NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

Committee Papers

SINGLE TECHNOLOGY APPRAISAL

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies [ID1115]

Contents:

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

Pre-meeting briefing

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma [ID1115]

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report
- comments received as part of the technical engagement

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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Abbreviation	In full
AE	Adverse events
ASCT	Allogenic stem cell transplantation
Axi-cel	Axicabtagene ciloleucel
BSC	Best supportive care
CAR	Chimeric antigen receptor
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
CR	Complete remission/response
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol five dimensions questionnaire
ERG	Evidence review group
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
KM	Kaplan-Meier
mITT	Modified intention to treat
MCM	Mixture cure model
NHL	Non-Hodgkin lymphoma
OR	Odds ratio
ORR	Objective response rate

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Abbreviation	In full
OS	Overall survival
PD	Progressed disease
PFS	Progression-free survival
PPS	Post-progression state
PMBCL	Primary mediastinal large B-cell lymphoma
QALY	Quality-adjusted life year
R/R	Relapsed or refractory
SCT	Stem cell transplant
TFL	Transformed follicular lymphoma
TTD	Time to treatment discontinuation

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Key issues – clinical effectiveness

- What is the correct placement of axi-cel in the treatment pathway?
- What is the appropriate comparator to axi-cel?
- High heterogeneity between studies included in SCHOLAR-1 raises concerns about pooled data. Is SCHOLAR-1 pooled data, the most appropriate source of data for the comparator?
- Is alternative data available for the comparator treatment arm?
- What adjustment to the SCHOLAR-1 data should be made to account for the inclusion of primary refractory patients, patients with ECOG score 0-4 and the high proportion of patients receiving SCT compared to clinical practice?
- What proportion of patients receiving 3rd line treatment are likely to become eligible for SCT in clinical practice?
- ZUMA-1 has limited follow up resulting in high levels of censoring around 12 months and uncertainty in OS and PFS results beyond this time point.
- 10% of patients treated with axi-cel were re-treated. Re-treatment is not likely to be reflective of future clinical practice, how should this be accounted for?

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Key issues – cost effectiveness

- What extrapolation is appropriate for axi-cel OS, taking into consideration the potential for long-term survivors and cure?
- What is the appropriate timing for a cure assumption?
- What is the most appropriate inclusion of HRQoL and costs of AEs in the model - specifically for long term survivors and CRS adverse events?
- What is the most appropriate way to include post-treatment SCT in the model?
- How should broader infrastructure and training requirements be incorporated into the model?
- Are QALYs from the group who did not receive axi-cel considered appropriately - should the model use the ITT or mITT population for axi-cel?
- End-of-life considerations and the appropriate discount rate

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B-cell non-Hodgkin lymphoma (NHL)

- B-cell lymphomas are a form of non-Hodgkin lymphomas (NHL). Three forms of B-cell lymphoma include:
  - Diffuse large B-cell lymphomas (DLBCL), a fast growing ('aggressive'), high grade form of NHL accounting for 30%-40% of all NHL cases
  - Follicular lymphoma (FL) - a slow growing, low grade form of NHL. 10-70% transform into high grade DLBCL (transformed high grade FL)
  - Primary mediastinal large B-cell lymphoma (PMBCL) is a rare type of NHL accounting for 2-4% of all NHL cases. Develops in the mediastinum
- These three forms have distinct clinical, pathological and molecular characteristics, but management is generally similar for all aggressive subtypes of B-cell NHL
- There were 6,322 people diagnosed with DLBCL in England in 2015
- DLBCL can occur at any age, but is most common in people aged over 50 years with average age at diagnosis of 65 years

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References:
Office for National Statistics. Cancer Registration Statistics, England, 2015. Office of National Statistics. Accessed November 2017.
High grade NHL. Cancer research UK. Accessed November 2017.
Low grade NHL. Cancer research UK. Accessed November 2017.
Diffuse B-cell lymphoma. Lymphoma association. Accessed November 2017.
Survival for high grade lymphomas. Cancer Research UK. Accessed November 2017.
Outcomes for R/R disease - Crump et al 2017

Diffuse large B-cell non-Hodgkin lymphoma (DLBCL)

- 5-year survival rates for DLBCL are around 65-70% for stage I and II and around 50% at stages III and IV
- The most widely used first-line treatment is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) for which 50% of people will be cured
- NICE guideline CG52 recommends salvage therapy with rituximab in combination with chemotherapy for relapsed or refractory disease* followed by stem cell transplantation
- If stem cell transplantation is not suitable chemotherapy or immunotherapy may be used alone
- NICE TA306 recommends pixantrone monotherapy for people who have multiply relapsed, been treated previously with rituximab and are on the third or fourth line of treatment
- Outcomes for people with R/R* disease treated with standard of care (SoC) are poor, with low levels of response and limited survival
- Many people with refractory DLBCL therefore have no curative treatment options

* People with refractory NHL have not responded to initial treatment. People with relapsed NHL have previously responded to treatment but malignancy then return

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References:

Office for National Statistics. Cancer Registration Statistics, England, 2015. Office of National Statistics. Accessed November 2017.
High grade NHL. Cancer research UK. Accessed November 2017.
Low grade NHL. Cancer research UK. Accessed November 2017.
Diffuse B-cell lymphoma. Lymphoma association. Accessed November 2017.
Survival for high grade lymphomas. Cancer Research UK. Accessed November 2017.
Outcomes for R/R disease - Crump et al 2017

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Axicabtagene ciloleucel (Kite-Gilead)

Mechanism of action		A chimeric antigen receptor (CAR) T cell therapy that uses autologous T cells engineered to express a novel surface receptor directed against the tumour antigen CD19
Administration and dosage		• Patients undergo conditioning chemotherapy of cyclophosphamide 500mg/m^2 IV and fludarabine 30mg/m^2 IV • Genetically altered T cells are administered as an intravenous infusion as 68mL bag containing a maximum 2 x 10^8 anti-CD19 CAR T-cells
Marketing authorisation	Current	• Approval from the Committee for Human Medicinal Products (CHMP) received 28th June 2018 "Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after two or more lines of systemic therapy"
	Regulatory status	• Orphan Medicine Designation: Granted by EMA in Feb 2015 • Priority Medicines (PRIME) Status: Granted by EMA in May 2016
List price		[redacted] per 68 ml single infusion bag

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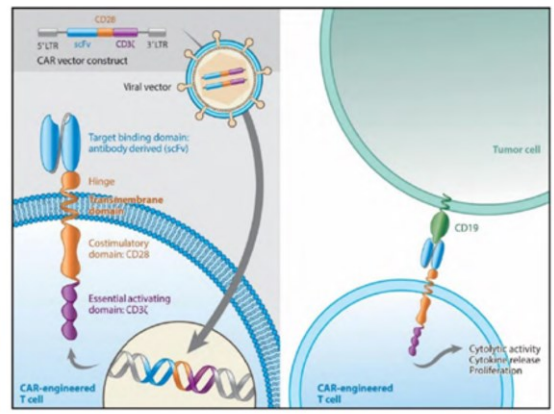
Source: Company submission Table 2

Chimeric antigen receptor (CAR) T-cell therapies (1)

- Axicabtagene ciloleucel (axi-cel) is the first chimeric antigen receptor (CAR) T-cell therapy to be appraised by NICE for use in the NHS
- CAR T-cell therapies employ an inactive virus to insert genes into autologous human T-cells.
- The engineered T-cells express a novel cell surface receptor fragment antibody.
- The new receptors identify and lock onto CD19 bearing cells.
- Once locked onto CD19 the T-cell is activated to destroy the cells.



Source: Figure 1 in company submission

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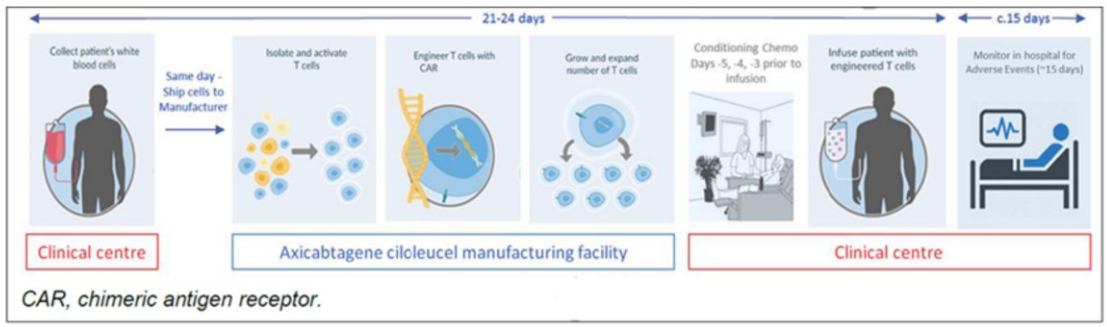
CAR T-cell therapy:

Engineered Autologous Cell Therapy is a process by which a patient's own T-cells are collected and genetically altered to recognise and target antigens expressed on the cell surface of specific malignancies. (Source: Kochenderfer JN, Dudley ME, Kassim SH, et al.). Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015; 33(6):540-9.)

CAR T-cell therapies (2)

Multistep process:



CAR, chimeric antigen receptor.

1. Leukapheresis - collection of T-cells from patient (SCT accredited setting)
2. T-cells reengineered and multiplied (laboratory setting outside UK)
3. Patients receive conditioning chemotherapy (hospital setting)
4. CAR T-cells are thawed and infused into the patient (SCT accredited setting)
5. Patients are monitored for AEs (hospital ~17 days, within 2hrs of hospital ~1 month) - requirement for availability of ITU beds for axi-cel patients

Source: Adapted from Figure 2 in company submission

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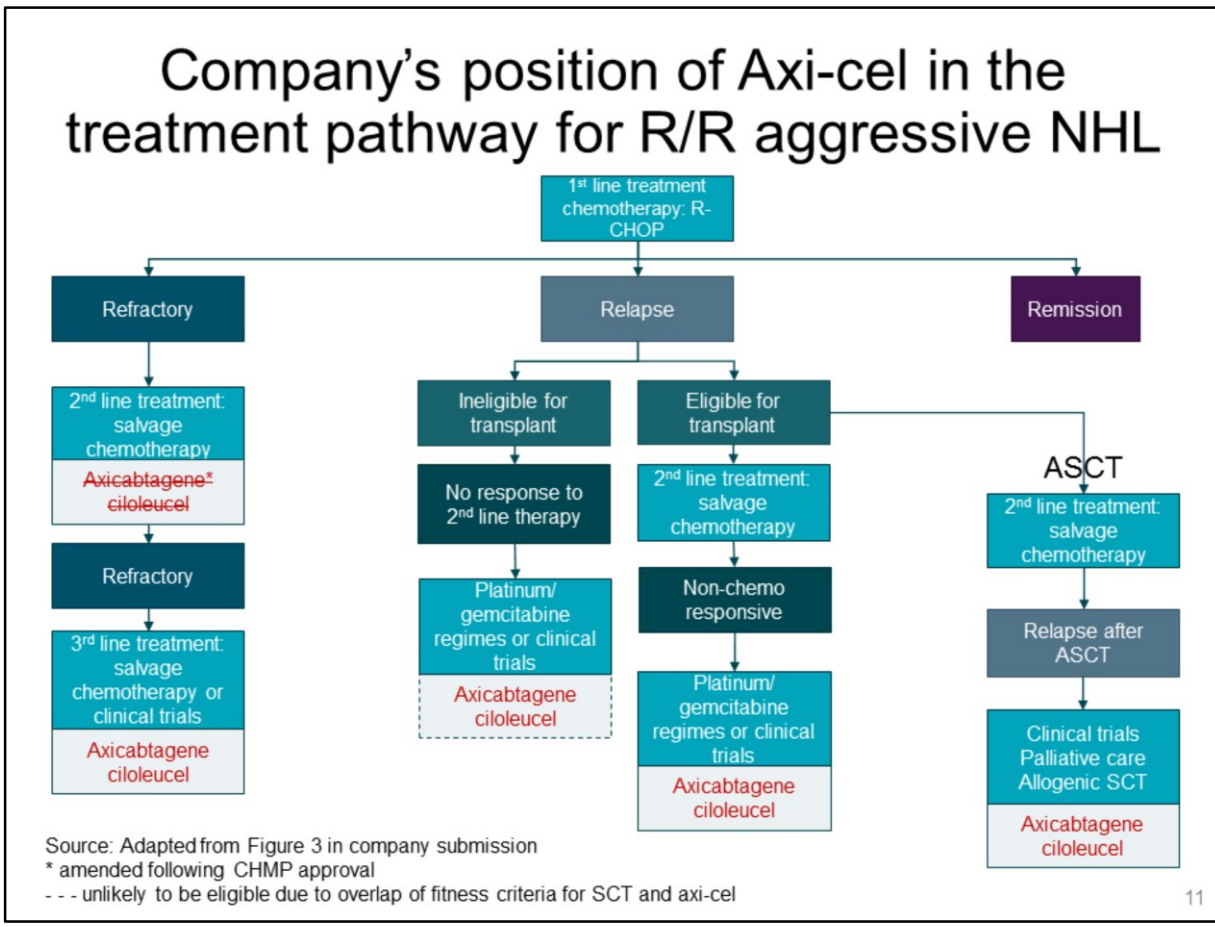

Source: Adapted from Figure 3 in company submission

Who is eligible for axi-cel treatment

NHS England's interpretation:

- Whether people had relapsed or refractory disease after 1st line treatment, to be eligible for axi-cel, standard 2nd line therapy would also have to have failed
- If a SCT was planned as part of 2nd line treatment and patients respond sufficiently to chemotherapy, those patients should proceed to SCT as currently commissioned and not to CAR T-cell therapy
- Patients who relapsed within 12 months of receiving the SCT would be eligible for axi-cel
- Fitness requirements for receiving axi-cel treatment would be very similar to those for patients requiring SCTs meaning patients would be required to have ECOG status 0-1

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Source: Submission from NHS England

Comments from patient groups

DLBCL and current treatment:

- Most common symptoms are swollen lymph nodes in the neck, armpit or groin. Patients may also experience chest or abdominal pain, bone pain, coughing or breathlessness
- People eligible for axi-cel have limited curative options currently. They have often experienced multiple courses of chemotherapy which results in harsh side effects including sickness, diarrhoea and mouth ulcers
- Currently unmet need for patients who have failed available treatments

CAR T-cell treatment:

- Treatment with CAR T-cell therapy can offer hope when all other treatments have failed
- A patient expect noted that they felt prepared for side effects from the CAR T-cell therapy as they received advice prior to treatment. They also noted the inconvenience of this period was insignificant when compared with the possibility that they would respond well to the treatment

Implementation:

- Treatment is intensive and requires patients to be admitted and/or stay in ambulatory care close to the hospital for several weeks – placing strain on patients, families and carers

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Comments from professional groups

Current treatment options:

- High level of unmet need
- Current treatment includes salvage chemotherapy and if remission is achieved this is followed by high dose chemotherapy and autologous/allogeneic transplantation
- Prognosis of patients whose second line treatments fail is very poor

CAR T treatment:

- For patients there would be a profound effect (step-change) if the preliminary results are substantiated
- CAR T-cell therapy is a potential game changer

Implementation:

- Referral guidelines and pathways of care will need to be carefully defined - [CAR T-cell therapy] requires properly resourced and trained teams in a few large centres
- To deliver CAR T-cell therapy there is an absolute need for a [specially trained] CAR T-cell therapy team comprising physicians (middle grade and senior), nurses, intensivists and technicians, a sufficient supply of in-patients beds and ready access to an on site ITU

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Statement from NHS England

- "Given the novelty, promise and toxicity of the treatment, it is expected axicabtagene ciloleucel will make fundamental differences to the treatment pathway compared to current care
- It will require new service specifications
- CAR T therapy will require substantial workforce and infrastructure changes
  - New training accreditation requirements
  - Changes to access arrangements to ITU support planning, booking and access
  - Use of other treatments and expertise to support its use.. tocilizumab may be required or patients may need rapid access to neurological care after treatment
- The impact on the provision of safe and effective CAR T-cell treatment is very high for commissioners both financially and because of the need to ensure capacity for the CAR T-cell service without any adverse effect on current services
- Given ..[this, and].. the need for many healthcare professionals to learn new and necessary skills, NHS England plans a phased implementation and ongoing evaluation of the capacity needs in the NHS in order to successfully and safely deliver the treatment required"

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Decision problem – Axi cel

	NICE scope	Company
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma or transformed follicular lymphoma	[redacted]
Comparators	• DHAP (w/wo rituximab) • GDP (w/wo rituximab) • ICE (w/wo rituximab) • IVE (w/wo rituximab) • Pixantrone monotherapy • Best supportive care	• DHAP (w/wo rituximab) • GDP (w/wo rituximab) • ICE (w/wo rituximab) • IVE (w/wo rituximab) • Best supportive care (including radiotherapy)
Outcomes	Overall survival (OS), progression-free survival (PFS), response rate (ORR), adverse effects of treatment, health-related quality of life	

*Transformed follicular lymphoma not included in the CHMP's positive opinion

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Source: Company's submission Table 1

Related NICE Guidance

Technology Appraisal 306

Pixantrone monotherapy is recommended as an option for treating adults with multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma only if:

- the person has previously been treated with rituximab
- the person is receiving third- or fourth-line treatment
- the manufacturer provides pixantrone with the discount agreed in the patient access scheme.

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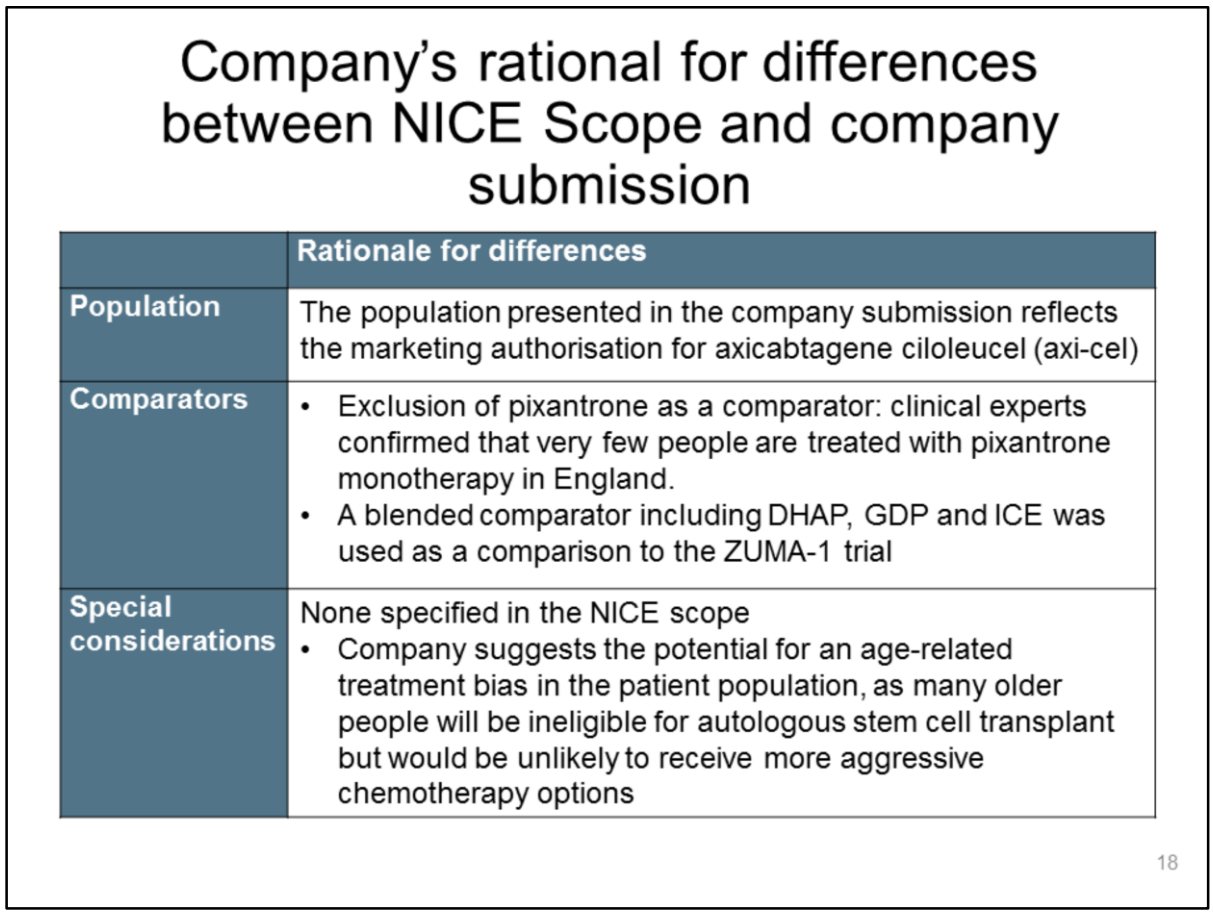

Company's rational for differences between NICE Scope and company submission

	Rationale for differences
Population	The population presented in the company submission reflects the marketing authorisation for axicabtagene ciloleucel (axi-cel)
Comparators	• Exclusion of pixantrone as a comparator: clinical experts confirmed that very few people are treated with pixantrone monotherapy in England. • A blended comparator including DHAP, GDP and ICE was used as a comparison to the ZUMA-1 trial
Special considerations	None specified in the NICE scope • Company suggests the potential for an age-related treatment bias in the patient population, as many older people will be ineligible for autologous stem cell transplant but would be unlikely to receive more aggressive chemotherapy options

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Source: Company's submission Table 1

ERG's comments – decision problem

1	• The CS defines the population in line with the final scope issued by NICE. • The MA is for patients R/R after two or more lines of systemic therapy, would ASCT eligible patients be included? • Submitted evidence includes the ASCT eligible population
2	• The company's decision problem excluded pixantrone as a comparator • The clinical advisor to the ERG supported the company's rationale for its exclusion
3	• The company's use of a blended comparator does not allow for comparison of axi-cel against any individual treatment • Given the heterogeneity of populations and availability of data, the ERG consider this a suitable pragmatic approach for the comparison
4	• The ERG do not agree with the company's placement of axi-cel in the treatment pathway. o Axi-cel is unlikely to be used as 1st line salvage therapy in UK (subsequent MA requires 2 previous therapies) o Patients ineligible for ASCT would not be eligible for axi-cel as there is considerable overlap between eligibility for ASCT and Axi-cel

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Source: ERG report page 13-14

Technical engagement comments: What is the appropriate comparator?

