scholar-5 study received idelalisib which is not NICE approved and might have improved the OS of the Scholar-5 study. There was some difference in ECOG 0-1 between the ZUMA-1 and SCHOLAR-5 study with more patients having an ECOG of 1 in the SCHOLAR-5 study. Overall I have no significant concern re generalisability of the S5 and Z5 study to the UK. The initial treatment lines for FL are very similar and patients who have failed three lines of therapy would have all followed similar treatment strategies with perhaps a variation in the sequencing of

	the treatment options but ultimately most patients would have been exposed to very similar medications before reaching 4th line of therapy.
Key issue 2: The proportion of patients who can be considered long term survivors following treatment with axicabtagene ciloleucel – Uncertainty around company's long-term survivor assumptions**.** No long-term survivor status data available to estimate the proportion of relapsed/refractory follicular lymphoma people treated with axicabtagene ciloleucel.	This is difficult to answer. I think that the assumption that 25% of patients will not relapse and that 43.8% of patients treated with axicel will be alive at 10 years based on the Weibull model chosen by the company for their base model is unrealistic and my assumption would be more conservative. At the moment due to the immaturity of data it is very difficult to predict what the long term survivor curve will look like. We know that the median PFS is just above 3 and the 2 year PFS was 63.4%. Hence so far no plateau is emerging and only longer follow up data will determine if a proportion will not relapse and a plateau will emerge. I can see that in a subset of patients 'a potential cure' might be the case but personally I would find it more realistic if the 10 year PFS would be between 15-20% and the 10 year OS between 35-40%
Key issue 3: The progression-free survival and overall survival	I agree that the OS and PFS curve modelling- after 5 years should include all patients including non-long-term and long-term survivors as at the moment the assumption that 25% of patients will be 'defacto cured' and hence follow the general population mortality is an assumption.

extrapolation assumptions modelling from 5 years for axicabtagene ciloleucel non-long-term survivors – extrapolation curves fitted to data for the whole ZUMA-5 cohort and assume 25% people achieve reduced hazard of mortality. From 5 years the company fitted progression-free survival and overall survival curves to model the hazard of progression and death only for non-long-term survivors.	In my opinion either the number of patients who have achieved a reduced hazard of mortality should be reduced from 25% to 15-20% or the Weibull model should be applied to all patients
Key issue 4: Health state utility values applied in the model - a lack of quality-of-life data available in people	I always find utility values difficult to interpret. I would think that patients receiving 4th line FL therapy have a slighter poorer health state then patients treated in 2nd line just due to the nature that they already had two further lines of chemotherapy. The health state would not have changed dramatically but probably slightly worsened. Hence the health state utility values

who would be eligible to receive axicabtagene ciloleucel in clinical practice.	applied in the model should be slightly worse than what was used in the FAD for the augment study (TA627).
Key issue 5: The capping of time on treatment for comparator therapies, and modelling subsequent treatment costs – uncertainty in the use of median time on treatment from the SmPCs which results in patients receiving current 4th line treatments and beyond progression. The distribution of subsequent treatment is equal in both the axicabtagene ciloleucel and	Realistically and based on experience we have gained from treating patients with Axicabtagene ciloleucel I would argue that the subsequent treatment will be not equal and that fewer patients who received Axicel will receive subsequent therapy especially due to cytopenias observed post CAR-T cell therapy compared to other therapies. Patients who progress on subsequent therapies will stop therapy on progression and is likely to be less than the median time on treatment as per SmPCs. Most of the median time on treatments mentioned in the SmPCs are based on earlier treatment settings when it is more likely to deliver all cycles. Difficult to say by how much the time on treatment will be reduced compared to median time on treatment as per SMPC as good data for 4th line therapy just not available.

current 4th line and beyond care arms of the model.	

Part 3: Key messages

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

Currently there are only limited 4th line treatment options available for FL patients with most of them only achieving short term responses
Axicabtagene ciloleucel could provide a novel way of treating these patients with limited treatment options
Response rates, PFS, DOR, TTNT and OS is significantly better than current standard therapies in this setting and would improve outcomes
Initial management needs to take place in dedicated CAR-T cell centres and side effects are manageable
Current long term data are insufficient to reliable predict 5 and 10 year PFS and OS

Thank you for your time.