- **Where is the correct placement of axi-cel in the treatment pathway?**
  Marketing authorisation is for people with relapsed/refractory disease after 2 lines of therapy. Current 3rd line treatment (and the appropriate comparator) for those not eligible for SCT is palliative care (salvage chemotherapy). Other options would be clinical trials of novel therapies and symptomatic therapy. A minority of people who respond to 3rd line chemotherapy and were fit would proceed to allogenic SCT
- **Should pixantrone be considered as a comparator?**
  All consultees in the technical engagement agreed pixantrone was not a relevant comparator as it is rarely used in clinical practice on account of poor efficacy.
- **Is a blended comparator appropriate?**
  There is no 3rd line standard therapy; one is clearly not superior to the others. 3rd line therapies would be one of DHAP/ESHAP/GDP/ICE/IVE ± rituximab with their use determined by local practice.

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Clinical and commissioning responses to technical engagement

Clinical effectiveness

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Company's evidence of clinical effectiveness

Evidence	Source	Used in clinical effectiveness	Used in cost effectiveness
ZUMA-1 updated analysis cohort (n=108)	CS pages 31-48; ERG report pages 38-46	Clinical trial results presented	Yes
ZUMA-1 primary analysis cohort (n=101)	CS pages 67-75; ERG report pages 38-46	Efficacy and adverse events	Adverse events only
ZUMA-1 safety management (n=34)	CS page 48; ERG report page 55-56	HRQoL only	Yes
SCHOLAR-1 historical cohort (n=636)	CS pages 54-57; Appendix 22-23; ERG report pages 46-48	Pivotal evidence	Yes
Indirect comparison; ZUMA-1 (n=101), SCHOLAR-1 (n=497)	CS pages 54-67; Appendix pages 22-23; Clarification response pages 6-8; ERG report pages 48-55	Yes	Yes
Abbreviations: CS, Company submission; NCI, National Cancer Institute			

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ZUMA-1 trial

	ZUMA- 1
Study design	International, multicentre, single-arm, open-label Phase 1/2 study
Population	119 adults with aggressive B-cell NHL (DLBCL, PMBCL, and TFL) that was either refractory to treatment or had relapsed ≤12 months after ASCT with ECOG performance status of 0 or 1
Exclusion criteria	• History of allogeneic cell transplant • Autologous stem cell transplant within 6 weeks of trial • Prior CD19 targeted therapy • Presence of uncontrolled fungal, bacterial, viral infection • History or presence of CNS disorder
Intervention	Axicabtagene ciloleucel (n=108)
Comparator	n/a (single-arm study)
Location	24 centres: (23) US and (1) Israel
Outcomes	Overall response rate (ORR) overall survival (OS) progression-free survival (PFS) duration or response (DoR) and safety

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Source: Company submission Table 5

mITT (n=108) = modified intention to treat **ITT (n=119)** = intention to treat
The full analysis population included all enrolled patients (N = 111). The modified intention-to-treat (mITT) population included all patients treated with at least 1.0 x 10^6 anti-CD19 CAR T-cells/kg (N = 101) and was the analysis population used for all efficacy analyses in ZUMA-1 Phase 2. The safety analysis population included all patients treated with any dose of axi-cel (N = 101).

SCHOLAR-1 cohort

	SCHOLAR-1
Study design	Patient level historical control study from 4 sources: • MD Anderson Cancer Centre (MDACC) n=191 • Mayo Clinic and University of Iowa (MC/IA) Specialised Program of Research Excellence (SPORE) n=107 • The National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) randomised Phase 3 study LY.12 n=353 • French Lymphoma Academic Research Organisation (LYSARC) randomised Phase 3 Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study n=210
Population	636 (497 evaluable for both survival and response) adults with refractory disease or who had relapsed ≤12 months after ASCT
Treatment options	Salvage chemotherapy Rituximab maintenance Observation post-ASCT (autologous stem cell transplant)
Comparator	n/a (retrospective cohort study)
Outcomes	Response rate (RR), complete response rate (CRR), and overall survival (OS)

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Source: Company submission Page 53-54

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ERG's comments – Clinical data availability

No clear exclusion criteria from the company's systematic review - was appropriate data for the comparator arm missed?

ZUMA-1	1. Patients in ZUMA-1 appear to be representative of clinical practice in the UK
	2. Appropriate outcomes were assessed in ZUMA-1, but immaturity of the data means there is uncertainty in the OS and PFS results beyond 12 months
	3. 10% of patients were re-treated with axi-cel (due to disease progression) - re-treatment is not reflective of future clinical practice and could inflate the efficacy results of ZUMA-1
SCHOLAR-1	1. The outcomes reported in SCHOLAR-1 were ORR and OS only
	2. The smallest study included in SCHOLAR-1 had lower 2-year and median survival than the other pooled studies which could effect heterogeneity and pooled results

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Source: ERG report pages: 38-46

Baseline characteristics ZUMA-1 and SCHOLAR-1 (1)

Characteristic	ZUMA-1 (n=101)	SCHOLAR-1 (n=497)
Age, years, median (range)	58 (23–76)	55 (19–81)
Male, n (%)	68 (67.3)	321 (64.6)
ECOG, n (%)		
0-1	101 (100.0)	226 (45.5)
≥ 2	0 (0.0)	55 (11.1)
Not available	0 (0.0)	216 (43.5)
IPI score, n (%)		
0-1	27 (26.7)	73 (14.7)
2	26 (25.7)	66 (13.3)
≥ 3	48 (47.5)	76 (15.3)
Not available	0 (0.0)	282 (56.7)
Disease stage		
I-II	15 (14.9)	75 (14.6)
III-IV	86 (85.1)	149 (30.0)
Not available	0 (0.0)	273 (47.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index

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Source: Company appendix Table 9

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Baseline characteristics ZUMA-1 and SCHOLAR-1 (2)

Characteristic	ZUMA-1 (n=101)	SCHOLAR-1 (n=497)
Refactory subgroup		
Primary refactory	2 (2.0)	100 (20.1)
Refactory to 2nd line or later	78 (77.2)	310 (62.4)
Relapse within 12m of ASCT	26 (20.8)	87 (17.5)
Number of previous lines of therapy		
1	2 (2.0)	100 (20.1)
2	29 (28.7)	204 (41.0)
3	30 (29.7)	91 (18.3)
≥ 4	40 (39.6)	15 (3.0)
Not available	0 (0.0)	87 (17.5)
Autologous stem cell transplant post treatment	[redacted]	[redacted]

ERG's comments

Missing data was an issue for all the covariates in the SCHOLAR-1 data set and could lead to biased results unless appropriate adjustments are made

Source: Table 9 company appendix

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Source: Company appendix Table 9

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Differences in baseline characteristics - SCHOLAR-1 & ZUMA-1

Differences in baseline characteristic between the two studies:

- [redacted] of patients in SCHOLAR-1 subsequently received ASCT compared with only [redacted] patients in ZUMA-1
- SCHOLAR-1 cohort included 20% primary refractory patients. Only patients relapsed/refractory to 2 lines of therapy would be eligible for axi-cel. ZUMA-1 included 2 (2%) primary refractory patients.
- SCHOLAR-1 included patients with ECOG scores 0-4 compared to ZUMA-1 only including those with ECOG score 0-1
- ZUMA-1 had a higher proportion of patients with Stage III-IV disease than SCHOLAR-1
- ZUMA-1 patients were more heavily pre-treated that those in SCHOLAR-1

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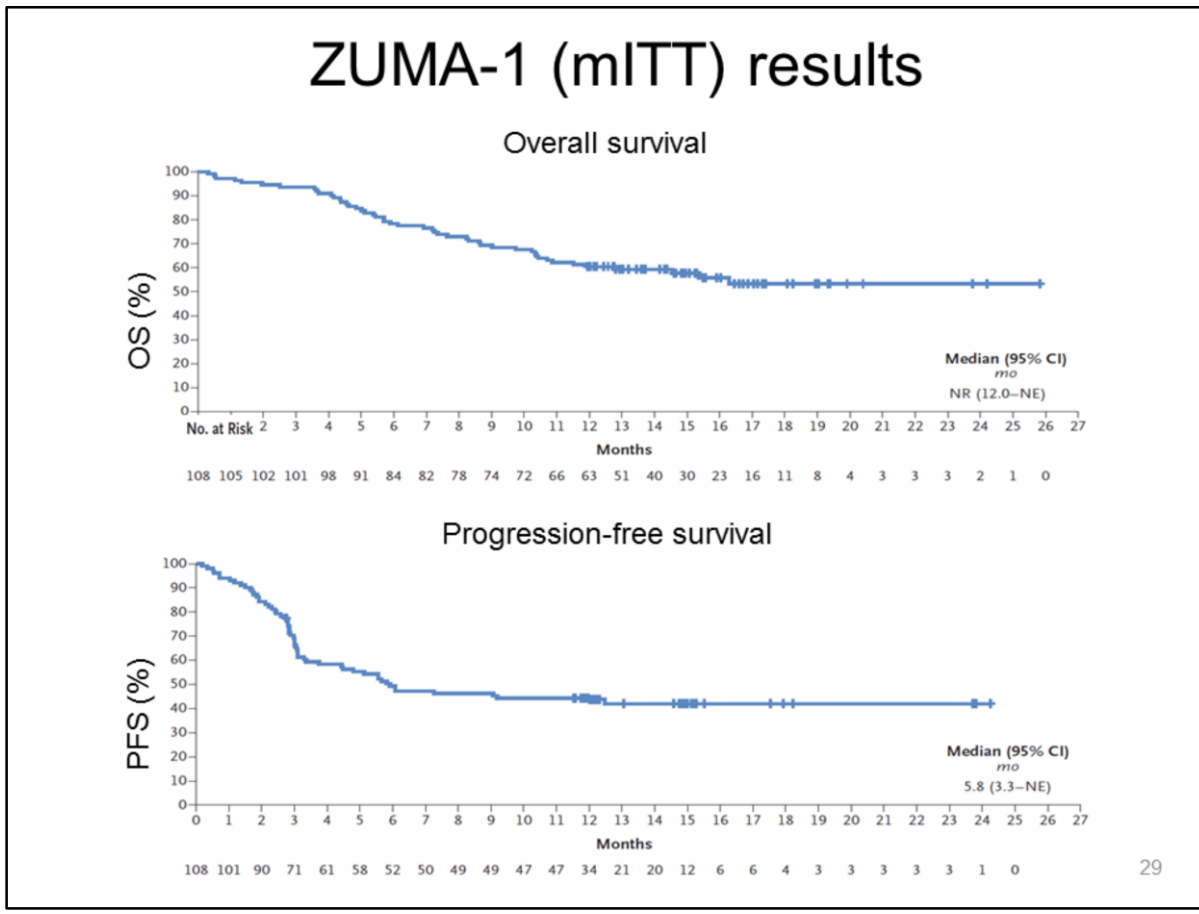

Source: Figures 5 & 6 company submission

ZUMA-1 (mITT) and SCHOLAR-1 results

	ZUMA-1 (n=101)	SCHOLAR-1*				
		CORAL (n=170)	LY12 (n=219)	MAYO (n=82)	MDACC (n=165)	Overall (n=636)
ORR , n (%)	83 (82)	53 (31.2)	28 (26.4)	21 (25.6)	33 (20.0)	135 (25.8)
CR, n (%)	55 (54)	26 (15.3)	2 (1.9)	6 (7.3)	11 (6.7)	45 (8.6)
Median, OS, m (95% CI)	NE	6.5 (5.8-8.7)	6.6 (5.7-8.1)	5.0 (4.1-6.0)	6.6 (5.7-7.8)	6.3 (5.9-7.0)

Abbreviations: CI, confidence interval; CR, complete response; ORR, overall response rate; NE, not evaluable; m, months

*The company assessed of heterogeneity in SCHOLAR-1 using Higgin's Q statistic p>0.1 suggesting data could be pooled

ERG's comments: The ERG is unaware of the "Higgin's Q statistic". It appears likely that Cochran's Q statistic was calculated which is known to be poor at detecting heterogeneity across studies. MAYO appears to be an outlier

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Source: Table 12 company submission

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Company's unadjusted ZUMA-1 (mITT) & SCHOLAR-1 results

	ZUMA-1 (n=108)	SCHOLAR-1 (n=508)	Difference (95% CI)	Odds ratio (95% CI)
ZUMA-1 (mITT) and SCHOLAR-1 (last refractory categorization)				
ORR (%)	[redacted]	[redacted]	[redacted]	[redacted]
CR (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months*	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; mITT, modified intention to treat; NE, not evaluable; ORR, objective response rate; OS, overall survival

- Last refractory categorisation excludes patients without a current line of therapy present in SCHOLAR-1 after reaching their latest designation of refractory status. Total sample size was 593, only 508 patients were evaluable for response and 497 for survival.

Source: Tables 1 & 2 in company response to clarification

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Company's adjustments for baseline characteristics

Company's base case adjusts for imbalance using patient level data to exclude people in SCHOLAR-1 who would not have been eligible for ZUMA-1

- Base case: adjusted for ECOG status
  Justification: inclusion criteria of ZUMA-1 only allows ECOG 0–1 patients
- Scenario 1: adjusted for ECOG status and subsequent ASCT treatment
  Justification: subjects with ECOG 2–4 at baseline (as above) are likely to have worse outcomes. Patients who received post-refractory SCT would not be eligible for axi-cel in clinical practice and likely to have improved outcomes
- Scenario 2: Propensity score adjusted, weights for each individual SCHOLAR-1 to adjust for the differences in baseline characteristics*
  Justification: Used in TSD17 to reduce the bias of estimating relative treatment efficacy based on single arm trials or observational studies

*Not presented as part of company's clinical effectiveness results

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Source: Company submission pages 63-67 and ERG report page 54 Table 9

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Company's standardised comparisons

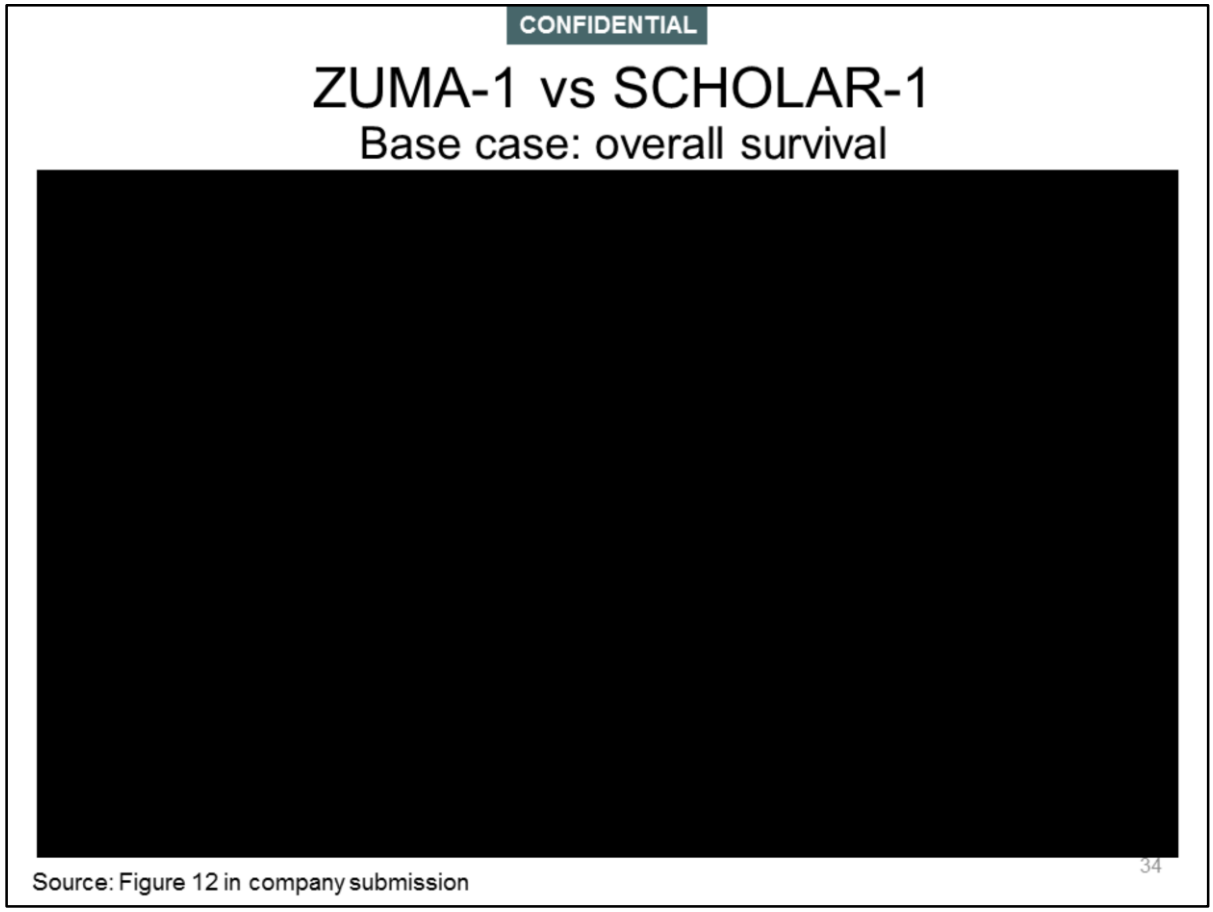
- ZUMA-1 mITT phase 2 population and SCHOLAR-1 last refractory categorisation (patients treated with chemotherapy after refractory status) n=508 for response n=497 for survival

	ZUMA-1 (n=101)	SCHOLAR-1 (n=508)	Odds ratio (p-value)
Base case: Standardised by ECOG status (excluded patients with ECOG 2-4)			
ORR (%)	[redacted]	[redacted]	[redacted]
CR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
Scenario 1: Standardised by ECOG status and subsequent ASCT			
ORR (%)	[redacted]	[redacted]	[redacted]
CR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]

*Stratified Cox model. Abbreviations: CR, complete response; mITT, modified intention-to-treat; NA, not applicable; NE, not evaluable; OS, overall survival ORR, overall response rate

33

Source: Company submission pages 63-67 Tables 15 & 18



Source: Company submission page 66 Figure 12

ERG's comments – Clinical results

1	The company's original standardised analyses (stratified for just ECOG and last refractory status) do not adequately adjust for important baseline imbalances • Patients with ECOG data "Not assessed" (43.5% of the SCHOLAR-1) were included in the adjustment for ECOG status • Adjustments for subsequent ASCT did not exclude patients (10%) re-treated with axi-cel • Propensity score did not adjust for covariates known to be relevant to outcome: ECOG, IPI score and number of lines of previous therapy
2	Restricting the patient population for SCHOLAR-1 to patients with known ECOG 0-1 status would provide a more appropriate comparison with the ZUMA-1 population
3	Differences in ECOG status, re-treatment with axi-cel, proportion of patients receiving SCT and substantial levels of missing covariate data have not been considered by the company in its reflection of bias

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Source: ERG report pages 50-56

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SCHOLAR-1 results – Overall survival by ECOG category

*Company note [redacted] of patients included in the EGOC score 0-1 group received subsequent ASCT

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Source: Company response to clarification pages 5-8 Figure 3

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Company's standardised analyses for patients with ECOG score 0-1

- Provided in response to clarification request - participants with missing ECOG status and ECOG 2-4 in the SCHOLAR-1 study excluded from the analysis

	ZUMA-1 (n=108)	SCHOLAR-1 (n=230)	Odds ratio (p-value)
ZUMA-1 phase I and II & SCHOLAR-1 ECOG 0-1 only (last refractory categorization)			
ORR (%)	[redacted]	[redacted]	[redacted]
CR (%)	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]
*Stratified Cox model. Abbreviations: CR, complete response; HR, hazard ratio; NE, not evaluable; OS, overall survival ORR, overall response rate			

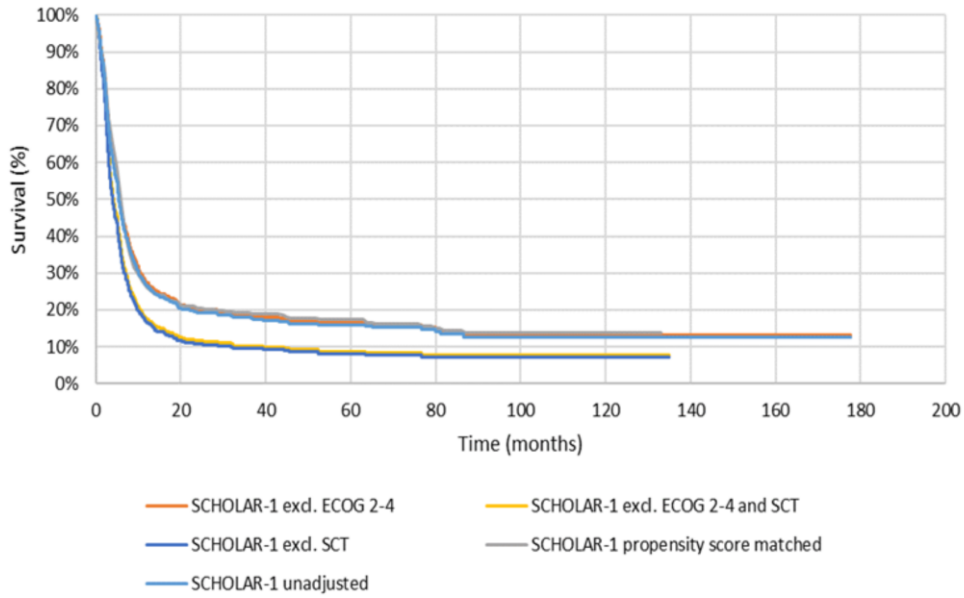
*Company note [redacted] of patients included in the EGOC score 0-1 group received subsequent ASCT

37

Source: Company response to clarification Tables 3 & 4

SCHOLAR-1 results – Overall survival scenario analyses

SCHOLAR-1 excluding SCT versus existing SCHOLAR-1 scenarios



38

Source: Figure 1 response to clarification after technical engagement

Comparative effectiveness results

- High heterogeneity in ZUMA-1 & SCHOLAR-1
- All consultees in the technical engagement agreed it would not be appropriate to include patients with ECOG score 2-4 in the comparison. Only patients with ECOG score 0-1 would be eligible for axi-cel and outcomes of patients with inferior ECOG score are likely to be worse.
- Clinical and commissioning experts were concerned the proportion of patients receiving SCT in the SCHOLAR-1 cohort does not reflect clinical practice in the UK.
- Consultees noted that this inclusion could inflate both survival and costs in the comparator arm.
- **In response to technical engagement the company noted that no suitable alternative data has been identified – the ORCHARRD study (suggested by clinical experts in response to technical engagement) is not deemed suitable due to the high number of primary refractory patients and high proportion of patients receiving subsequent SCT**

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ZUMA-1 Adverse events (1)

- **No AE data were collected in the SCHOLAR-1 study**

Outcome	ZUMA-1 (n=101)
Patients with an AE, n (%)	101 (100)
Average duration of follow-up (months)	8.7
Patients with Grade ≥3 AE, n (%)	96 (95.0)
Grade ≥3 CRS	13 (12.9)
Grade ≥3 neurological event	28 (27.8)
Patients with an SAE, n (%)	[redacted]
Patients with Grade ≥3 SAE, n (%)	[redacted]
Deaths, n (%)	[redacted]
Death from PD	[redacted]
Death due to AE	[redacted]
Other	[redacted]
Abbreviations: AE, adverse event; CRS, cytokine release syndrome; PD, progressed disease; SAE, severe adverse event	

Source: Table 19 in company submission

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Source: Company submission Table 19

ERG's comments – Adverse events

1	• Adverse events are likely to occur in all patients • Serious adverse events occurred in around half of patients who received axi-cel
2	• Cytokine release syndrome, neurological adverse events and B-cell aplasia often occur following axi-cel treatment
3	• The company present data on the rate of AEs across recruitment phases. The ERG noted although there may be a reduction in the incidence of ≥ grade 3 events with clinician experience, the absolute reductions in AEs for CRS and neurological are small
4	• Long-term term follow up data is required to fully understand the effects of adverse events occurring after treatment with axi-cel

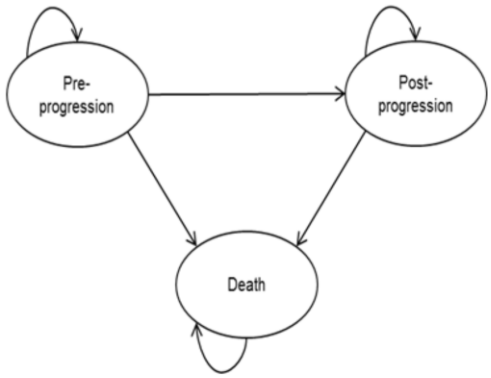
41

Source: ERG report page 57

Cost effectiveness

42

Company's model



- Partitioned survival model - OS and PFS modelled independently
- Cycle length: 1 month
  Time horizon: 44 years
  Discount rate: 3.5%
- Axi-cel OS and PFS KM data from ZUMA-1 mITT population median 15.4 months follow-up
- After 24 months in the pre-progression state utilities/costs matched to general population
- OS for BSC from adjusted SCHOLAR-1. PFS (not recorded) uses OS:PFS ratio from ZUMA-1

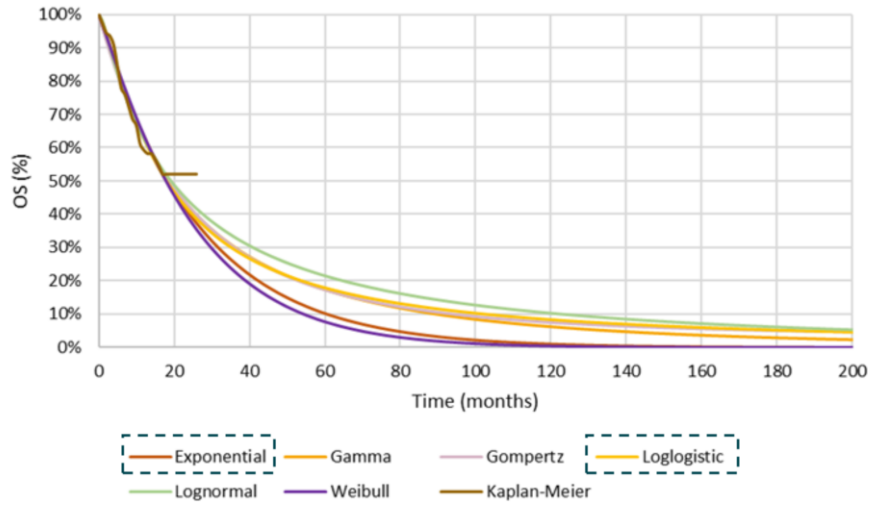
ERG's comments on model structure

Model structure appropriate. Company amended the model to include AE treatment costs after clarification. However, the ERG considers the concept of 'cure' and the assumptions around mortality risks for long term survivors to be subject to considerable uncertainty

43

Source: Figure 14 company submission

Axi-cel overall survival – company's extrapolation: parametric curves



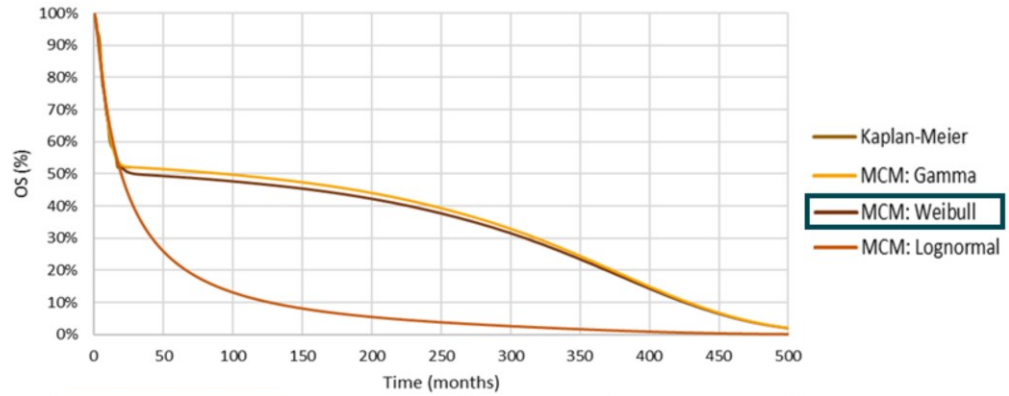
Axi-cel

- Uses clinical data from ZUMA-1 (n=108)
- Based on AIC and BIC statistics, loglogistic/exponential curves preferred
- However, neither fit the KM curve or provide plausible extrapolation of the long-term survival for axi-cel

44

Source: Company submission Figure 18

Axi-cel overall survival – company's extrapolation: mixture cure model



Distribution	Lognormal	Weibull	Gamma
Cure Fraction	1%	50%	53%

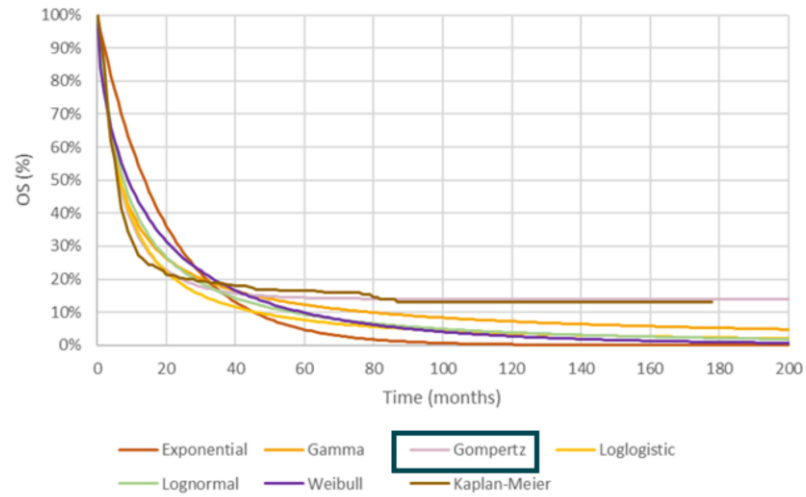
Axi-cel

- Mixture cure model use patient level data in a logistic regression model to estimate the "cure fractions". Cured patients follow general population health from time of infusion.
- Standard parametric curve estimates survival for those without long-term remission
- General population health assumed for long term survivors after 24m

45

Source: Company submission Figure 20

BSC overall survival – company's extrapolation: parametric curves



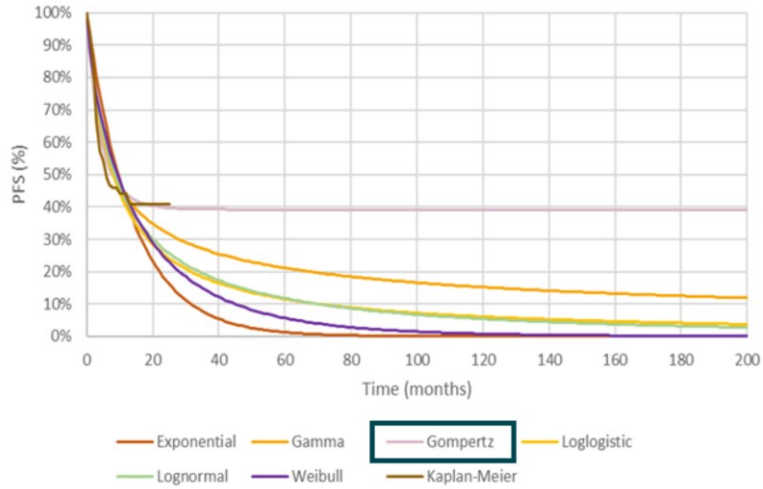
BSC

- SCHOLAR-1 adjusted to remove patients with ECOG score of 2-4
- Based on AIC and BIC statistics, visual inspection and clinical opinion Gompertz curve demonstrates the best fit
- Mixture-cure models are not used for BSC arm as simpler parametric curves are preferred by the company

46

Source: Company submission Figure 23

Axi-cel progression-free survival – company's extrapolation: parametric curves



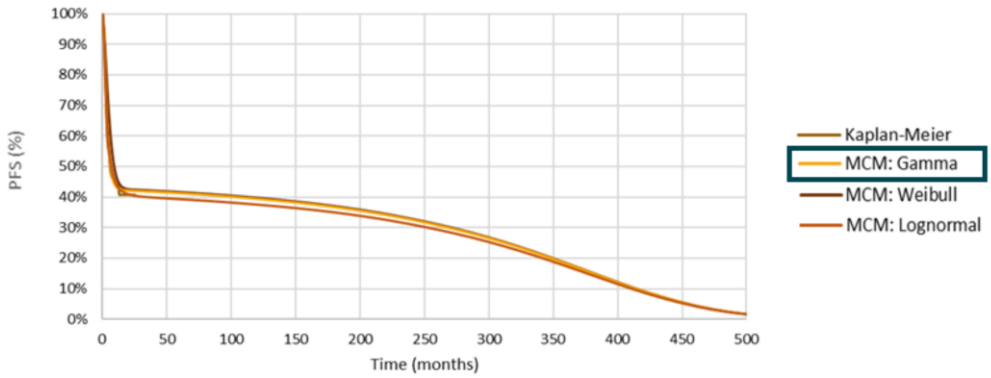
Axi-cel

- Based on AIC and BIC statistics, visual inspection and clinical opinion Gompertz curve demonstrates the best fit
- Alternative curves were explored as part of the scenario analysis
- MCM model is not used as the company argue there is no consensus on the validity of using MCM for PFS

47

Provided after clarification.
Source: clarification response Figure 28 corrected graph

Axi-cel progression-free survival – company's extrapolation: mixture cure model



Distribution	Lognormal	Weibull	Gamma
Cure Fraction	41%	43%	42%

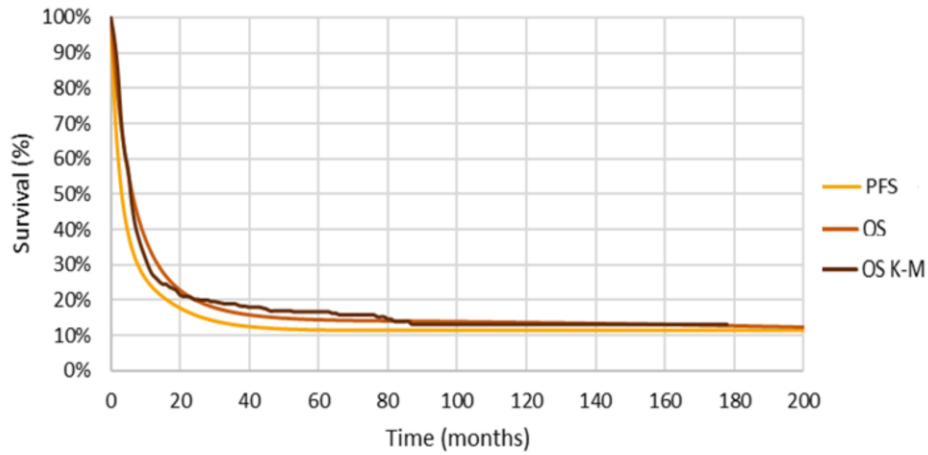
Axi-cel

- Provided after clarification
  - Company – "PFS end points do not have clear meaning"
- Background mortality used to estimate 'cure fraction' in OS and PFS
- More events in PFS allows the lognormal model to adjust to a more reasonable position than in the OS MCM modelling
- Single parametric curve preferred

48

Source: Response to clarification Figure 11

BSC progression-free survival – company's extrapolation



BSC

- PFS not recorded in SCHOLAR-1 study
- PFS for BSC estimated by assuming the same ratio between PFS and OS at each time point in the axi-cel arm can be applied to BSC
- 2 scenario analyses explored:
  - People receiving BSC spend 100% of time progression-free
  - People receiving BSC spend 100% of time in progressed state

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Source: Company submission Figure 31

Company's survival functions

Outcome		Extrapolation	Base case	Scenarios
Overall survival	Axi-cel	• Extrapolation needed • Parametric for long-term survival curves implausible • MCM accounts	MCM Weibull	MCM gamma
	BSC	• Data almost complete • Simple single parametric curves preferred to MCM	Gompertz	Baseline adjustments & all distributions
Progression-free survival	Axi-cel	• Extrapolation needed • Parametric curves preferred • MCM end points have no clear meaning	Gompertz	Gamma MCM Gamma
	BSC	• Not recorded for SCHOLAR-1	Time-dependent ratio of axi-cel OS to PFS	PFS=0 PFS=100
TTD		• Axi-cel assumes a one time infusion • BSC average no. cycles, average no. of days per cycle		

Key: BSC, best supportive care; MCM, mixture cure model; OS, overall survival; PFS progression-free survival; TTD, time to treatment discontinuation

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Source: Company submission Pages 91-119

Time on treatment was not explicitly reported in the SCHOLAR-1 study and is not relevant to the ZUMA-1 trial, as axi-cel is given as a one-off infusion. For the modelled BSC regimens, the number of treatment cycles and the days per cycle for each component of each regimen are taken from the South East London Cancer Network and the Thames Valley Strategic Clinical Networks (CS page 116)

ERG's comments – extrapolation of OS

Axicabtagene ciloleucel	The use of single parametric survival curves to model axi-cel OS would produce implausible results
	The difference in the cure fractions across alternative models of OS for axi-cel is likely to be caused by immature data
	The base-case mixture-cure model overly optimistic as: • The timing of cure is uncertain - survival data in ZUMA-1 is too immature with < 2 years follow-up • Robust estimates require: (i) long follow-up period, (ii) large numbers of patient at risk at the end of follow-up (high levels of censoring in ZUMA-1) • Excess mortality risks appear likely to persist for at least 5 years (Howlader et al. 2017) but are not included in the company base case
BSC	The OS modelling approach for the BSC is inconsistent with that of axi-cel: • Mixture-cure models for BSC OS fit the observed data with robust estimates of cure fraction across distributions
	There is high heterogeneity between study populations. The ERG prefers to include only patients of known ECOG 0-1 in the base-case comparison

51

Source: ERG report pages 72-81

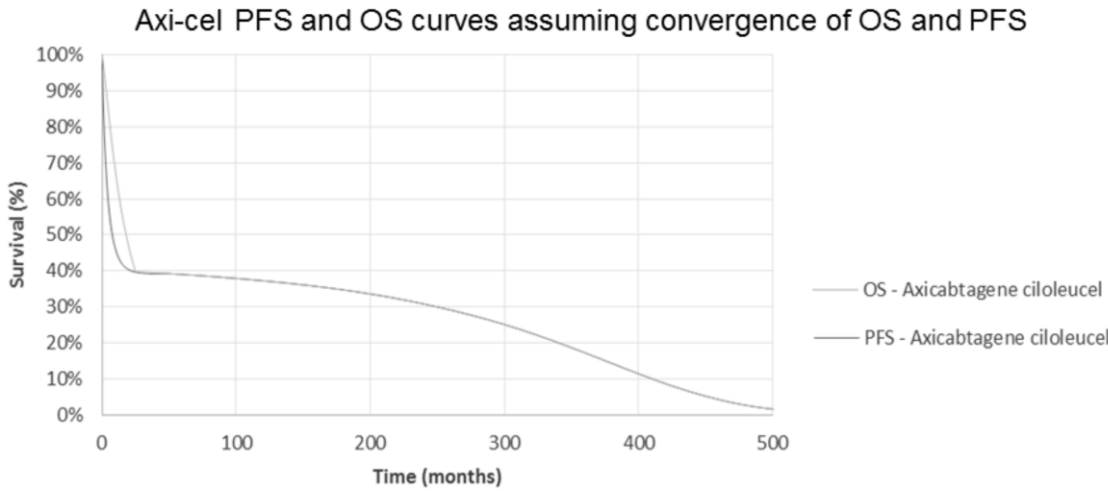
ERG's comments – extrapolation of PFS

Axicabtagene ciloleucel	The use of different survival models for PFS and OS results in an important disconnect: patients can be cured in terms of survival but not from disease progression
Axicabtagene ciloleucel	MCM for PFS showed less variation in cure fraction than those of OS • Due to patients being cured following progression • Immature OS data The ERG considers that the inclusion of patients re-treated with axi-cel leads to a potentially positive bias in the OS data.
BSC	There is limited rationale for the companies approach to modelling PFS for BSC. The scenarios tested by the company correspond to the two extremes
BSC	Given the different mechanisms of action it is possible the relationship between PFS and OS for BSC is different than for axi-cel
BSC	An alternative modelling approach, assuming the proportional relationship between PFS and OS from a different published study in the US may have been more appropriate

52

Source: ERG report pages 82-86

ERG's preferred approach to modelling OS and PFS for axi-cel



- The ERG selected the best fitting single parametric OS curve for axi-cel (loglogistic) and constrained it so patients transitioned to general population mortality once the OS curve converged with the PFS curve
- This allowed for long-term survival in the model, but for a smaller cure fraction (approximately 40%) occurring around 52 months

53

Source: ERG report Figure 18

Technical engagement comments: extrapolation of ZUMA-1 survival data

- **Clinical, patient and commissioning experts:** Patients with progressed disease are not expected to survive for an extended period of time. It would therefore be reasonable to use the cure fraction estimated from progression free survival (PFS) for the extrapolation of survival in the axi-cel arm
- **Company:** There are a number of patients who have progressed but are alive at 12 months. It is plausible a minority of patients that have progressed may have some clinical benefit from the persistence of CAR-T cells and have prolonged survival
- **The ERG:** The OS data is immature, only 15.4 months median follow up, meaning high censoring of patients where the curve appears to plateau. This is reflected in wide range of cure fraction from the MCM of axi-cel OS data.
  The company has also not accounted for the retreatment of patients with axi-cel as a potential confounder for survival in patients with progressed disease

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Technical engagement comments: Mortality risks for long term survivors

- An age matched general population cohort would be expected to have considerable prevalence of diabetes, ischaemic heart disease, chronic renal disease, respiratory disease etc.
- Consultees agreed there is potential for long term survival in both treatment arms. Clinical experts suggest excess mortality related to toxicities of previous chemotherapy treatment, cardiovascular and immunosuppression side effects would be expected to persist for several years
- In response to the technical engagement clarification questions the company noted that the use of age-matched general population mortality for patients in pre-progression state after 3-5 years is not compatible to the mixture cure model approach as the cured proportion follow age-matched general population mortality (from time zero) and the majority of uncured patients (>99%) will have been dead by 2-3 years

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ERG's preferred approach to modelling BSC overall survival

The ERG digitised the KM data from SCHOLAR-1 for patients with known ECOG 0-1 status (n=226) to provide a more appropriate basis for comparison with the ZUMA-1 population

56

Source: ERG report Figure 17

Health related quality of life (HRQoL)

- HRQoL data were collected in a safety management cohort of ZUMA-1
  - Small sample of patients (87 observations from 34 patients)
  - Crosswalk algorithm (van Hout et al) used to map EQ-5D-5L to EQ-5D-3L
  - Alternative utilities identified from the literature were used in scenario analyses (NICE TA306)
  - People return to general population health after 2 years in the pre-progression state (alternative scenarios explored by ERG)

State	Utility value: mean (standard error)	Scenario analyses	Source
Progression-free (base case)	0.72 (0.03)	0.76 (0.70-0.82)	Health-related quality-of-life EQ-5D data from ZUMA-1 Scenario from TA306
Progressed disease (base case)	0.65 (0.06)	0.68 (0.6-0.7)	
Progression-free after 2 years in PFS health state	General population	10% percentage decrement	Maurer et al (2014)

57

Source: ERG report Table 14, company submission Table 43

Company's adverse event disutility values

Adverse event	Utility decrement	Source	Duration (days)
Anaemia	-0.12	Swinburn et al., 2010	14
Cytokine release syndrome	-0.72	Equal value as utility of PFS Assumption as in the York study	4
Neutropenia	-0.09	Nafees et al., 2008	47
Platelet count decreased	-0.11	Tolley et al., 2013	50
Thrombocytopenia	-0.11	Tolley et al., 2013	63
Encephalopathy	-0.15	Disutilities that could not be identified were assumed to be equal to the maximum non-CRS AE disutility value identified. Assumption as in the pixantrone submission to NICE (TA306)	9
Febrile neutropenia	-0.15		6
Hypophosphatemia	-0.15		16
Hypotension	-0.15		5
Leukopenia	-0.15		21
Lymphocyte count decreased	-0.15		64
Neutrophil count decreased	-0.15		17
Pyrexia	-0.11		2
White blood cell count decreased	-0.15		40

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Source: ERG report Table 15, company submission Table 43

Only adverse events that had an incidence equal or greater than 10% were included in the economic model.