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Axicabtagene ciloleucel for treating relapsed or refractory low-grade non-Hodgkin lymphoma [ID1685]

ERG critique of the company's response to technical engagement

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Date completed **24 May 2022**

Contains [redacted]

In their response to the technical engagement report, the company addressed each of the issues raised in the ERG report and provided some revised economic analyses. This addendum to the ERG report provides a brief critique of the company response to the issues raised. It should be read in conjunction with the company's technical engagement response document, dated 11 May 2022.

The key issues raised in the ERG report are outlines in Table 1. A detailed summary of each issue can be found in the Executive summary of the main ERG report:

Table 1 Summary of key issues identified by the ERG

Issues	Summary of issue	Report sections
Issue 1	Differences between the ZUMA-5 and SCHOLAR-5 cohorts in term of prior treatment received by SCHOLAR-5 patients	Section 3.3 and 3.6
Issue 2	The proportion of patients who can be considered long term survivors following treatment with axi-cel	Section 4.2.6
Issue 3	The PFS and OS extrapolation assumptions for axi-cel non-long-term survivors	Section 4.2.6
Issue 4	Health state utility values applied in the model	Section 4.2.7
Issue 5	The capping of time on treatment for comparator therapies, and modelling subsequent treatment costs	Section 4.2.8

Issue 1

The ERG highlighted an uncertainty related to the propensity score weighted comparison between ZUMA-5 and the SCHOLAR-5 cohort. The ERG also queried the generalisability of the SCHOLAR-5 outcomes to the UK NHS, where the mix of 4L+ treatments differs somewhat to those received by patients in SCHOLAR-5. On balance, however, it was the ERGs opinion that the use of SCHOLAR-5 may overestimate survival for current 4L+ care in the NHS in England. This was based on the ERGs understanding that the DELTA sub-cohort of SCHOLAR-5 had received idelalisib, which isn't routinely available in the NHS in England, as their 4L+ treatment. The DELTA cohort was included in the OS survival curve for current 4L+ care but excluded from the PFS analysis after propensity score weighting, because timing of progression was not identifiable for this group. The ERG believed that this approach could overestimate OS, and potentially overestimate time in the post-progression state for the current 4L+ care cohort. The ERG had, therefore, suggested in their report that the company might be better excluding the DELTA cohort from both the PFS and OS curves. The company have done this prior to propensity score weighting in their response to technical engagement. The impact on the PFS curves of dropping the DELTA cohort prior to

propensity score weighting is minimal, but as anticipated it results in more pessimistic OS curves for the 4L+ care cohort. This translates into shorter life expectancy in the current 4L+ care arm of the model, which increases the QALY gain for axi-cel and reduces the ICER.

Whilst no comparison of the post-propensity weighted baseline characteristics between ZUMA-5 and SCHOLAR-5 (with DELTA excluded) is provided, in principal the ERG agrees with the more consistent approach of using exactly the same cohort to inform PFS and OS in the model. However, the company response appears to suggest that patients from the DELTA cohort were included in the SCHOLAR-5 cohort from the point of progression on idelalisib, and so represented a group of 4L+ patients with prior exposure to idelasib, not a group receiving idelalisib at 4L+ as the ERG had understood. Nevertheless, it is still plausible that a 4L+ cohort with prior idelalisib exposure could do better than one without since the cohort will not have been so heavily exposed to the prior treatment regimens that are available routinely in the NHS. Therefore, the ERG accepts the company's revised survival modelling for current 4L+ care but highlight the remaining uncertainty regarding the expected survival of relapsed or refractory FL patients at treatment line 4L+ in the NHS in England. Given the uncertainty, scenarios that show the impact of reverting to the company's original survival curves, which included DELTA patients for OS, may be considered to illustrate the upward uncertainty in the ICER for axi-cel.

It may also be noted that there was limited discussion of the parametric curve selection for the revised OS analysis with exclusion of DELTA. Figure 1 in the company's response document illustrates the impact of excluding DELTA on the OS Kaplan Meir curve and the fitted parametric curves. However, it is just noted in the company response that three curves (gamma, exponential, and Weibull) produce plausible long-term extrapolations and that the gamma was selected in line with the original submission (which included DELTA in the OS data). There is no discussion of statistical or visual fit. However, we can see from the model that it is the generalised gamma, loglogistic and lognormal that provide the best statistical fits.

Clinical experts offered some further sources as alternatives to SCHOLAR-5 for informing outcomes in relapsed or refractory FL patients after multiple lines of therapy. However, neither provided an exact match to the company's proposed positioning (or comparator treatment distribution) for axicel in this indication. Casulo et al report on 441 patients, recruited from multiple US sites, receiving mostly third line (415) treatment for relapsed or refractory FL.[1] Five-year overall survival in this cohort was reported to be 75%. A sensitivity analysis which included 35% of patients at fourth line or greater, showed OS of 71% at 5

years, and further analysis indicated a decline in PFS and OS with increasing lines of prior therapy.[1] The clinical expert highlights the finding from Casulo et al, that patients refractory to alkylating agents have a particularly poor prognosis. Batlevi et al,[2] report on a retrospective analysis of data on 1088 patients with FL from a single large US centre. Whilst a comparable population (4L+) with similar clinical characteristics and treatment history to ZUMA-5 cannot be identified from the published paper, this cohort study does clearly illustrate an inverse relationship between increasing treatment line and OS, with a median OS of 5.3 years reported for fourth line treatment, reducing to 3.1 for fifth line, and 1.9 for sixth line.[2]

Issue 2 and 3

In their response to technical engagement, the company have generally agreed with ERGs concerns and their suggested modelling changes around issues 2 and 3. The company have implemented the following revisions in their new base case:

- With respect to issue 3, they have:
    - allowed the proportion of non-long-term survivors to update (reduce) dynamically over time in the model, reflecting the assumed higher rate of progression and death in this sub-cohort
    - uplifted the hazard of progression and death for non-long-term survivors from the timepoint that the long-term survivor proportion and assumptions are applied. This is to counter the risk of overestimating PFS and OS for non-long-term survivors that arises from using curves fitted to the whole ZUMA-5 cohort with three or more lines of prior therapy. An SMR of 1.2 was chosen, in line with the base case in the main ERG report. The company acknowledge the arbitrary nature of this parameter. It remains an uncertainty in the model.
    - Implemented a fix to ensure that the hazard of death for non-long-term survivors never falls below that of long-term survivors in the model.

The company further agrees that the proportion of axi-cel treated patients that achieve long-term survivorship, and the relative increase in morality that these patients face compared to the age matched general population, remain uncertainties in the absence of longer-term data.

The ERG is satisfied with the company's response to issues 2 and 3. However, we would note that the long-term survivor proportion and the mortality assumptions/adjustments for long-term survivors and non-long-term survivors remain key uncertainties in the economic

case. The company acknowledge this and suggest that approval for use on the cancer drugs fund will allow for the collection of more data to better inform these inputs.

It may also be noted that clinical expert responses to technical engagement provided mixed opinion on the long-term survivor proportion and assumptions; one expert suggesting that the assumption of 25% achieving long-term survivorship with axi-cel was reasonable; another suggesting 25% never relapsing, and [redacted] being alive at 10 years based on the chosen Weibull extrapolation, to be unrealistic. Based on the fact there is no plateau yet emerging in the PFS data from ZUMA-5, the second expert suggested they would find a 10-year PFS between 15-20% and a 10 year OS between 35-40% more realistic. They further suggested that "either the number of patients who have achieved a reduced hazard of mortality should be reduced from 25% to 15-20%, or the Weibull model should be applied to all patients". The company have provided a scenario analysis where they reduce the proportion achieving long-term survivorship (LTS) to 10% but they have not applied the Weibull to all patients with no LTS assumption. It should also be noted that the 10-year survivor proportion is [redacted] when the LTS proportion of 25% is applied at 5 years, and it is [redacted] if it is switched off with the Weibull curve applied to all. This suggests that the Weibull curve, applied to all patients, may still be optimistic according to the second experts' expectations. However, there is no alternative parametric curve that provides a 10-year OS projection between 35-40%.

To cover this, the ERG suggest a scenario that switches the LTS proportion/assumption off, applies the Weibull OS extrapolation to all (10-year survival [redacted]), and applies the generalised gamma extrapolation to all for PFS (10 year PFS [redacted]).