ERG's comments – HRQoL and adverse events

1	The exclusion of adverse events for BSC appears conservative
2	The safety management cohort of ZUMA-1 (source of EQ-5D data) has a small sample size (n=34)
3	Only adverse events that had an incidence equal or greater than 10% in ZUMA-1 were included in the economic model
4	It is not clear how the health state utilities were estimated but unlikely to be a key driver of cost effectiveness
5	There is limited evidence to support cure at two years post-treatment The company's scenario analysis explores an arbitrarily lower HRQoL of 0.09
6	Patients considered cured are assumed to have the same mortality as the general population from the moment of infusion – would this be expected in clinical practice?
7	The uncertainties around the requirement and usage of ICU beds for CRS has not been fully addressed by the company

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Source: ERG report pages 91-102

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Company costs – One time costs for axi-cel (1)

Axi-cel	Cost	Assumption
Leukopheresis	£1,415.63	Weighted average + uplifting factor (1.102) for patients in ITT who did not receive axi-cel
Conditioning chemotherapy	Hospital £5,062.63 Chemo £208	Optimal drug combination based on BSA data from ZUMA-1 (assumes drug wastage). Multiplier of 1.019 for the 2 patients who received conditioning therapy, but not axi-cel infusion. NHS reference costs 2015/2016
Drug acquisition	[redacted]	Includes shipping, engineering and generation of CAR T-cells. Assumes that cost of the drug will only be reimbursed if axi-cel is administered to the patient
Drug administration	£6,760.37	Cost of elective inpatient HRGs from NHS national schedule of reference costs for 17.6 days from ZUMA-1 trial (7.2 additional bed days)
Re-treatment	£12,031.47	Multiplier of chemotherapy and infusion costs to account for retreatment of 9.25% of patients

Key: BSA, body surface area; CRS, cytokine release syndrome; HRGs, healthcare resource group; ICU, intensive care unit; ITT, intention to treat

60

Source: Company submission pages 128-132

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Company costs – one time costs for axi-cel (2)

Axi-cel		Cost	Assumption
Training		£83	1 consultant time (x2 days) per centre for an annual number of patients per centre (10) with 2 years before retraining. NHS reference costs 2015/2016
Subsequent stem cell transplant		£75,385	Weighted average of allogeneic SCT HRGs applied for [redacted] of patients Costs taken from NHS National Schedule of Reference Costs. Includes follow up costs
Adverse events	CRS	£1,392 £1,363	Model updated after clarification response: Drug cost applied for the [redacted] of patients who receive tocilizumab ICU costs applied for [redacted] of patients who required hospitalisation (ICU stay) as a result of CRS
	All	£204	Cost of IVIG therapy applied for [redacted] patients who experienced Grade 1 or 2 hypogammaglobulinemia

Key: CRS, cytokine release syndrome; HRGs, healthcare resource group; ICU, intensive care unit; IVIG, intravenous immunoglobulin treatment

61

Source: Company's response to clarification Table 19

Technical engagement comments: costs for axi-cel

- **Storage**: there is uncertainty around the requirement for additional storage requirements for CAR T therapy – dedicated equipment for storage, temperature monitoring and thawing may be required if already used at capacity for allogenic SCT
- **Training:** consultees all agree administration of axi-cel will require a large multidisciplinary team. Training costs were included in the company's cost-effectiveness model, but other consultees and the ERG believe this could be a vast underestimate
- **ICU bed availability:** ICU beds would not need to be reserved prior to treatment, but the treatment centre would need to have the capacity at a high level facility for any serious adverse event reaction
- **Ambulatory care:** the pre-existing NHS model of allogenic SCT would be an appropriate example for CAR T. Costs of patients and 1 accompanying person remaining close to treating centres for 1 month should be included.

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Costs – One time costs for BSC

BSC	Cost	Assumption
Drug acquisition	Month1: £1,415 Month 2: £1,415 Month 3: £1,264 Month 4: £781	Blended comparator is applied for BSC, comprised of four different regimes Equal efficacy is assumed for all comparator regimens Equal distribution is assumed for each regimen Drug costs calculated based on optimal vile usage, BSA and wastage is assumed.
Drug administration	£5,063	Cost per patient for the administration of BSC assumed a non-elective stay in hospital for 10.4 days
Subsequent stem cell transplant	£75,385	Weighted average of allogeneic SCT HRGs taken from NHS National Schedule of Reference Costs and follow up costs (applied for [redacted] of patients)
Adverse events	-	No adverse events are assumed in BSC

Key: BSC; best supportive care; BSA, body surface area; HRGs, healthcare resource groups; SCT, stem cell transplant

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Source: Company submission pages 128-132

Resource use - progression-free (PFS) and post-progression (PPS) health states

Resource	PFS	PPS	Source
Professional and social services	£406.54	£607.89	Includes: residential care, day care, home care and hospice
Healthcare professionals	£571.28	£1,255.90	Includes: oncologist, haematologist, radiologist, nurse, palliative care team, specialist nurse, GP, district nurse and CT scans
Treatment follow up	£29.60	£8.58	Includes: Full blood count, liver function, renal function, immunoglobulin and calcium phosphate tests No monitoring costs are assumed in the PFS state from month 24 for axi-cel
Hospitalisation	£160.38	£134.03	Includes: Inpatient days, haematologist visits, radiologists visits, specialist nurse visits, nurse visits, oncologist visits and GP visits
Total per cycle cost	**£1,167.80**	**£2,006.40**	

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Source: Company submission Tables 51-54

PSSRU Unit Costs of Health and Social Care & National Audit Office.
Healthcare professionals - NHS national schedule of reference costs & PSSRU Unit Costs of Health and Social Care.
NHS national schedule of reference costs.
NHS national schedule of reference costs, PSSRU Unit Costs of Health and Social Care, ZUMA-1 & Hospital Episode Statistics.

ERG's comments – on the company's model costs

BSC	• The company's rationale for using a blended comparator is reasonable but does not account for the cost of rituximab and non-rituximab based regimens
BSC	• The company assumed BSC would be administered in an inpatient setting but possible to be provided in outpatient settings (ERG scenario analysis)
BSC	• The cost of SCT is considered but the potential impact on HRQoL was not captured in the model. The ERG considers this a conservative approach
Axi-cel	• The approach of including the costs of grade 3-4 AEs within the costs of hospitalisation and administration of axi-cel costs is reasonable
Axi-cel	• Potential error: the unit costs used by the company for critical care represented a cost per diem as opposed to the average ICU hospitalisation period. The ERG considered that the unit cost should have been applied to the duration of the Grade 3-4 CRS AE event
Axi-cel	• There is uncertainty in the assumptions around the cost of training. In clinical practice it is likely all staff involved in patient management will require training

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Source: ERG report pages 91-102

Summary of company's base case model

	Assumptions and adjustments
Clinical comparison	• Adjusted SCHOLAR-1 cohort removes patients with a baseline ECOG score of 2–4
Extrapolation	• Mixture cure model for OS axi-cel – 50% cure fraction follow general population health from time of infusion • PFS axi-cel and OS BSC: single parametric curve • PFS BSC estimated using ratio of axi-cel OS-PFS
HRQoL	• Utility values derived from ZUMA-1 trial and literature review • Disutilities associated with AEs applied to axi-cel only • General population utilities at 24m patients in pre-progression state
Costs	• Blended comparator used for BSC in a 1:1:1:1 ratio • No costs applied after 2 years in progression-free health state • Treatment costs for AEs include only IVIG and CRS treatment • Undiscounted stem cell transplant long-term costs • All stem cell transplants assumed allogeneic • Training costs for one healthcare professional

Key: AEs, adverse events; BSC, best supportive care; CRS, cytokine release syndrome; HRQoL, health related quality of life; OS; overall survival; PFS, progression-free survival

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Source: Company submission table 59 & ERG report page 126

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Company's cost effectiveness results

	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	ICER threshold
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**>£50,000**

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

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Source: Company submission Table 60

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Company's cost effectiveness results

	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	ICER threshold
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**>£50,000**

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

- Revisions included additional costs associated with the treatment of CRS and B-cell aplasia:
  - Costs for cytokine inhibitors (tocilizumab) for [redacted] of patients (ZUMA-1)
  - Costs of IVIG acquisition and administration for [redacted] patients who experienced hypogammaglobulinemia
- Company did not provide sensitivity results or probabilistic results for the revised base case

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Source: Company response to clarification Questions B.10 & B.11

After company's response to technical engagement clarification company acknowledges ICU stay should be 4 days rather than 1 (Table 6) 0.2% change from base case ICER.

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Company one-way sensitivity analysis

The ICER was most sensitive to

- The cure fraction used in the mixture cure model of axi-cel OS
- The constant coefficient for axi-cel PFS and BSC OS. Lowering the constant of axi-cel increases the time spent in pre-progression state, whilst lowering the value of the constant for BSC increases survival

Key: AC, axi-cel; BSC, best supportive care; MCM, mixture cure model; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; SCT, stem cell transplant; WTP, willingness to pay

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Source: Company submission Figure 37

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Company scenario analyses

- Scenario analyses explored by the company included:
  - Adjustments to SCHOLAR-1 cohort to account for baseline imbalances (SCT removal, propensity scoring)
  - Alternative distributions for extrapolation of axi-cel OS and PFS
  - Alternative distributions for extrapolation of BSC OS
  - Alternative assumptions for estimation of BSC PFS
  - Alternative time horizon (10-20 years)
  - Alternative discount rate (1.5%)
  - Alternative utility values (from pixantrone appraisal)
  - Inclusion of costs for ambulatory care, new storage equipment and additional training requirements

ICERs from the scenario analyses ranged between [redacted] (scenario where BSC patients were assumed to progress upon model entrance) and [redacted] per QALY (time horizon of 10 years)

Key drivers were: time horizon, discount rate, PFS for BSC and axi-cel and OS for BSC

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See company submission Table 61 page 153 and response to technical engagement clarification questions page 4 for further details

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Company's scenario analyses – excluding patients who received SCT

	Total			Incremental				
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	ICER (£/QALY)	ICER range
Scenario 1: excludes patients with subsequent ASCT from SCHOLAR-1 cohort								
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**>£50,000**
Scenario 2: excludes patients with known ECOG status 2-4 and subsequent ASCT								
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**>£50,000**

Key: BSC, best supportive care; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

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Source: Company's response to technical engagement clarification Table 2 & Company submission Table 61

NB. Scenario analysis provided by the company includes the costs of only 1 day of ICU care ~ After company's response to technical engagement clarification company acknowledges this should be 4 days (Table 6) 0.2% change from base case ICER.

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Company's probabilistic sensitivity analysis

- Deterministic changes in costs and QALYS of [redacted] and [redacted] respectively resulted in a difference in ICER of ~ **2%**
- The probability of axi-cel being the most cost effective treatment is [redacted] for a willingness-to-pay (WTP) threshold of £50,000.

ERG's comments:

- The company did not provide justification for selection of parameters in the PSA
- The range of parameters varied appears to be arbitrary and may not represent the true uncertainty

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Source: Company submission Figure 35 & 36
ERG report Table 26, page 110

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Use of ITT vs mITT population

ERG's comments:

- The company's rationale for using the mITT population (patients who received axi-cel are compared to patients who received BSC) is reasonable
- Costs of conditioning chemotherapies and leukopheresis for patients unable to receive axi-cel are included but QALYs are not considered

Technical engagement responses:

- Time to treatment initiation is likely to be markedly lengthened for CAR T compared to conventional chemotherapy

ITT scenario was provided by the company in response to clarification
• For [redacted] patients who did not receive axi-cel due to death and [redacted] due to AE a one off QALY (0.19) and a one off cost for post-progression monitoring was applied
• For [redacted] patients who did not receive axi-cel due to disease progression the discounted QALY and costs from BSC were applied
• For the mITT group progression-free utility was applied from time from leukapheresis to axi-cel treatment ([redacted] days)
• Overall costs and QALYs were calculated using a weighted average of the 3 populations

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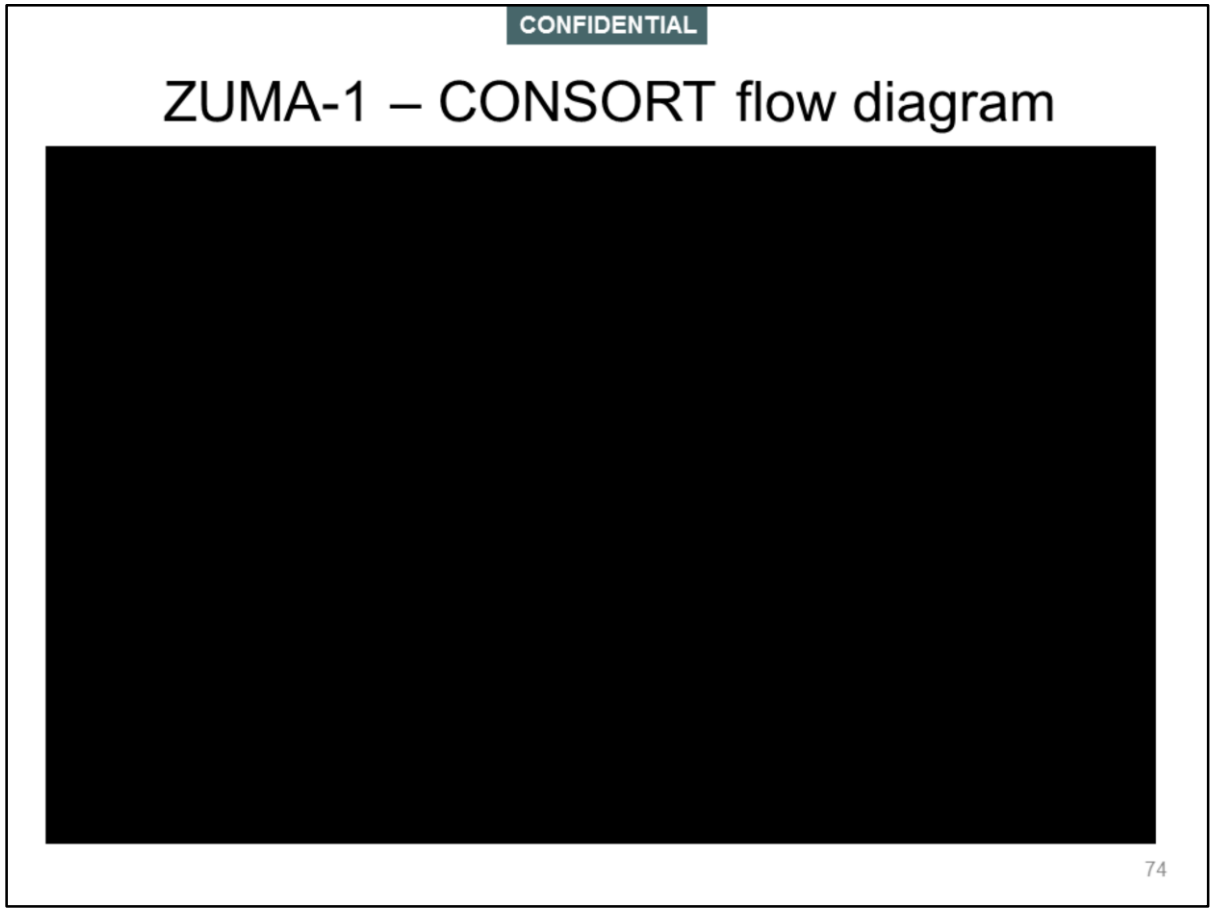
Source: company's response to clarification, ERG report Table 27



Source: Adapted from company's response to clarification Figures 1 & 2

Summary of ERG's preferred assumptions

	Assumptions and adjustments
Clinical comparison	• Adjusted SCHOLAR-1 cohort includes only patient with ECOG score 0-1
Extrapolation	• Axi-cel OS is based on a loglogistic parametric model constrained by the PFS curve. • General population mortality risk applied at the point of convergence
HRQoL	• Those in the pre-progression state assume general population utility and costs at 52m • mITT population does not account for QALYs in those w/o axi-cel, consider use of ITT population
Costs	• CRS management occurs for 4 days • Discounted SCT long-term costs • BSC patients who received SCT all receive ASCT • Training costs for 5-10 healthcare professional
Key: AEs, adverse events; BSC, best supportive care; CRS, cytokine release syndrome; HRQoL, health related quality of life; ITT, intention to treat, OS; overall survival; PFS, progression-free survival	

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Source: Company submission table 59 & ERG report page 126

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ERG's preferred base case

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)	ICER threshold
Company base case						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £50,000**
ERG's base case						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**> £100,000**

ERG's assumptions:

- BSC OS based on ECOG 0-1 in SCHOLAR-1
- Alternative axi-cel OS extrapolation assumptions
- Alternative structural cure assumptions
- CRS management occurring for 4 days
- Discounted SCT long-term costs
- BSC patients who received SCT are assumed to have all undergone ASCT

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Source: ERG report Table 38, page 128

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ERG's exploratory analyses (1):

The ERG considers that that there are imbalances in baseline characteristics between the studies and the company's cure assumptions are overly optimistic

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	ICER threshold
Company's base case						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £50,000
Scenario 1: BSC OS based on ECOG 0-1 SCHOLAR-1 subgroup						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £50,000
Scenario 2: ERG's alternative axi-cel OS extrapolation assumptions						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £50,000
Scenario 3: BSC OS based on ECOG 0-1 in SCHOLAR-1 and the ERG's alternative axi-cel OS extrapolation assumptions						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £100,000

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Source: ERG report Tables 33-34

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ERG's exploratory analyses (2):

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	ICER threshold
Scenario 4: Combining alternative axi-cel and BSC OS extrapolation assumptions and cure at 52 months for people in the pre-progression state						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £100,000
Scenario 5: ERG's alternative survival and cure assumptions with ZUMA-1 ITT population						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £100,000
Scenario 5: ERG's alternative survival and cure assumptions with ZUMA-1 mITT population and 1.5% discount rate						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £50,000
Scenario 5: ERG's alternative survival and cure assumptions with ZUMA-1 ITT population and 1.5% discount rate						
BSC	[redacted]	[redacted]	-	-	-	
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	> £50,000

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Source: ERG report Tables 35-37

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ERG's additional scenario analyses:

	Company's base-case	Incremental costs	ICER (£/QALY)	ICER range
Company's revised base-case		[redacted]	[redacted]	> £50,000
CRS management: [redacted] days ICU	CRS management: 1 day ICU stay	[redacted]	[redacted]	> £50,000
CRS management: [redacted] days ICU		[redacted]	[redacted]	> £50,000
Discounted SCT long-term costs	Undiscounted SCT costs assumed allogeneic	[redacted]	[redacted]	> £50,000
Discounted SCT costs BSC SCT assumed autologous		[redacted]	[redacted]	> £50,000
BSC administered in outpatient setting	Inpatient setting	[redacted]	[redacted]	> £50,000
Blended comparator 50:50 of 2 rituximab	Blended comparator equal ratio 4 regimes	[redacted]	[redacted]	> £50,000
Blended comparator 50:50 of non-rituximab		[redacted]	[redacted]	> £50,000
Training for 5 healthcare professionals	Training costs for one healthcare professional	[redacted]	[redacted]	> £50,000
Training for 10 healthcare professionals		[redacted]	[redacted]	> £50,000

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Source: ERG report Table 37 – All changes made to costs, QALYs do not change.

Summary of preferred assumptions

	Company	ERG
Clinical comparison	• Adjusted SCHOLAR-1 cohort removes patients with a baseline ECOG score of 2–4	• Adjusted SCHOLAR-1 cohort includes only patient with ECOG score 0-1
Extrapolation	• Mixture cure model for OS axi-cel – 50% cure fraction • PFS axi-cel and OS BSC: single parametric curve • PFS BSC estimated using ratio of axi-cel OS-PFS • Structure cure assumption at 24m	• Axi-cel OS is based on a loglogistic parametric model constrained by the PFS curve. • General population mortality risk applied at the point of convergence • Structure cure assumption at 52m
HRQoL	• Disutilities associated with AEs applied to axi-cel only	• mITT population does not account for QALYs in those w/o axi-cel
Costs	• Treatment costs applied in 1st cycle • No costs applied from 24m in PFS • Treatment costs for grade ≥3 AEs include only IVIG and CRS • Undiscounted SCT long-term costs • All SCT assumed allogeneic • Training costs for one healthcare professional	• CRS management occurs for 4 days • Discounted SCT long-term costs • BSC patients who received SCT all receive ASCT • Training costs for 5-10 healthcare professional

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Source: Company submission table 59 & ERG report page 126

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Discount rate

Discount	Incremental costs	Incremental QALYs	Company's ICER	ICER threshold	% change from base-case ICER
1.5%	[redacted]	[redacted]	[redacted]	> £50,000	[redacted]

NICE methods guide	Company	ERG
• The reference case should use a discount rate of 3.5% for both costs and benefits. • Differential discounting should be applied where treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years)	• Axi-cel can provide long-term survival (model estimates a mean undiscounted OS of >10 years) • Total acquisition cost is incurred within the first model cycle	Criteria for applying a 1.5% discount rate were not met • Evidence submitted is not sufficiently mature to robustly demonstrate cure • The ERG notes the duration of health benefits is driven by a highly uncertain extrapolation of survival estimates

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End of life

Criterion	Company	ERG
Short life expectancy: The treatment is indicated for people with a short life expectancy, normally less than 24 months	Yes • Canadian database study in R/R DLBCL patients ineligible for ASCT median OS 3.9m • SCHOLAR-1 study of SoC median OS: 6.3 months	Maybe • Dependent on adjustment to SCHOLAR-1 data. Base case OS lies between 5m-6.6m, but ERG noted differences between the mean and median model estimates
Extension to life: There is sufficient evidence to indicate that the treatment offers an extension to life, (normally >3 months) compared with current treatment	Yes • Median OS for axi-cel in the ZUMA-1 study was not reached; lower 95% CI was 12.0m with an 18m OS rate of 52%. If current survival trends continue, improvement would be >5.7m	Yes • Submitted evidence shows OS will be greatly extended • However, the evidence submitted does not have appropriately long term follow-up to support the company's cure claim

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Equality

- Company consider a potential age effect where axi-cel is a more suitable alternative for older men due to the epidemiology of the disease and likely treatment outcomes higher up the pathway

ERG's comments:
The ERG suggest the company presents consistent results by age and gender and consideration for the burden of CAR-T therapy has not been fully considered for elderly patients when compared to being ASCT ineligible.