Issue 4

The ERG were of the opinion that the company's reliance on general population health state utility (for the progression free state), based on the approach taken in TA627 (lenalidomide with rituximab for treated FL)[3], may not be appropriate given the later lines of treatment being considered in the current appraisal (4L+). The company have acknowledged in their response that more than 75% of patients in the AUGMENT study,[3,4] from which this assumption was derived, were in earlier treatment lines and so may be expected to have better HRQoL. Clinical experts responding to technical engagement also suggest that patients in later treatment lines (4L+) may be expected to have slightly lower HRQoL than patients in earlier lines due to greater prior exposure to chemotherapy. However, the clinical experts believed the difference would not be great.

In response, the company have accepted the ERGs preferred utilities from Wild et al.,[5,6] which do lead to slightly lower values being applied to the progression free (PF) and progressive disease (PD) health states in the model. However, the ERG argued in their original base case that long-term survivors following axi-cel treatment would remain at the PF health state utility value derived from Wild et al. rather than improve to general population utility from five years onward - as assumed in the company's original scenario analysis using Wild et al utilities. In their response, the company note that this is inconsistent with previous NICE appraisals of CAR-T cell therapies in advanced lymphoma indications, where long-term survivors have been assumed to achieve general population utility. Hence, they retain general population utility for axi-cel treated long-term survivors (from 5 years) in their revised base case, but otherwise use Wild et al utilities for the PF and PD health states. To address the uncertainty around the health state utility of long-term survivors following axi-cel treatment, the company provide a scenario that assumes it lies halfway between the Wild et al. PF utility and general population utility.

The ERG are broadly satisfied with the company's revised approach. However, the assumption that long-term survivors achieve health state utility in line with the general population, whist experiencing an elevated mortality risk does seem inconsistent. For this reason, the ERG believe it important to consider the range of assumptions around long-term survivor utility, including the ERGs originally preferred approach, which the company have usefully provided.

Issue 5

With respect to issue 5, the company have agreed with the ERG that comparator treatment costs should be capped on progression free survival, rather than overall survival, which implies that treatment could continue beyond progression. The company have implemented this in their revised base case. Clinical expert opinion received during technical engagement seems to concur with this. The company also accept that their original approach could lead to overestimation of comparator and subsequent treatment costs when applied in conjunction with the assumption that all patients receive the costs of subsequent treatment upon progression.

The ERG is satisfied with the company's response and associated model revisions addressing this issue. Nevertheless, time on treatment with comparator therapies, at this point in the care pathway (4L+), are not well informed in the model, and also remain uncertain.

Summary

In summary, the ERG find the company's revised base case reasonable in light of the data limitations but highlight key remaining uncertainties in the case - In particular, the long-term survivor proportion and survival extrapolations for axi-cel treated patients, the relative survival outlook for non-long-term survivors versus the axi-cel 4L+ cohort as a whole, and expected PFS and OS with current 4L+ care in the NHS in England. Further scenario analysis around the company's revised base case, as justified in the preceding sections, are provided in Table 1 below.

Table 1 Additional scenario analyses around the company's revised based case

Setting	Company revised base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Base case			[redacted]	[redacted]	£47,905	N/A
OS and PFS extrapolation (Axi-cel)	OS, Weibull OS; PFS Weibull (25% of treated patients long-term survivors)	OS, Weibull OS; PFS generalised gamma (no long-term survivorship)	[redacted]	[redacted]	£56,533	£8,628
OS and PFS (Current 4L+ care)	OS, gamma; PFS, exponential (DELTA excluded prior to propensity score weighting)	OS, gamma; PFS, exponential (DELTA included in OS, as per original company submission)	[redacted]	[redacted]	£55,383	£7,478
		OS, lognormal; PFS, exponential	[redacted]	[redacted]	£55,998	£8,093
Health state utility of long-term survivors	Age/sex match general population norms	Progression free utility from Wild et al.	[redacted]	[redacted]	£48,606	£701
Comparator treatment costs	Capped on PFS	Capped on OS	[redacted]	[redacted]	£42,471	-£5,434

Setting	Company revised base case	Scenario	Incremental costs	Incremental QALYs	ICER	Change from base case
Long-term survivor proportion	25%	15%	[redacted]	[redacted]	£52,810	£4,905
		20%	[redacted]	[redacted]	£50,242	£2,337
Mortality ratio for non-long-term survivors versus full ZUMA-5 4L+ cohort	1.2	1.09	[redacted]	[redacted]	£46,805	-£1,100
		1.5	[redacted]	[redacted]	£50,552	£2,647
		2	[redacted]	[redacted]	£54,064	£6,159

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