- NHS England:
  Due to the novelty of the treatment, the expertise required and the logistics involved all key stakeholders have indicated the need for a phased implementation period if approved. This is likely to mean that geographical access at the start will be worse than current access to chemotherapy/HSCT Clinical prioritisation of patients will be required

ERG's comments:
Equality considerations made in the company submission are not clear and fail to address high priority issues such as equality of delivery.

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Innovation

- **Company considers axi-cel to be innovative**:
  - Axi-cel represents a step-change in disease management in a population for whom there is a poor prognosis, significant unmet need and limited treatment options
  - First in a breakthrough class of CAR T-cell therapies that provides complete personalised immunotherapy
  - Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy and their associated toxicity
  - Survival data from ZUMA-1 suggests significant improvement in OS, company argue axi-cel offers a potential cure

- **Clinical expert statements:**
  - For patients beyond second failure there would be a profound effect (STEP CHANGE) if the preliminary results are substantiated
  - CAR T-cell therapy is a potential game changer

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Authors

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  Technical Lead
- **Nicola Hay**
  Technical Adviser
- with input from the Lead Team (Nigel Langford, Mike Chambers and Judith Wardle)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma [ID1115]

Document B

Company evidence submission

15 February 2018

File name	Version	Contains confidential information	Date
Kite a Gilead Company Axi-cel NICE STA Document B_AiC_CiC	**1.0**	**Yes**	**15 February 2018**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

In this template any information that should be provided in an appendix is listed in a box.

Highlighting in the template (excluding the contents list)

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

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Contents

Tables

Figures

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

B.1.1. Decision problem

The 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

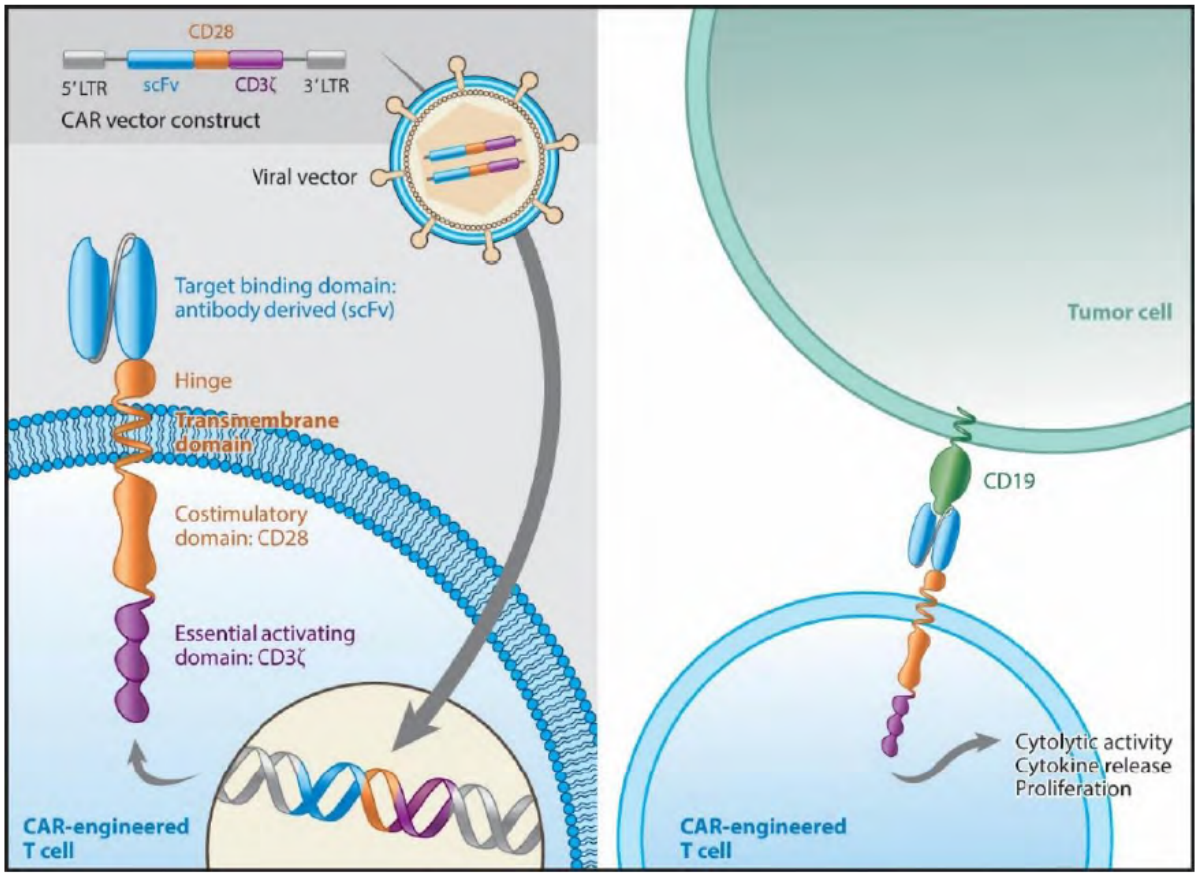
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma or transformed follicular lymphoma.	[redacted]	The population presented in this submission is the population for which marketing authorisation for axicabtagene ciloleucel (axi-cel) is anticipated to be given, which more closely reflects the patients included in the pivotal ZUMA-1 trial that the draft SmPC is based upon. As discussed in Section B.1.3 and confirmed by clinical experts, this population was likely to be equivalent to an autologous stem cell transplant (ASCT) ineligible population.[1, 2]
Intervention	Axicabtagene ciloleucel	Axicabtagene ciloleucel	NA
Comparator(s)	• DHAP, cisplatin, cytarabine, dexamethasone (with or without rituximab) • GDP, cisplatin, gemcitabine, dexamethasone (with or without rituximab)	• DHAP (with or without rituximab) • GDP (with or without rituximab)	While the final scope issued by NICE also included pixantrone monotherapy (in people who have had 2 of more prior therapies, including rituximab) as a potential comparator, clinicians confirmed at a recent clinical ad-board that very few patients are treated with pixantrone monotherapy in NHS

	• ICE, ifosfamide, carboplatin, etoposide (with or without rituximab) • IVE, ifosfamide, epirubicin and etoposide (with or without rituximab) • pixantrone monotherapy (in people who have had 2 of more prior therapies, including rituximab) • best supportive care (including radiotherapy)	• ICE (with or without rituximab) • IVE (with or without rituximab) • best supportive care (including radiotherapy)	England as it does not improve outcomes.[1, 2] Therefore, pixantrone is not seen as a relevant comparator and has not been included in this submission. Furthermore, recently published BSH Guidelines (2016) on the management of DLBCL do not recommend pixantrone as a treatment option for DLBCL.[3] Due to the paucity of data for patients relapsing after two or more prior lines of therapy, and the heterogeneity between ZUMA-1 and other comparator studies, four studies for which patient-level data were available were combined in the SCHOLAR-1 analysis to allow a more appropriate comparison to ZUMA-1 attempting to account for population differences, using a blended comparator including DHAP, GDP and ICE.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	NA
Subgroups to be considered	None specified	No subgroups have been specified by NICE and therefore no subgroups are considered as relevant to this submission	
Special considerations including issues related to equity or equality	None specified	There currently exists the potential for an age-related treatment bias in this patient population. Older patients (≥70) are likely to be ineligible for stem cell transplant and would also likely be unable to receive more aggressive chemotherapy options, either to achieve a response, or to respond and receive a stem cell transplant. Some of these patients, for whom limited other treatment options are available (see Section B.1.3), may be able to benefit from treatment with axi-cel, which would increase eligibility for treatment.	

B.1.2. Description of the technology being appraised

Axicabtagene ciloleucel (YESCARTA® described as axi-cel in the submission) is the first in a breakthrough class of chimeric antigen receptor (CAR) T-cell therapies, which consists of autologous human T-cells that have been engineered to express a novel cell surface receptor fragment antibody that will identify and lock onto CD19 bearing cells. The T-cell receptor complex is comprised of a single-chain variable region fragment (scFv) with specificity for CD19, that is linked to an intracellular signalling part comprised of signalling domains from CD28 and CD3ζ molecules arranged in tandem.[4] Further details of the structure of the anti-CD19 CAR construct, the innovative mechanism of action and method of administration of axi-cel are described in Figure 1 and Table 2.

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



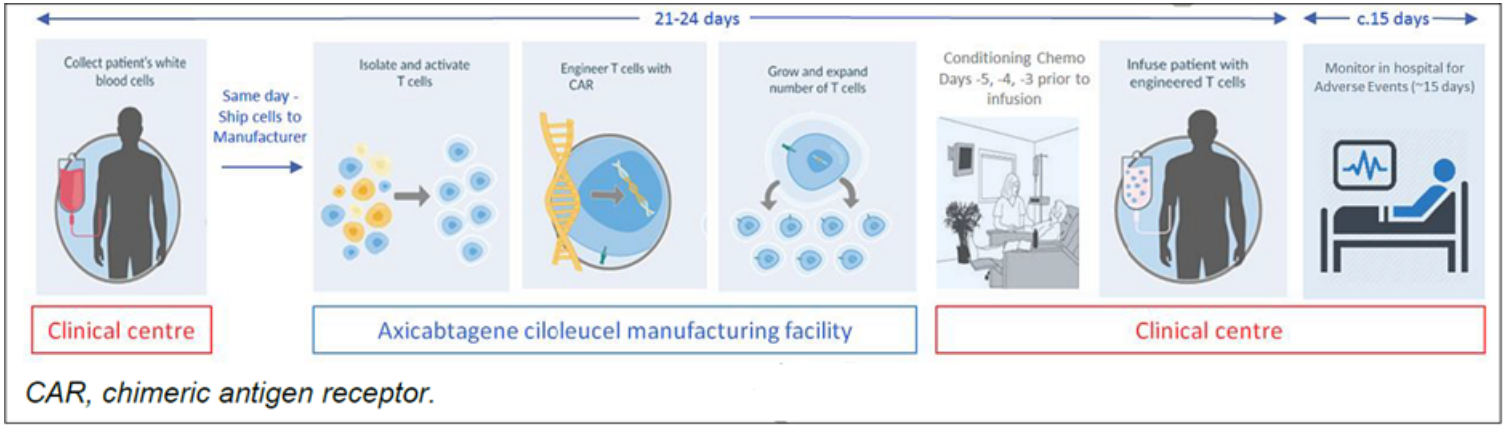
Key: axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptors; scFv, single-chain variable region fragment.
Source: ZUMA-1 CSR[5]

Axi-cel is currently being developed for the treatment of patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), transformed

follicular lymphoma (TFL) and primary mediastinal large B-cell lymphoma (PMBCL), where malignant B-cells express the CD19 antigen on their surface. Although these malignancies are somewhat clinically and pathologically distinct from one another, they are treated similarly in clinical practice – with a chemotherapy regimen containing rituximab in both front line and salvage. The current prognosis for patients with relapsed/refractory disease is extremely poor where the patient is ineligible to ASCT and therefore is left with no curative options. There is a significant unmet need in this group. A recent large, pooled, database analysis reported an objective response rate (ORR) to the next line of treatment of 26% (complete response [CR] 7%) and a median overall survival (OS) of 6.3 months.[6] In the pivotal ZUMA-1 trial, axi-cel produced a previously unseen response rate of 82% (CR = 58%) with median OS not reached in this patient population, suggesting a long term freedom from disease and cure in a significant proportion of patients.[7]

Since they are derived from the patient's own T-cells, axi-cel is a highly innovative approach that provides a complete personalised immunotherapy, that targets and eliminates CD19-expressing B-cells.[5] Axi-cel is given as *a single infusion, single treatment* and the timescale from collection of the patient's white blood cells by leukapheresis, through transportation to the manufacturing facility, product manufacture, delivery to the clinical centre and conditioning chemotherapy, culminating in administration of axi-cel to the patient, is 21–24 days (Figure 2). For further details of the manufacturing process of axi-cel, see Appendix M.

Figure 2: Process of manufacturing and administering axi-cel



Source: Axi-cel SmPC[8] and ZUMA-1 CSR[5]

Engineered Autologous Cell Therapy is a process by which a patient's own T-cells are collected and genetically altered to recognise and target antigens expressed on the cell surface of specific malignancies.[9] The ability to genetically engineer human T-cells to express CARs may overcome some of the main limitations of the endogenous immune system and of other cancer immunotherapies, providing a new approach to treat cancer. CARs are synthetic immunoreceptors whose extracellular domain is typically an antibody-derived scFv that recognises a tumour cell surface protein. Engineering T-cells with a CAR involves using a replication-incompetent retroviral vector containing the CAR construct to transduce T-cells. This approach has already been demonstrated in a range of studies and has opened possibilities for the treatment of patients with a wide variety of cancer types including B-cell malignancies expressing the CD19 antigen.[5]

The safety profile of axi-cel is well described, with established protocols to manage adverse events (AEs) to ensure an acceptable risk-benefit ratio for the target patient population, whose therapy options are otherwise limited to palliative. Increasing familiarity with the side effect profile of CAR-T cells in general and axi-cel in particular has meant the incidence and severity of adverse events is decreasing over time.[5]

The summary of product characteristics (SmPC) for axi-cel is provided in Appendix D.

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 eliminate all CD19 expressing target cells, including B-cell malignancies and normal B-cells. To produce axi-cel, patient T-cells are extracted via leukapheresis and activated with IL-2 and an anti-CD3 monoclonal antibody (mAb), and then transduced with the anti-CD19 CAR transgene-containing γ-retroviral vector. The structure of the anti-CD19 CAR construct is shown in Figure 2. The 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 2. 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.[10] Together, these signals act in concert resulting in proliferation of the axi-cel CAR T-cells and apoptosis and necrosis of the CD19 expressing target cells. In addition, activated T-cells secrete cytokines and other molecules that can recruit and activate additional anti-tumour immune cells.[11]
Marketing authorisation/CE mark status	The application for marketing authorisation with the European Medicines Agency (EMA) was submitted on 31 July 2017 and is currently ongoing. Approval from the Committee for Human Medicinal Products (CHMP) is expected in April 2018. Axi-cel also holds the following regulatory designations by the EMA: • Orphan Medicine Designation: Granted by EMA in Feb 2015 for patients with DLBCL and subsequently for patients with PMBCL (Oct 2015), follicular lymphoma (FL) (Nov 2015).[12] • Priority Medicines (PRIME) Status: Granted by EMA in May 2016 for treatment of adult patients with refractory DLBCL who have not responded to their prior therapy, or have had disease progression after ASCT.[13]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	[redacted].[8]
Method of administration and dosage	Axi-cel is a single infusion product, for autologous and intravenous use only.[8] Each single infusion bag of axi-cel contains a suspension of anti-CD19 CAR T-cells in approximately 68mL for a target dose of 2 × 10^6 anti-CD19 CAR T-cells/kg body weight (range: 1 x 10^6 – 2.4 x 10^6 cells/kg), with a maximum of 2 x 10^8 anti-CD19 CAR T-cells. <u>Pre-treatment:</u> Prior to hospitalisation for infusion of axi-cel, patients are treated in the outpatient setting with low-dose conditioning chemotherapy that eliminates the patient's lymphocytes, allowing space for the T-cells to expand. • A conditioning chemotherapy regimen consisting of cyclophosphamide 500mg/m^2 IV and fludarabine 30mg/m^2 IV

	should be administered on the 5th, 4th, and 3rd day before infusion of axi-cel • If axi-cel infusion is delayed for more than 2 weeks, consider re-administration of the conditioning chemotherapy regimen • Paracetamol and diphenhydramine approximately 1 hour before axi-cel infusion is recommended • Prophylactic use of systemic steroids is not recommended as it may interfere with the activity of axi-cel <u>Monitoring:</u> • Hospitalisation is recommended for axi-cel infusion • Patients may be discharged as deemed appropriate by the treating physician <u>Preparation of axi-cel</u>: • Verify that the patient's identity matches the patient identifiers on the axi-cel cassette • Do not remove the axi-cel product bag from the cassette if the information on the patient-specific label does not match the intended patient • Once patient ID is confirmed remove the axi-cel product bag from the cassette • Inspect the product bag for any breaches of container integrity before thawing • Thaw axi-cel at approximately 37°C and gently agitate the bag. Thawing should take approximately 3 to 5 minutes <u>Administration of axi-cel</u>: • Central venous access is recommended for the administration of axi-cel • Use non-filtered tubing • Verify again that the patient's identity matches the patient identifiers on the axi-cel product bag • Begin IV infusion of axi-cel after thawing • Infuse the entire contents of the axi-cel bag over 30 minutes by either gravity or a peristaltic pump within 3 hours after thaw • Gently agitate the product bag during axi-cel infusion to prevent cell clumping • After the entire content of the product bag is infused, the tubing should be back flushed at the same infusion rate with normal saline to ensure all axi-cel is delivered
Additional tests or investigations	No additional tests or investigations are anticipated, beyond what is already performed in clinical practice, to identify the patients eligible to receive axi-cel.
List price and average cost of a course of treatment	[redacted] is the average price of a course of treatment (see Section B.3.5)
Patient access scheme (if applicable)	No patient access scheme has been applied for

Key: ALL, acute lymphoblastic leukaemia; axi-cel, axicabtagene ciloleucel; ASCT, autologous stem cell transplant; CAR, chimeric antigen receptors; CHMP, Committee for Human Medicinal Products; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FL, follicular lymphoma; IL, interleukin; mAb, monoclonal antibody; MCL, mantle cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; TFL, transformed follicular lymphoma.

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

Summary

- Aggressive subtypes of B-cell NHL include DLBCL, PMBCL, and TFL. Although they have distinct clinical, pathological and molecular characteristics, the approach to management is generally similar, which consists of combination therapy with rituximab and chemotherapy.
- In the UK around 70% of newly diagnosed cases of DLBCL are cured with standard of care frontline therapy[14], approximately 10% of patients have primary refractory disease and 20% of patients who do respond to front-line treatment will relapse.[14] Failure to achieve a good response to salvage chemotherapy indicates a poor prognosis.[15]
- Outcomes for R/R patients are generally poor, with only a small minority of patients achieving long-term survival with salvage therapies with a median overall survival of 6.3 months.[6] For relapsed or refractory (R/R) patients who are ineligible for ASCT, outcomes are even worse, with median overall survival between 3.3 and 3.9 months.[16, 17]
- Treatment options for R/R DLBCL, PPMBCL and TFL patients are limited:
  - First line R/R patients who are eligible for ASCT receive salvage chemotherapy (e.g. RICE, R-DHAP, R-GDP) followed by ASCT if chemo-responsive.
  - First line R/R patients who are ineligible for ASCT receive platinum- and/or gemcitabine-based regimens or are considered for clinical trials. Very few of these patients are long-term survivors.[18]
  - Second line or later R/R patients have extremely limited treatment options, including clinical trials with novel agents or palliative care, with allogeneic transplantation also an option for those small numbers patients who are eligible but only if they achieve good partial remission with further salvage therapy.[18]
- There are significantly high levels of unmet need among target patients for axi-cel, who have primary refractory disease or are non-responsive to salvage therapy (and therefore ineligible for ASCT).

Disease overview

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B-cells (and, to a lesser extent, in T-cells and natural killer cells). The prognosis depends on the histologic type, stage, along with other factors including the patient's age and comorbidities, tumour genetics, the amount of lactate dehydrogenase (LDH) in the blood.[19] Aggressive subtypes of B-cell NHL include DLBCL, PMBCL, and TFL. All of these express CD-19 antigen on the cell surface.

DLBCL

DLBCL is the most common subtype of B-cell NHL, accounting for approximately 30% of newly diagnosed cases of NHL.[20] With an annual incidence of around 5.9 per 100,000 in adults, DLBCL is the most common lymphoma subtype, accounting for around 40% of the total based on the HMRN Network. Around 3,400 people are diagnosed with DLBCL each year in England and Wales.[1, 2, 21] Newly diagnosed DLBCL patients in the UK have a median age of 61 (ranging from 19 to 88 in a large UK-based RCT).[14]

PMBCL

PMBCL arises from thymic (medullary) B-cells and has distinct clinical, pathological, and molecular characteristics from other subtypes. PMBCL represents approximately 5% of patients diagnosed with NHL[22], and each year, approximately 380 people are diagnosed with PMBCL in England/Wales.[1, 2, 21] PMBCL is typically identified in younger patients (median age 35 years) and, unlike DLBCL, has a female predominance.[23-25]

PMBCL typically presents as a large, fast-growing mass, with invasion usually limited to the anterior-upper mediastinum.[23]

TFL

Follicular lymphoma (FL) is the second most common form of NHL in Western countries, accounting for approximately 20% of patients diagnosed with NHL.[26] FL can occur at any age, but the average age at diagnosis is around 65.[27] Some patients with FL will transform to a high grade DLBCL (known as TFL), which is much more aggressive and is associated with worse outcomes than FL.[28] Histological transformation to TFL occurs at an annual rate of approximately 3%. Thus, TFL accounts for approximately 1% of all NHL cases.[29] Each year, approximately 662 people are diagnosed with TFL in the England and Wales.[1, 2, 21]

Outcomes for relapsed or refractory patients

Outcomes for R/R patients treated with standard of care (SoC) are poor, with low levels of response and limited survival. Table 3 presents a summary of reported outcomes from the evidence base for R/R patients.

Table 3: Summary of outcomes for R/R aggressive B-cell NHL patients treated with current SoC

Setting	Outcome to subsequent salvage therapy
Refractory to first-line	
Philip et al. 1995[30] (n=28)	ORR 21%
Josting et al. 2000[31] (n=64)	ORR 15%, median OS 6 months
Ardeshna et al. 2005[32] (n=5)	ORR 0%
Hitz et al. 2010[33] (n=33)	Proceeded to ASCT 9%, 3% survived > 1 year
Telio et al. 2012[34] (n=111)	ORR 23%, median OS 10 months
Matasar et al. 2013[35] (n=10)	ORR 10%
SCHOLAR-1; Crump et al. 2017[6] (n=101)	CR 2.9%, ORR 20.2%, Median OS 7.1 months
Refractory to second-line or later therapy	
Mosokowitz et al. 1999[36] (n=55)	Median OS 5 months
Ardeshna et al. 2005[32] (n=28)	ORR 18%, median OS (aggressive NHL) <6 months
Seshadri et al. 2008[37] (n=73)	ORR 14%
SCHOLAR-1; Crump et al. 2017[6] (n=316)	CR 10%, ORR 26.1%, Median OS 6.1 months
Relapse within 12 months of ASCT	
PARMA; Guglielmi et al. 1988[38] (n=111)	ORR 40%, 8-year OS 13%
CORAL; Gisselbrecht et al. 2012[39] (n=105)	4-year EFS 48%
Nagle et al. 2013[40] (n=45)	Median OS 8 months
SCHOLAR-1; Crump et al. 2017[6] (n=91)	CR 14.7%, ORR 33.8%, Median OS 6.2 months
CORAL; Van Den Neste et al. 2017[41] (n=75)	Median OS 5.7 months
Relapse after second-line or later therapy	
N/A	There is limited evidence available for this patient population, but clinicians agreed that at this stage of the disease, patients would progress quickly and current treatments were unlikely to work; therefore, treatment for these patients would likely be palliative.[1, 2]
Key: ASCT, autologous stem cell transplant; CR, complete response; EFS, event free survival; ORR, objective response rate; OS, overall survival.	

Burden of disease – Quality of life

Limited data are available on the health-related quality of life (HRQL) burden for patients with R/R DLBCL, PMBCL and TFL ineligible for ASCT. One small, single-arm, open-label, Phase 1/2 study in 30 patients aged ≥60 years with R/R DLBCL who had received one or two prior chemotherapy regimens, but were ineligible for ASCT, compared baseline Functional Assessment of Cancer Therapy – General (FACT-G) scores at baseline against general population and cancer-specific norms.[42] It was reported that these patients had lower FACT-G scores than both the general population and cancer-specific norms (75.5 vs 80.1 and 80.9, respectively), with the comparison to the cancer-specific population reaching a pre-defined minimally important difference (MID) threshold of 5-points (which is in line with commonly accepted MID thresholds[43]). Within the FACT-G individual components, baseline scores for emotional wellbeing, functional wellbeing and physical wellbeing were significantly worse (lower) when compared to the general population and cancer population norms. However, the social/family wellbeing score was significantly better. All of the comparisons for the individual component scores reached a pre-defined MID threshold of 2-points (which is in line with commonly accepted MID thresholds[43]).

Given this evidence, there is likely to be a high HRQL burden for these patients.

Clinical pathway of care

Clinical guidelines

Clinical guidelines specific to R/R DBLCL, PMBCL and TFL are extremely limited.

The British Society for Haematology (BSH) guidelines state that the most commonly used conditioning regimen for ASCT is BCNU, etoposide, cytarabine and melphalan (BEAM).[3]

The NICE clinical pathway recommends the use of rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP) as a salvage therapy or as a consolidation therapy with ASCT or allogeneic SCT.[44] Pixantrone monotherapy is recommended for patients with R/R aggressive NHL if they have been previously treated with rituximab and they are receiving third- or fourth-line treatment.[44, 45] However, in a

recent clinical ad-board, clinicians confirmed that very few patients are actually treated with pixantrone monotherapy in NHS England.[1, 2] Furthermore, BSH Guidelines do not recommend pixantrone as a treatment option for patients with R/R DLBCL.[3]

The European Society for Medical Oncology (ESMO) guidelines for treating R/R DLBCL[18] are presented in Table 4; the relevant comparators to consider for axi-cel would be those for patients who are not eligible for transplant.[18]

Table 4: ESMO recommended treatment strategies for R/R DLBCL[18]

R/R after first-line therapy	
Eligible for transplant	**Not eligible for transplant**
• Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE, R-GDP) as salvage treatment • For chemo-sensitive patients: R-HDCT with ASCT as remission consolidation • Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor-risk factors at relapse	• Platinum- and/or gemcitabine-based regimens • Clinical trials with novel medicines
R/R after second- or later-line therapy	
Eligible for transplant	**Not eligible for transplant**
• Allogeneic transplantation • Clinical trials with novel medicines	• Clinical trials with novel medicines • Palliative care
Key: ASCT, autologous stem-cell transplant; DHAP, cisplatin, cytarabine, dexamethasone; DLBCL, diffuse large B-cell lymphoma; ESMO, European Society for Medical Oncology; GDP, gemcitabine, dexamethasone, cisplatin; HDCT, high-dose chemotherapy; ICE, ifosfamide, carboplatin, etoposide; R, rituximab; R/R, relapsed or refractory. **Source:** ESMO guidelines for DLBCL[18]	

Clinical pathway

Figure 3 presents the clinical pathway of care for patients with DLBCL, PMBCL and TFL and highlights the patients for whom axi-cel therapy would be considered. A similar figure showing the proportions of patients who progress through each section of the pathway and the proportions that clinicians expect they would treat with CAR T-cell therapy are presented in Section 3.1 of the budget impact analysis submission. The eligible population for axi-cel is estimated to consist of 972 patients in 2018.

There are four groups of patients who would be considered eligible for axi-cel therapy:

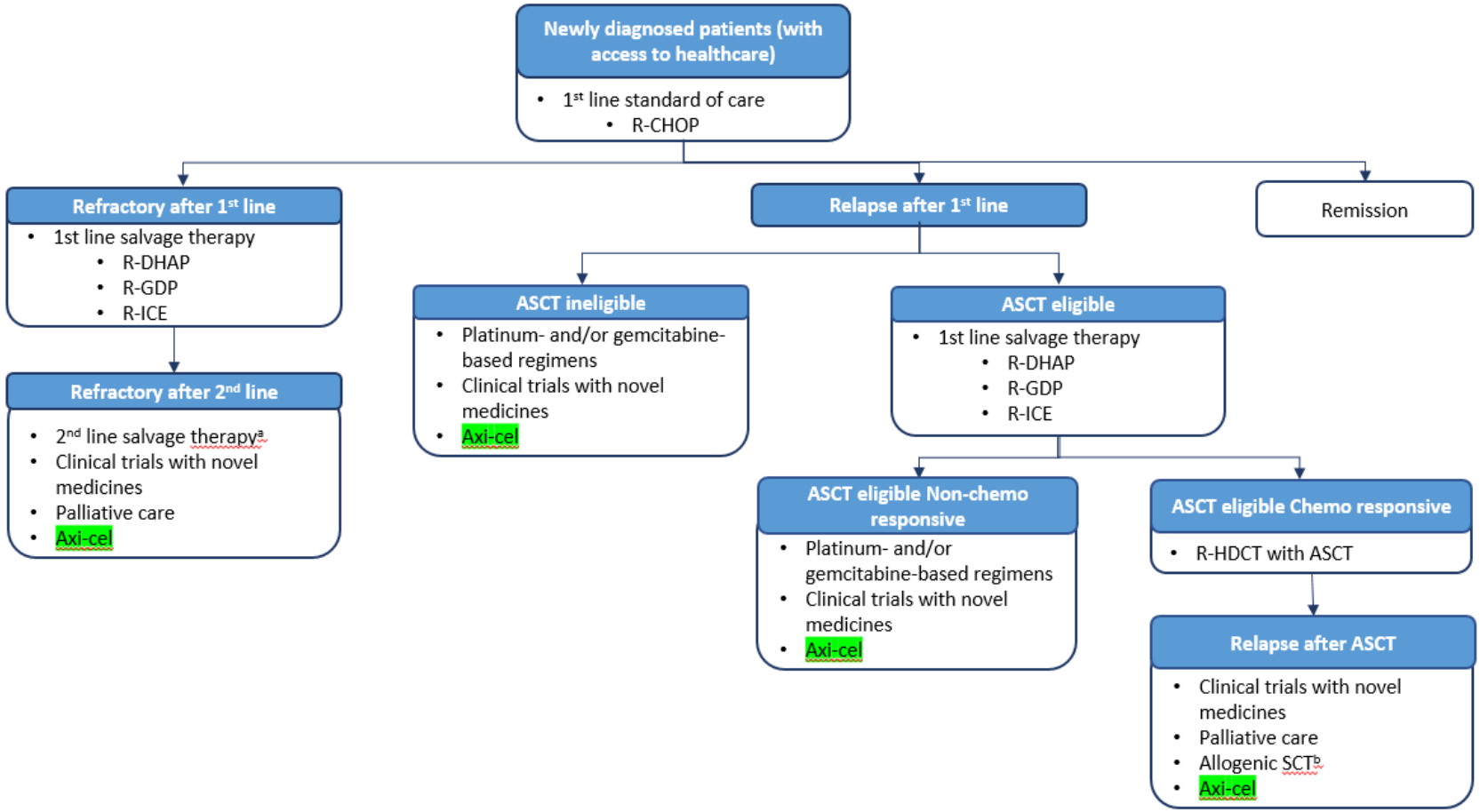
- Patients who were refractory after first-line therapy (primary refractory)
- Patients who relapsed after first-line therapy, but were ineligible for ASCT following second-line therapy for reasons of age and comorbidities (as very small number of patients)
- Patients who relapsed after first-line therapy, and would be eligible for ASCT at second-line but who do not respond to salvage therapy
- Patients who relapsed after first-line therapy, were eligible and treated with chemotherapy and ASCT and subsequently relapse (a small number of these patients who are young may progress to allogeneic SCT)

Ineligibility for ASCT is based on a number of factors[1, 2], including:

- Age >70 years or ≥65 with comorbidities
- Inadequate response to salvage therapy or early relapse (within 12 months) after first ASCT.
- Relapse after second or later line of therapy
- Failure to mobilise stem cells for ASCT
- Presence of significant comorbidities or unresolved toxicities

Figure 3 presents the current treatment options for patients with R/R DLBCL, PMBCL and TFL. As confirmed by clinicians in a recent clinical ad-board, PMBCL and TFL are generally treated using regimens similar to those used for DLBCL.[1, 2]

Figure 3: Clinical pathway of care for patients with R/R aggressive NHL and proposed placement for axi-cel



Key: ASCT, autologous stem cell transplantation; BEAM, BCNU, etoposide, cytarabine and melphalan; HDCT, high-dose chemotherapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, cisplatin, cytarabine, dexamethasone; R-GDP, rituximab, gemcitabine, dexamethasone and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; SoC, standard of care.
Notes: a, For second-line salvage therapy, patients may be treated with an option that they did not use for first-line salvage, i.e. one of R-DHAP, R-GDP or R-ICE; b, a small proportion of patients who relapse after ASCT may be eligible to receive allogenic SCT, and would be considered for conditioning therapy, followed by allogenic SCT if they are able to achieve a response.
Source: BSH guidelines for DLBCL treatment[3], NICE clinical pathway for DLBCL[44]; EMSO guidelines for treating R/R DLBCL[18]

The current standard of care (SoC) for first-line treatment of aggressive B-cell NHL is R-chemotherapy.[3, 18, 44, 46]

Patients who are refractory to first line therapy (primary refractory) will usually receive salvage therapy with the objective of ASCT. Outcomes in this group are extremely poor.[15] Clinicians agreed that as long as the disease was not progressing too rapidly to allow CAR T manufacture then this patient group could be eligible for axi-cel therapy (Figure 3: Clinical pathway of care for patients with R/R aggressive NHL and proposed placement for axi-cel).[1, 2] Clinicians also stated that given the poor response of these patients to subsequent lines of therapy, and their limited expected survival, early CAR T treatment should be considered instead of follow-on chemotherapy, and care should be taken to ensure that any chemotherapy used is not impactful to future CAR T treatment (such as min-BEAM).[2]

For patients who relapse after first-line therapy and are deemed ineligible for ASCT, the only current treatment options are either platinum- and/gemcitabine-based regimens, or to be entered into a clinical trial (Figure 3).[18] There may be a small group of patients who are not eligible for ASCT whose comorbidities preclude ASCT but not axi-cel therapy.

Apart from the groups described in the two paragraphs above, other patients that can be considered for axi-cel are:

- Chemo-responsive patients who proceed to ASCT but then relapse
- Those who do not respond to chemotherapy, and therefore cannot proceed to ASCT

Limitations with current treatment and unmet need

For newly diagnosed DLBCL, PMBCL and TFL patients, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is SoC.[25, 47] A large prospective database study demonstrated that 71% of patients with newly diagnosed DLBCL remained event-free 2 years after diagnosis, when treated with SoC R-CHOP.[48] Furthermore, the OS in these patients was equivalent to that of the age- and sex-matched general population.[48] Similarly, a large UK randomised controlled study (RCT) confirmed the potential for positive outcomes in first-line

treatment with R-CHOP, with 75% of patients achieving 2-year progression free survival (PFS) and 2-year OS rates of up to 83%.[14] Therefore, for these patients, remaining event-free (in ongoing CR) for 2-years is consistent with long term disease free survival or cure.

In DLBCL, PMBCL and TFL around 10% of patients will not respond to treatment (primary refractory).[14] Outcomes in patients with refractory disease are poor with a median OS of less than 6 months. For primary refractory patients, published ORRs to second-line chemotherapy range from 0 to 23% (Table 3)[30-35], and primary refractory disease was found to be a significant risk factor for failing response to second-line therapy.[36] Furthermore, most of these patients are not eligible for transplant due to their chemotherapy-resistant disease. Published ORR for patients refractory to second- or third-line therapy were 18% and 14%, respectively (Table 3).[32, 37] Similarly, a recent pooled database analysis (SCHOLAR-1) demonstrated that only 2.9% of primary refractory patients and 10% of patients refractory to second-line or later therapy achieved CR (ORR 20.2% and 26.1%, respectively) with SoC (Table 3).[6] Furthermore, primary refectory and refractory to second-line or later therapy patients had median OS of 7.1 months and 6.1 months, respectively (Table 3).[6] In an analysis of SCHOLAR-1 versus ZUMA-1, standardised for subsequent ASCT, which is likely to be more aligned to the relevant patient population for axi-cel, median OS was only 3.9 months (see Section B.2.9).

For DLBCL, PMBCL and TFL who respond to first-line SoC, around 20% of all patients will relapse.[14] Results of the PARMA trial[30] demonstrated superior outcomes for second-line chemotherapy plus autologous stem cell transplant (ASCT) compared with second-line chemotherapy alone in patients with relapsed DLBCL, leading to the adoption of second-line chemotherapy plus ASCT as the SoC for the relapsed population.[49] However, although ASCT is a treatment option for patients with relapsed disease, studies in relapsed B-cell NHL indicate that only half of patients who respond to second-line therapy and are then able to proceed to ASCT.[30, 36, 39, 50] Of those half will subsequently relapse and not be cured. So only 25% have a potential for cure.[15]

Relapse after ASCT, has a poor prognosis in patients with DLBCL. In those relapsing in less than 12 months it is particularly poor. Similarly, in the Collaborative

Trial in Relapsed Aggressive Lymphoma (CORAL), 4-year event-free survival (EFS) for patients who had early relapse after ASCT was significantly lower than that of patients who relapsed more than 12 months after ASCT (48% vs 56%; p<0.05; Table 3).[39] In a recent analysis of the CORAL data, the median OS was significantly shorter among patients who relapsed <6 months after ASCT (5.7 months) compared with those relapsing ≥12 months after ASCT (12.6 months, P=0.0221; Table 3). The SCHOLAR-1 database study demonstrated that 14.7% of patients with early relapse after ASCT achieved CR and median OS of 6.2 months with SoC (Table 3).[6] In an analysis of data from the PARMA trial, the ORR to subsequent therapy was 40% for those with an early relapse and 69% for those with relapse more than 12 months after ASCT (p<0.0001), and 8-year OS rates were 13% and 29% (p<0.0001) for the two subsets (Table 3).[38] Similarly, in the Similar results are found in other studies.[40] Patients with R/R DLBCL ineligible for transplant have a poor prognosis with a median OS ranging from 4 to 13 months for patients with transplant-ineligible R/R DLBCL.[51] In the CORAL trial, 129 of 193 patients who received third-line therapy, but did not undergo subsequent transplant, had worse survival than patients who underwent ASCT or allogeneic SCT (34/193 patients): median survival was 3.3 months vs 11.1 months, respectively, and 2-year OS was 9.3% vs 33.9%, respectively.[17] Finally, a large Canadian database study demonstrated an OS of 3.9 months in R/R disease patients who are ineligible for ASCT.[16] In the recent SCHOLAR-1 database study, patients who were ineligible for ASCT had OS of 5.1 months. For SCHOLAR-1 patients matched to ZUMA-1 trial patients for comparison, median OS was even lower at 3.9 months.

Therefore, there is an obvious unmet need in these patients:

- Patients who were refractory after first-line therapy (primary refractory)
- Patients who relapsed after first-line therapy, but were ineligible for ASCT following second-line therapy for reasons of age and comorbidities
- Patients who relapsed after first-line therapy, and would be eligible for ASCT at second-line but who do not respond to salvage therapy
- Patients who relapsed after first-line therapy, were eligible and treated with chemotherapy and ASCT and subsequently relapse

B.1.4. Equality considerations

There is the potential for treatment in NHL to raise some issues of equality. The odds ratios for developing DLBCL for men compared with women is 1.7.[52] Treatment effects also seem to be influenced by gender, with outcomes improving by a greater amount for women with the introduction of rituximab, i.e. moving from first-line CHOP to R-CHOP as the SoC (from 68% to 84% and from 64% to 77%, respectively), and a higher median OS for women (90.6 months compared to 55 months; hazard ratio [HR]: 1.2, p=0.0681).[53] Therefore, women generally have better outcomes than men, with median PFS of 90.6 months compared to 55 months (HR: 1.2; p=0.02).[54] This difference was most significant in patients over 60 years of age.[54] Therefore, as more men than women are likely to develop NHL and their treatment outcomes are expected to be worse, there are likely to be a greater number of men progressing to the R/R setting, where their prognosis will be even worse. In addition to this, older patients are likely to be considered ineligible for stem cell transplant (age ≥70 is an ineligibility criteria) due to the burden of salvage chemotherapy and would also be less likely to be able to receive more aggressive chemotherapy options, either to achieve a response, or to achieve response in order to receive a stem cell transplant. Conditioning chemotherapy for CAR-T is less burdensome than salvage therapy, making axi-cel an acceptable alternative for this group of patients. The subgroup analyses from ZUMA-1 (see Appendix E) also showed consistent results for patients by both age and gender, which would help to reduce some of the equality associated with SoC for patients with DLBCL, PMBCL and TFL.

B.2. Clinical effectiveness

Axi-cel provides a potentially curative therapy options for patients with otherwise limited treatment options and high unmet need (median follow-up 15.4 months; N=108)

- The OS rate at 18-months was 52% and PFS rate at 15-months was 41%, with few events occurring towards the end of the KM curves. The curves are stable at this point suggesting patients may be cured

Axi-cel demonstrated significant clinical benefits for these patients (median follow-up 15.4 months; N=108)

- Response was durable, with 42% remaining in response at the data-cut off (median follow-up 15.4 months), including 40% with CR
- Median OS has not yet been reached (95% CI: 12.0, not reached), with OS rates of 78%, 59% and 52% at 6-, 12- and 18-months, respectively
  - This suggests that, if current survival trends continue, then median OS could be greater than 18-months
- Overall median PFS was 5.8 months (95% CI: 3.3, not reached) but in patients achieving a CR median PFS has not been reached suggesting many of these patients will have long term disease free survival and potential cure

Axi-cel demonstrated significant improvements compared to SoC

- A Cox model of survival indicated a [redacted] of risk of death with axi-cel ([redacted])
- Odds ratios for ORR and CR were [redacted], demonstrating significant improvements for axi-cel [redacted]

AEs associated with CAR T are manageable with existing safety protocols and the majority of events resolved within a month of axi-cel infusion (median follow-up 8.7 months; N=101)

- [redacted] of patients experienced CRS, but only [redacted] experienced ≥ grade 3. There were [redacted] but all Grade ≤3 CRS events [redacted]
- [redacted] of patients experienced neurological events, however the majority were mild. [redacted]

[redacted]Grade 4 neutropenia, thrombocytopenia, and anaemia occurred in [redacted] of patients, respectively. [redacted]

Increased clinician experience led to reductions in AE rates over the duration of the trial

- Between the interim and primary analyses Grade ≥ 3 AEs [redacted] CRS [redacted] neurological events [redacted] and there were [redacted]

B.2.1. Identification and selection of relevant studies

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

B.2.2. List of relevant clinical effectiveness evidence

Evidence in support of axi-cel comes from the following sources:

- ZUMA-1 study
  - ZUMA-1, combined Phase 1 and 2 data (median follow-up 15.4 months)[7]
  - ZUMA-1, Phase 2 data (median follow-up 8.7 months)[5, 7]
  - ZUMA-1, Phase 1 data[55]
- NCI-09-C-0082: NCI proof-of-concept study[56]
- National Cancer Institute (NCI) preliminary dose-finding study[9, 57]

The pivotal, regulatory evidence to support axi-cel is the ongoing, single-arm, Phase 1/2 study, ZUMA-1, and this study is the focus of this submission. A summary of the ZUMA-1 study is presented in Table 5.

Table 5: Clinical effectiveness evidence

Study	ZUMA-1; NCT02348216[7]				
Study design	ZUMA-1 is an ongoing Phase 1/2, single-arm, multi-centre, open-label study				
Population	Patients with aggressive B-cell NHL (DLBCL, PMBCL, and TFL) that was either refractory[a] to treatment or had relapsed ≤12 months after ASCT. Patients had prior therapy with an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen; no CNS lymphoma; no history of allogeneic SCT; and no prior anti-CD19, CAR, or other genetically modified T-cell therapy.				
Intervention(s)	Axicabtagene ciloleucel (N=108)				
Comparator(s)	ZUMA-1 is a single-arm trial				
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-1 presents the pivotal, regulatory, clinical evidence in support of axi-cel in the population directly relevant to the decision problem.				

Study	ZUMA-1; NCT02348216[7]
Reported outcomes specified in the decision problem	• Response rate • **Overall survival** • **Progression-free survival** • **Adverse effects** • **Health-related quality of life**
All other reported outcomes	• CAR T-cell levels

Key: ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphomas; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma.
Notes: a, Primary refractory disease was defined as either progressive disease (PD) to first-line therapy or stable disease (SD) after at least 4 cycles of first-line therapy and duration of SD ≤6 months from last dose of therapy. Refractory to second or later lines of therapy was defined as either best response of PD to most recent therapy regimen or best response of SD after at least 2 cycles of last line of therapy and ≤ 6 months duration of SD from last dose of therapy.
Source: Neelapu et al., 2017[7] and ZUMA-1 CSR[5]

NCI-09-C-0082 (a National Cancer Institute [NCI] proof-of-concept study)[56] and an NCI preliminary dose-finding study[9, 57] were not used to populate the economic model but are included in section B.2.6. The results of these studies provide longer-term evidence to support axi-cel. NCI-09-C-0082 and the NCI preliminary dose-finding study were not included in the economic model because evidence was used from the pivotal, regulatory ZUMA-1 study, including combined data from the 108 Phase 1 and 2 patients.

A clinical SLR was performed, in line with NICE guidance, in order to identify evidence relevant to this submission. Full details on the methods of the SLR are presented in Appendix D. Due to the large amounts of heterogeneity between the comparator studies identified, and the limited evidence available in a comparable population to the ZUMA-1 trial and the anticipated axi-cel licence (the majority of the comparator studies included patients with R/R disease after first-line treatment, compared to the heavily pre-treated patient population in ZUMA-1), it is extremely difficult to make any valid comparisons between these studies and ZUMA-1. Therefore, it was considered more appropriate to use studies for which patient-level data were available to inform a historical comparator study; SCHOLAR-1. There were still differences between SCHOLAR-1 and ZUMA-1 (including a more severe, more heavily pre-treated population in ZUMA-1 and higher use of ASCT in SCHOLAR-1, which may bias outcomes against axi-cel), but the availability of

patient-level data meant that comparisons could be performed that would attempt to account for some of these differences in the patient populations and allow for a more appropriate comparison. Details on the studies identified in the clinical SLR, including methods, baseline characteristics and outcomes, all compared to ZUMA-1, are presented in Appendix D. The results of the comparison of ZUMA-1 to SCHOLAR-1, including further discussion on the limitations of this analysis, is presented in Section B.2.9.

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

ZUMA-1

A summary of the methodology used in the Phase 1/2 clinical trial, ZUMA-1, is presented in Table 6.

Table 6: Summary of the trial methodology for ZUMA-1

Trial number (acronym)	NCT02348216 (ZUMA-1)
Location	The study was conducted at 24 centres (23 in the US and 1 centre in Israel).
Trial design	ZUMA-1 is an ongoing Phase 1/2 multicentre, open-label study that is evaluating the safety and efficacy of axi-cel in patients with refractory aggressive NHL.
Eligibility criteria for participants	**Inclusion criteria:** • Histologically confirmed DLBCL, PMBCL, or TFL • Chemotherapy-refractory disease, defined as one or more of the following: – No response to first-line therapy (primary refractory disease); patients who are intolerant to first-line therapy chemotherapy were excluded – No response to second or later lines of therapy • Refractory after ASCT, defined as occurrence of disease progression or relapse ≤ 12 months after ASCT (must have biopsy proven recurrence in relapsed patients) or, if salvage therapy was given after ASCT, the patient must have had no response to or relapsed after the last line of therapy • Prior therapy including anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen • Measurable disease according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (hereafter referred to as IWG 2007 criteria)[58] • No evidence of CNS lymphoma

	• Age 18 or older • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Adequate haematologic, renal, hepatic, pulmonary and cardiac function **Exclusion criteria:** • History of allogeneic SCT • Autologous stem cell transplant within 6 weeks of informed consent • Prior CD19 targeted therapy with the exception of patients who received axi-cel in this study and are eligible for retreatment • Prior CAR therapy or other genetically modified T-cell therapy • Presence of fungal, bacterial, viral, or other infection that was uncontrolled or requiring IV antimicrobials for management • History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/haemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
Settings and locations where the data were collected	Patients were hospitalised for at least 7 days of observation and management of treatment-emergent acute AEs. Subsequently, subjects returned to the clinic at Week 2 (± 2 days), Week 4 (± 3 days), Month 2 (± 1 week), and Month 3 (± 1 week). Long-term follow-up for disease status (among patients remaining in response) and survival continued every 3 months through Month 18, then every 6 months through 5 years, and then annually for a maximum of 15 years.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Patients received a single infusion of axi-cel at a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg (± 20%). The minimum dose to be administered was 1 x 10^6 anti-CD19 CAR T-cells/kg. For patients weighing >100kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T-cells was to be administered. The entire bag of axi-cel was to be infused. Axi-cel is administered after a conditioning chemotherapy regimen consisting of cyclophosphamide 500mg/m^2 IV and fludarabine 30mg/m^2 IV on the 5th, 4th, and 3rd day before infusion of axi-cel. Paracetamol 650mg given orally and diphenhydramine 12.5mg IV or orally approximately 1 hour before axi-cel infusion is also recommended. 111 patients were enrolled and leukapheresed (81 with DLBCL in Cohort 1 and 30 with PMBCL/TFL in Cohort 2). 101 patients were treated with axi-cel; 77 in Cohort 1 and 24 in Cohort 2. Concomitant medication: • Corticosteroid therapy at a dose ≥5mg/day of prednisone or equivalent doses of other corticosteroids and other immunosuppressive drugs were to be avoided for 7 days prior to leukapheresis and 5 days prior to axi-cel administration. • Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after axi-cel administration, unless used to manage axi-cel-related toxicities. Other medications that might interfere with the evaluation of the investigational product were

	also to be avoided for the same period unless medically necessary. • Treatment for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than the investigational product in this protocol, and other investigational agents, were prohibited, except as needed for treatment of disease progression after the axi-cel infusion. • The investigator was allowed to prescribe medications deemed necessary to provide adequate supportive care. All concomitant medications used during the 3 months following infusion of axi-cel (and a limited set of selected concomitant medications through 24 months beyond disease progression) were to be recorded in the case report form (CRF).
Primary outcomes (including scoring methods and timings of assessments)	The primary analysis was conducted at the point when 92 patients could be evaluated 6 months after the axi-cel infusion. The primary outcome of the study was ORR, defined as CR or PR per International Working Group (IWG) response criteria for Malignant Lymphoma[58] as determined by the study investigators in the pre-planned set of 92 patients. All patients who did not meet the criteria for an objective response by the analysis cut-off date were considered non-responders.
Other outcomes used in the economic model/specified in the scope	Key secondary endpoints included: • ORR according to central review, based on the IWG 2007 criteria[58] • DoR according to the investigator's assessment, and by central review, both based on the IWG 2007 criteria[58] • PFS according to the investigator's assessment, and by central review, both based on IWG 2007 criteria[58] • OS • Safety: Incidence of AEs, significant laboratory abnormalities, and presence of replication competent retrovirus (RCR) or antibodies to FMC63 or bovine serum albumin in patients' blood • HRQL, as measured by the EQ-5D-5L in the safety management cohort
Pre-planned sub-groups	
Key: AE, adverse event; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CRF, case report form; DLBCL, diffuse large B-cell lymphoma; DoR, duration or response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; IWG, International Working Group; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; SCT, stem cell transplantation; TFL, transformed follicular lymphoma. **Source:** Neelapu et al., 2017[7] and ZUMA-1 CSR[5]	

Table 7 presents the outcomes of the ZUMA-1 trial that are presented in the submission by data-cut and whether they were used to inform the economic model. Due to the differences in analysis timepoints, and the patients included in these analyses (i.e. Phase 2 alone or Phase 1 and 2 combined), it is important to be clear

which data are being used. The focus of the submission is on the updated analysis, when all 108 Phase 1 and 2 patients had been followed up for at least 12 months (median follow-up 15.4 months), where these data are available, as this provides longer-term evidence in support of axi-cel.

Table 7: ZUMA-1 outcomes presented in the submission

Outcome	N	Presented in submission	Used in Model?
Updated analysis (Phase 1 and 2 combined; median follow-up: 15.4 months)			
ORR	108	Section B.2.6	×
CR	108	Section B.2.6	×
PR	108	Section B.2.6	×
DoR	108	Section B.2.6	×
OS	108	Section B.2.6	✓
PFS	108	Section B.2.6	✓
Primary analysis (Phase 2; median follow-up: 8.7 months)			
ORR	101	Appendix L	×
CR	101	Appendix L	×
PR	101	Appendix L	×
DoR	101	Appendix L	×
OS	101	Appendix L	×
PFS	101	Appendix L	×
CAR T-cell levels	101	Section B.2.6	×
Safety management cohort (N=34)			
EQ-5D	34	Section B.2.6	✓

Key: AE, adverse event; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CRF, case report form; DLBCL, diffuse large B-cell lymphoma; DoR, duration or response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; IWG, International Working Group; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; SCT, stem cell transplantation; TFL, transformed follicular lymphoma.
Source: Neelapu et al., 2017[7] and ZUMA-1 CSR[5]

Baseline characteristics

Baseline characteristics for patients in ZUMA-1 Phase 2 are summarised in Table 8. The median age of patients in the ZUMA-1 trial was 58, with 24% of patients aged ≥65, which is similar to the median age of 61 for these patients in clinical practice in the UK.[14] UK clinical experts agreed that the patients treated in ZUMA-1 were likely to be reflective of the UK patients who would be considered for treatment with CAR T

therapy and they believed that the ZUMA-1 trial population overall was generally reflective of patients who would be seen in clinical practice.[1, 2]

It is also important to note that ZUMA-1 patients were a heavily pre-treated patient population (69% had received ≥3 prior treatments and 40% of patients received ≥4 prior treatment), which suggests that patients have received all standard available therapies, none of which had been effective, and are likely to have limited, palliative options remaining to them.

Table 8: Baseline characteristics of patients in ZUMA-1, Phase 2

	Phase 2 Overall
Patients, n	101
Disease type, n (%)	
DLBCL	77 (76)
PMBCL	8 (8)
TFL	16 (16)
Age, median (range) [years]	58 (23–76)
Age ≥65 years, n (%)	24 (24)
Sex, n (%)	
Male	68 (67)
Female	33 (33)
ECOG PS, n (%)	
0	42 (42)
1	59 (58)
Disease Stage III/IV, n (%)	
I/II	15 (15)
III/IV	86 (85)
IPI score 3–4, n (%)	
0–2	53 (52)
3–4	48 (48)
CD19 status, n/N (%)	
Negative	8/82 (10)
Positive	74/82 (90)
≥3 prior therapies, n (%)	70 (69)
History of primary refractory disease, n (%)	26 (26)
History of refractory to 2 consecutive lines, n (%)	54 (53)
Response to last chemotherapy regimen, n (%)	
Stable disease	14 (14)
Progressive disease	66 (65)
Refractory subgroup, n (%)	

Primary refractory	2 (2)
Refractory to ≥second-line	78 (77)
Relapse post-ASCT	21 (21)
Key: ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, international prognostic index; PMBCL, primary mediastinal B-cell lymphoma; PS, performance status; TFL, transformed follicular lymphoma. **Source:** Neelapu et al., 2017[7] and ZUMA-1 CSR[5]	

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

For Phase 2 of the ZUMA-1 study, Cohort 1 (DLBCL patients) and Cohort 2 (PMBCL and TFL patients) were designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the ORR for patients treated with axi-cel in Cohorts 1 and 2 is significantly greater than 20%. The pre-specified 20% control response rate was based on a review of published outcome data for patients with refractory DLBCL, defined as those who either never responded (i.e. progressive disease [PD] or stable disease [SD] as best response to the last line of therapy) or relapsed within 12 months after ASCT.

The full analysis population included all enrolled patients (N = 111). The modified intention-to-treat (mITT) population included all patients treated with at least 1.0 x 10^6 anti-CD19 CAR T-cells/kg (N = 101) and was the analysis population used for all efficacy analyses in ZUMA-1 Phase 2. The safety analysis population included all patients treated with any dose of axi-cel (N = 101).

Two pre-specified interim analyses (IA1 and IA2) and one primary analysis were planned. IA1 was a futility analysis conducted when 20 patients in the mITT set of Cohort 1 had the opportunity to be assessed for response at the 3-month disease assessment. IA2 was to be conducted when 50 patients in the mITT set of Cohort 1 had the opportunity to be assessed for response at the 3-month disease assessment. The nominal alpha level used for the assessment of efficacy in IA2 was 0.017. The primary analysis of Cohorts 1 and 2 combined was to be conducted when 72 patients in the mITT set of Cohort 1 and 20 patients in the mITT set of Cohort 2 had had the opportunity to be assessed for response at the 6-month disease

assessment. Both the IA1 and IA2 analyses have been completed. Cohort 1 met the primary endpoint at IA2. Therefore, in the primary analysis, which is the focus of this dossier, the inferential testing is presented only for Cohorts 1 and 2 combined. Nine additional patients had been enrolled at the time when the inferential analysis was met; all were treated with axi-cel and are included in the mITT assessment of efficacy.

The pre-specified primary analysis of the primary endpoint compared ORR for the 92 patients in the mITT (inferential) analysis set to the prespecified rate of 20% using a 1-sided exact binomial test. The nominal 1-sided alpha used to test for efficacy in this combined set was 0.0075. This analysis used the investigator's assessment of response according to International Working Group (IWG) 2007 criteria.[58] The ORR was also analysed using response based on a central review. Duration of response (DoR), PFS, and OS were analysed using the Kaplan–Meier (KM) method.

A summary of the statistical analyses used in the ZUMA-1 Phase 2 study are presented in Table 9.

Table 9: Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
NCT02348216 (ZUMA-1)	The hypothesis was that the ORR for patients treated with axi-cel in Cohorts 1 and 2 was significantly greater than 20%.	Cohort 1 and Cohort 2 in Phase 2 were designed to differentiate between a treatment that has a true response rate of ≤20% and a treatment with a true response rate of ≥40%.	In Phase 2, the pre-specified primary analysis of the primary endpoint compared ORR for the 92 patients in the mITT (inferential) analysis set to the prespecified rate of 20% using a 1-sided exact binomial test. The nominal 1-sided alpha used to test for efficacy in this combined set was 0.0075. This analysis used the investigator's assessment of response according to IWG 2007 criteria.[58]	All subjects who did not meet the criteria for objective response by the analysis data cut-off date were considered non-responders. Subjects not meeting the criteria for progression or death due to disease relapse or drug-related toxicity by the analysis data cut-off date were censored at their last evaluable disease assessment date. Subjects who had not died by the analysis data cut-off date were censored at their last date known to be alive prior to the data cut-off date with the exception that subjects known to be alive or determined to have died after the data cut-off date for the analysis were censored at the data cut-off date. Subjects not meeting the criteria for progression by the analysis data cut-off date were censored at their last evaluable disease assessment date.

Key: axi-cel, axicabtagene ciloleucel; IWG, International Working Group; mITT, modified intent-to-treat population; ORR, objective response rate.
Notes: Cohort 1 included DLBCL patients and Cohort 2 included PMBCL and TFL patients.
Source: ZUMA-1 CSR[5]

See Appendix D for the number of participants eligible to enter the study and the CONSORT flow diagram for ZUMA-1.

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

ZUMA-1 was considered to be a good quality study and was conducted according to Good Clinical Practices (GCP). See Appendix D for full details of the quality assessment for ZUMA-1.

B.2.6. Clinical effectiveness results of the relevant trials

The primary analysis of ZUMA-1 was conducted at the point when the pre-specified 92 patients from the Phase 2 portion of the study could be evaluated 6 months after axi-cel infusion, which resulted in a median follow-up was 8.7 months.[5]

To evaluate the durability of response with axi-cel, an updated analysis was performed when the 108 patients in the Phase 1 and 2 portions of ZUMA-1 had been followed for a minimum of 1 year, which resulted in a median follow-up of 15.4 months.[7]

The focus of this submission is the updated analysis (median follow-up 15.4 months), where available, as this provides more long-term data and is consistent with the data used to inform the economic model. Relevant pharmacokinetic and pharmacodynamic outcomes are presented using the primary analysis results (median follow-up 8.7 months), as these outcomes were not updated for the latest data-cut. The results of the Phase 2 primary analyses are presented in Appendix L and were generally consistent with the updated results.

ZUMA-1, updated analysis (N = 108; median follow-up 15.4 months)

Response and duration of response

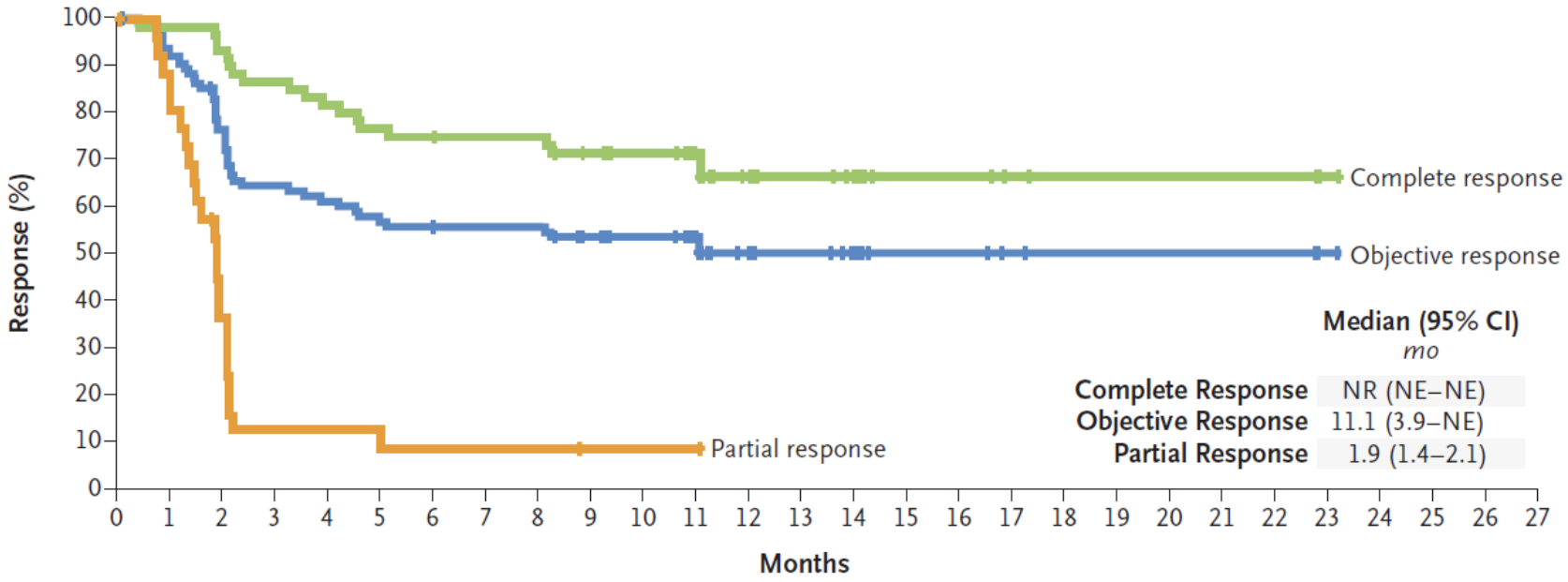
In the updated analysis of ZUMA-1 Phase 1 and 2 patients (N = 108; median follow-up 15.4 months), the ORR was 82%. At the data cut-off (median follow-up 15.4 months), 42% remained in response, including 40% with a CR. Of the 7 patients in Phase 1 of the study, 3 had an ongoing CR at 24 months. Of the patients who did not have a CR at the time of the first tumour assessment (1 month after the infusion

of axi-cel), 23 patients (11 of 35 with a PR and 12 of 25 with SD) subsequently had CR in the absence of additional therapies as late as 15 months after treatment.

ORRs response rates were consistent across key covariates, including the use of tocilizumab or glucocorticoids. Figure 4 presents the KM curve for the DoR. The median DoR was 11.1 months (95% CI, 3.9 to could not be estimated). The figure shows that a higher proportion of patients who achieved CR were able to remain in response long term. There is a long tail on the KM curve after 5 months, with few events occurring and no new events after 11-12 months. The majority of patients who only achieve PR lose this response very quickly (within the first couple of months), however, the KM curve is again flat after 2-months with few events and around 10% of patients able to maintain response. As ORR includes both CR and PR patients it is a combination of the two, but again it is important to note the long, flat tail on the KM curve. This suggests that axi-cel can be seen as a curative therapy option, especially for patients who can achieve CR.

Only [redacted] patients who had a response subsequently received an allogenic SCT, which emphasises that axi-cel should be considered as a definitive therapy aiming to provide patients with a cure and not a bridge to subsequent therapy. However, receipt of axi-cel does not preclude patients who may have been ineligible for SCT to start with from subsequently receiving SCT when responding to axi-cel therapy.

Figure 4: Duration of response in the ZUMA-1 updated analysis (n=108, median follow-up 15.4 months)



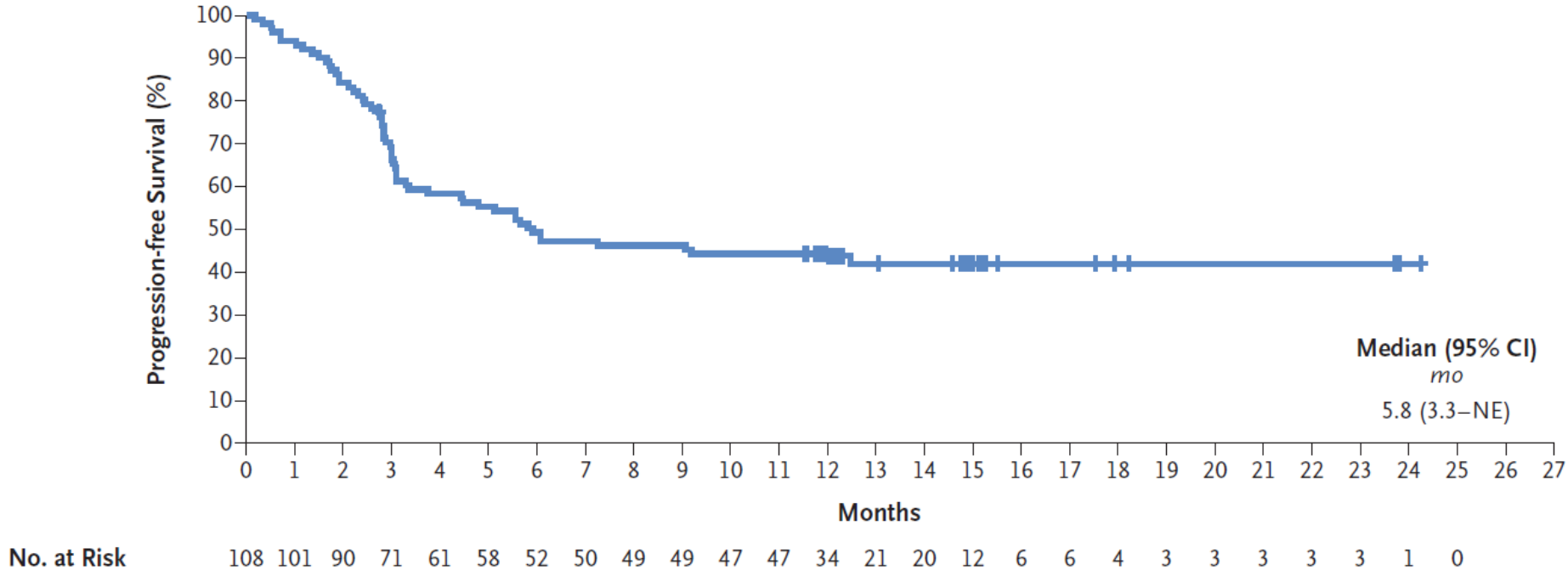
No. at Risk																									
Complete response	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
Objective response	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
Partial response	26	21	9	3	3	2	2	2	2	1	1	1	0												

Key: CI, confidence interval; mo, months; NE, could not be estimated; NR, not reached.
Source: Neelapu et al., 2017[7]

Progression-free survival

Figure 5 presents the KM curve for PFS. The median duration of PFS was 5.8 months (95% CI, 3.3, not reached), with PFS rates of 49% (95% CI, 39 to 58) at 6 months, 44% (95% CI, 34 to 53) at 12 months, and 41% (95% CI, 31 to 50) at 15 months. The KM curve for PFS also has a long tail from around 5 to 6 months, following an initial drop, again suggesting the potential for cure, with few patients experiencing progression after they have remained progression-free for this initial 6-month period.

Figure 5: Progression-free survival in the ZUMA-1 updated analysis (n=108, median follow-up 15.4 months)



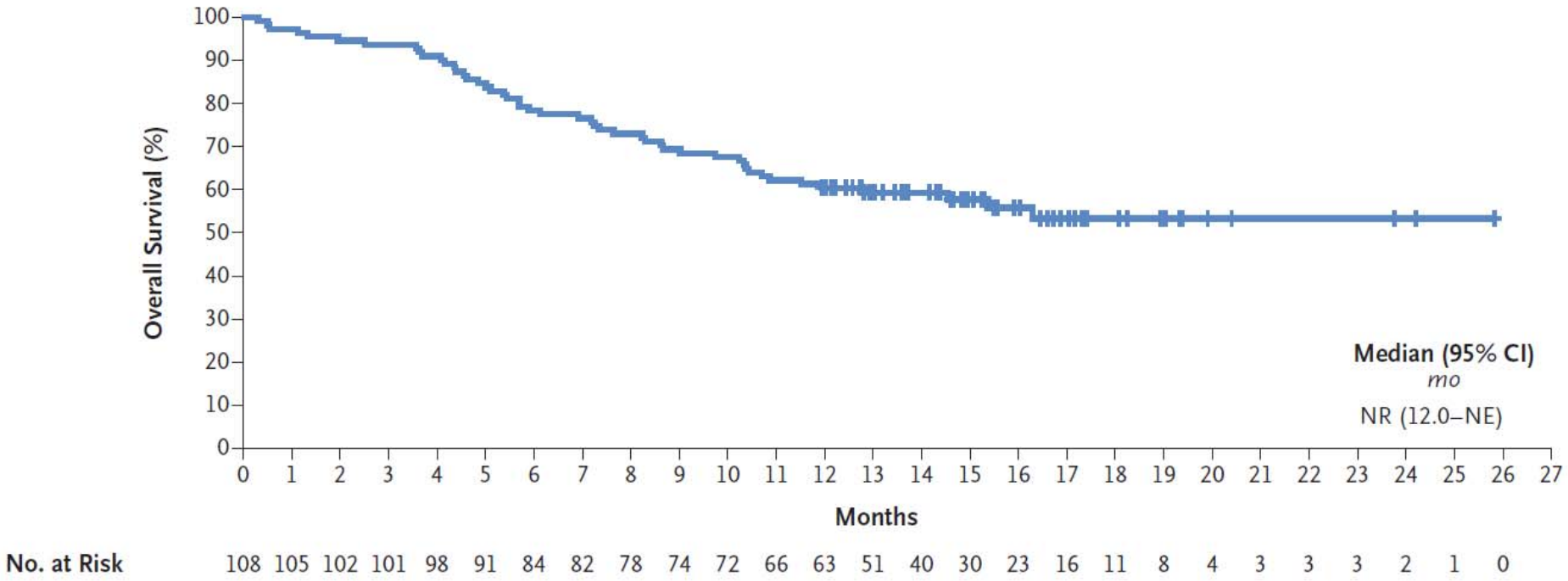
Key: CI, confidence interval; mo, months; NE, could not be estimated.
Source: Neelapu et al., 2017[7]

Overall survival

Figure 6 presents the KM curve for OS. The median OS was not yet reached (95% CI, 12.0 months, not reached), with OS rates of 78% (95% CI, 69 to 85) at 6 months, 59% (95% CI, 49 to 68) at 12 months, and 52% (95% CI, 41 to 62) at 18 months. A total of 56% of patients were still alive at the time of the data cut-off (median follow-up 15.4 months). Again, the KM curve has a long tail, with few events occurring after 10 months. This supports the narrative from the DoR and PFS results with patients who are able to achieve and maintain CR considered to be cured, with few events occurring in those patients.

There are two groups of patients seen with axi-cel therapy, those who respond to therapy and are able to maintain this response and survival long-term and can be considered cured, and those who do not respond and continue to progress. This explains the flattening of the KM curves, as those patients who are not able to achieve CR drop out, while those who are able to achieve CR maintain their response and can be considered cured.

Figure 6: Overall survival in the ZUMA-1 updated analysis (n=108, median follow-up 15.4 months)



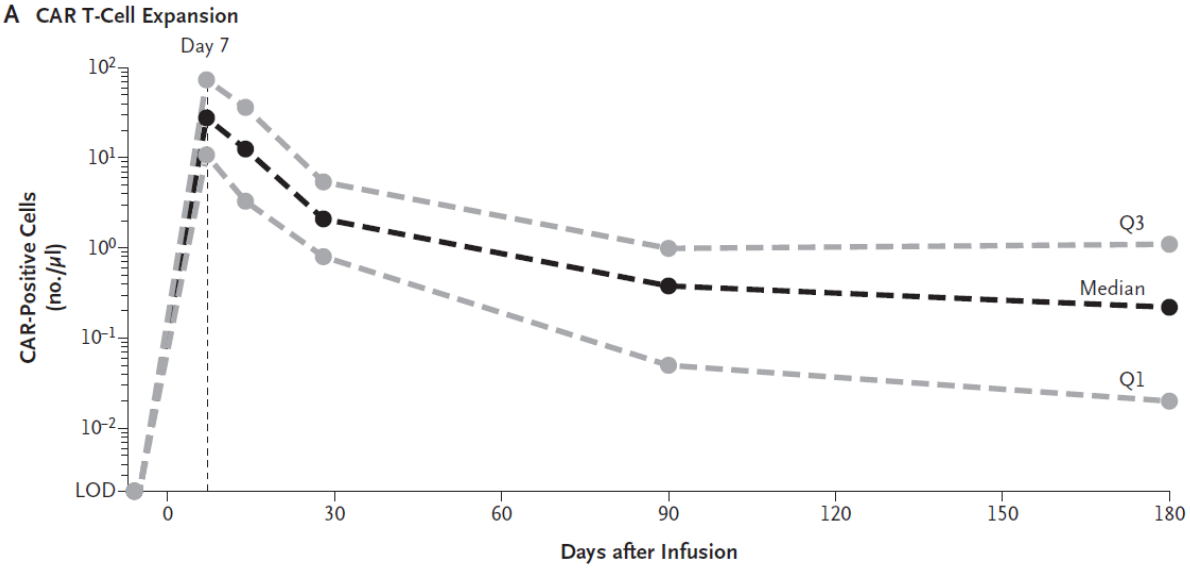
Key: CI, confidence interval; mo, months; NE, could not be estimated; NR, not reached.
Source: Neelapu et al., 2017[7]

ZUMA-1, primary analysis (median follow-up 8.7 months)

CAR T-cell levels

Following the administration of the CAR-T cells to the patient the cells rapidly multiple ("the expansion phase"), peaking in the circulation within 1-2 weeks after administration before declining slowly thereafter (see Figure 7). Expansion was significantly associated with response to axi-cel, with an area under the curve (AUC) within the first 28 days [redacted] times as high in patients who had a response compared to those who did not. The correlation between peak and AUC T-cell numbers and response appears in Figure 8 and Figure 9. Most patients at 180 days post infusion, and [redacted] patients with ongoing CRs at 24 months, still had detectable circulating CAR-T cells. Persistence of anti-CD19 CAR-Ts would ensure ongoing destruction of malignant CD19+ cells and ongoing CR and remission. However, persistence of CAR-T cells in the circulation may not be required for long term remission as in the longer term NCI follow up ongoing remission could be present in the absence of detectable CAR-T cells in the blood and recovery of non-malignant CD19+ B cells.[57] Presumably in this scenario the malignant clones are eradicated completely leading to long term remission.

Figure 7: CAR T-cell expansion in ZUMA-1 (mITT)



Key: CAR, chimeric antigen receptor; mITT, modified intend-to-treat
Notes: Serial blood samples were analyzed for CAR T-cell levels and serum biomarkers in all 101 patients who were treated with axi-cel. Figure shows CAR T-cell expansion and persistence with median values and interquartile ranges (Q1 and Q3).
Source: Neelapu et al, 2017[7]

Figure 8: Peak Number of Anti-CD19 CAR T-cells in Blood (/µL) by Best Response (mITT)

Key: CAR, chimeric antigen receptor; CR, complete response; mITT, modified intend-to-treat; PR, partial response.
Notes: To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Peak is defined as the maximum number of CAR T measured post infusion. Diamonds represent mean values; circles represent the outliers

Figure 9: AUC for Number of Anti-CD19 CAR T-cells in Blood (/µL) by Best Response (mITT)

Key: CAR, chimeric antigen receptor; CR, complete response; mITT, modified intend-to-treat; PR, partial response.
Notes: To apply the log scale on y-axis, zero values were adjusted by adding 0.001. Area under curve (AUC) is defined as the area under curve in a plot of number of CAR T-cells against scheduled visit from Day 0 to Day 28. Diamonds represent mean values; circles represent the outliers.

ZUMA-1, safety management cohort

A safety management cohort of 34 patients was studied to examine the impact of pre-emptive safety management. This cohort also captured HRQL data for these patients using the EQ-5D-5L at screening, Week 4, Month 3 and Month 6 post axi-cel infusion, as well as results by response category and for progression-free and progressed patients. A crosswalk algorithm was used to convert EQ-5D-5L to EQ-5D-3L (as preferred by NICE) and then a UK valuation algorithm was applied to convert EQ-5D-3L descriptive scores to the EQ-5D-3L index with UK population-based health utility values. This is discussed as part of the economic analysis in Section B.3.4.

Health-related quality of life

Patients experienced [redacted] in utility scores from screening ([redacted]) to Week 4 ([redacted]), most likely because of a disutility associated with the timing of the transient toxicities associated with CAR T therapy (see Section B.2.10). By Month 3 and Month 6, the patient utilities had [redacted], respectively), showing that patient HRQL is improved by axi-cel therapy. This is particularly evident when the results are broken down by response category and by health state, with patients in response experiencing [redacted], respectively) than patients who have not responded to treatment ([redacted] and [redacted], respectively) and patients with progression-free disease experiencing [redacted] ([redacted]) than patients with progressed disease ([redacted]).

Table 10: EQ-5D-3L utility scores from the ZUMA-1 safety management cohort

Results by time point, mean (SD)	N	EQ-5D-3L index score
Screening	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Month 3	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
Total	[redacted]	[redacted]
Results by response category		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
PD	[redacted]	[redacted]

Total	[redacted]	[redacted]
Results by health state		
Progression-free health state	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
Key: CR, complete response; EQ-5D-3L, EuroQol 5-dimension 3-level; N, number of patients; PD, progressive disease; PR, partial response; SD, standard deviation. **Source:** Analysis of ZUMA-1 data performed to inform the economic model.		

Supporting evidence for axi-cel (including longer-term data)

In addition to the pivotal Phase 2 data from ZUMA-1, supporting evidence for axi-cel is available from the following three studies:

- ZUMA-1, Phase 1 data[55]
- NCI-09-C-0082: NCI proof-of-concept study[56]
- National Cancer Institute (NCI) preliminary dose-finding study[9, 57]

ZUMA-1, Phase 1[55]

ZUMA-1, Phase 1: Methodology

As described in Section B.2.3, ZUMA-1 was a Phase 1/2, multicentre, open-label, single-arm study. The primary objective of Phase 1 was to evaluate the safety of axi-cel regimens in seven patients with refractory DLBCL, PMBCL, and TFL. Methods, inclusion/exclusion criteria and treatment were the same as described for Phase 2 in Section B.2.3, and the primary endpoint was the incidence of dose limiting toxicities.

ZUMA-1, Phase 1: Patient characteristics

Seven patients in the ZUMA-1 Phase 1 study were treated with axi-cel. Patients had a median age of 59 (range: 29 to 69), with 3 patients (43%) ≥65 years. 71% of patients were male and all 7 patients had DLBCL. Four patients had received prior ASCT, and six patients had received 3 or more prior therapies.

ZUMA-1, Phase 1: Efficacy results

Five of seven (71%) patients achieved an objective response within 1 month of axi-cel infusion, with four of seven (57%) achieving a CR. Three patients (43%) were in ongoing CR at 12 months post-infusion. All three patients with ongoing CR had previously relapsed within 5.8 months of ASCT.

NCI proof-of-concept study[56]

NCI study: Methodology

The NCI study (NCI-09-C-0082) was a single-arm, open-label study. Twenty-two patients received a single dose of axi-cel 2 days after a low-dose chemotherapy conditioning regimen of cyclophosphamide plus fludarabine.

The primary study objective was to determine the safety and feasibility of the administration of the axi-cel cryopreserved anti-CD19 CAR T-cells following a nonmyeloablative chemotherapy regimen in participants with B-cell lymphoma. The secondary objective was to determine the *in vivo* survival of the axi-cel anti-CD19 CAR T-cells, and to determine if the treatment regimen could cause regression of B-cell malignancies.

NCI study: Patient characteristics

In the NCI study, 22 participants with advanced NHL received axi-cel preceded by low-dose chemotherapy. Nineteen patients had DLBCL/PMBCL/TFL (13 patients were “DLBCL, not otherwise specified”; 2 patients were “PMBCL”; 3 patients were “DLBCL, transformed from FL”; 1 patient was “DLBCL transformed from CLL”), two patients had follicular lymphoma (FL), and one patient had mantle cell lymphoma (MCL).

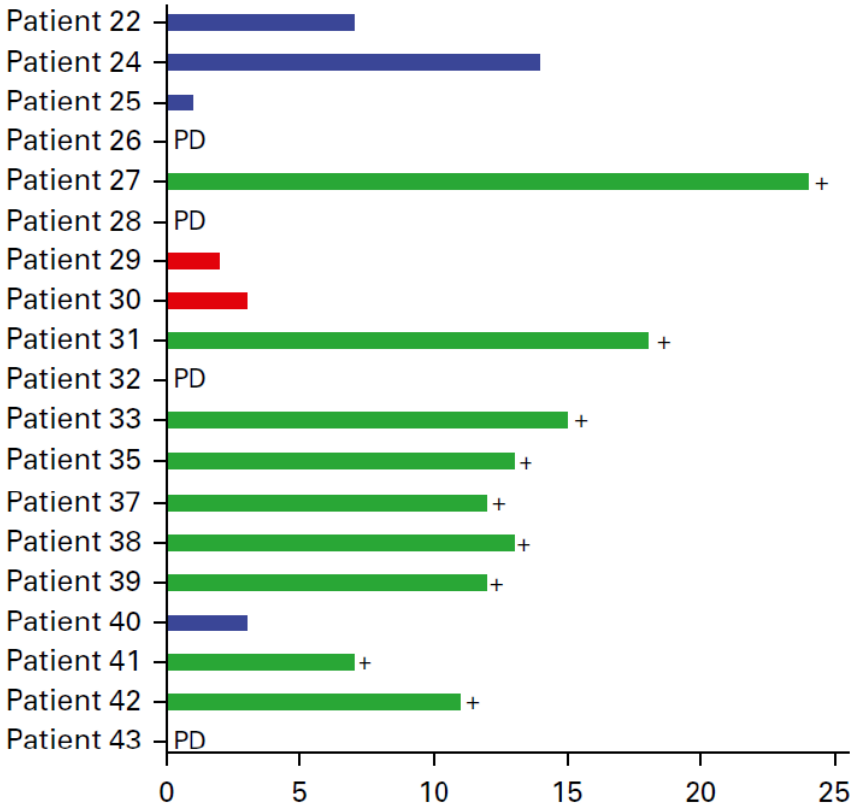
Eleven of 19 patients with DLBCL/PMBCL/TFL had chemotherapy-refractory lymphoma. Five other patients with DLBCL/PMBCL/TFL had lymphoma that had relapsed 10 months or less after ASCT as their last treatment prior to protocol enrolment. Eleven patients with DLBCL/PMBCL/TFL were high risk by second-line, according to the age-adjusted International Prognostic Index (sAAIPI). The median number of unique lymphoma therapies received before protocol enrolment was four (range one to seven).

NCI study: Efficacy results

The duration of response among the 19 patients with DLBCL/PMBCL/TFL is presented in Figure 10. Nine (47%) patients achieved CR, and four (21%) patients had PR, giving an ORR of 68%. In the nine (47%) patients who achieved CR, this was ongoing 7+ to 24+ months after axi-cel infusion (green bars). Of the remainder,

4 (21%) achieved PR of 1–14 months' duration (blue bars), 2 (11%) had stable disease of 2 and 3 months' duration (red bars), and 4 (21%) had progressive disease (PD).

Figure 10: Duration of response among the 19 DLBCL/PMBCL/TFL patients in the NCI study



Key: +, CR is ongoing; CLL, chronic lymphocytic leukaemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphoma; PR, partial response; SD, stable disease; TFL, transformed follicular lymphoma.
Notes: Green bars, ongoing CR; blue bars, PR; red bars, SD.
Source: Adapted from data presented in the NCI study[56]

Preliminary dose-finding study[9, 57]

Dose-finding study: Methodology and patient characteristics

A dose-finding study conducted at the NCI included seven refractory DLBCL patients plus two refractory PMBCL patients. All patients received a single dose of axi-cel 2 days after a low-dose chemotherapy conditioning regimen of cyclophosphamide plus

fludarabine. It is worth noting that this conditioning chemotherapy dose was lower than that currently recommended in the draft SmPC.

Dose-finding study: Efficacy results

Four (44%) of these patients (two DLBCL, two PMBCL) had achieved complete remission during the 9-month period following axi-cel infusion.

Moreover, long-term follow-up of seven of the original nine DLBCL/PMBCL patients treated in the dose-finding study demonstrated that four (44%) patients (two DLBCL, two PMBCL) were in ongoing complete remission between 38+ and 56+ months after infusion of axi-cel. Out of these four patients with ongoing CR, recovery of normal B-cells was observed in three patients.

B.2.7. Subgroup analysis

In the ZUMA-1 study, pre-specified subgroup analyses were performed using key baseline and prognostic factors for ORR and the PFS rate at 6 months using the primary analysis data (N=101, median follow-up: 8.7 months) (the updated 12-month analysis was conducted to focus on OS and DoR and did not include an update of subgroup analyses), based on the following factors:

- ECOG PS (0 vs 1)
- Age (<65 vs ≥65 years)
- Disease type (DLBCL vs PMBCL vs TFL)
- Refractory to first-line therapy, i.e. primary refractory (yes vs no)
- Refractory to ≥2 lines of therapy (yes vs no)
- Number of prior chemotherapies (1 vs 2–3 vs ≥4)
- History of bone marrow involvement (yes vs no)
- Tumour burden (≤median vs >median)
- Sex (male vs female)
- Race (White vs Asian vs other)
- CD19 at baseline (positive vs negative)
- Refractory subgroup (refractory to ≥second-line therapy vs relapse post ASCT)
- Disease stage (I–II vs III–IV)
- IPI risk (0–2 vs 3–4)

- CD19 H-score (≤150 vs >150)
- CD4/CD8 ratio (>1 vs ≤1)
- Steroid use (yes vs no)
- Tocilizumab use (yes vs no)

However, the study was not designed to distinguish between these patient groups, and therefore, all tests are descriptive. A summary of the results of the subgroups analyses are presented in Appendix E. Both the ORR and PFS rate at 6 months were consistent across subgroups, with similar efficacy across all NHL prognostic factors. Of particular interest to NICE in the decision problem meeting was the potential difference between the different disease groups (DLBCL, PMBCL and TFL) and the difference between the primary refractory and relapsed populations. Both ORR and PFS rates at 6 months were consistent across all of these subgroups of patients, and all showed significant results for patients treated with axi-cel.

B.2.8. Meta-analysis

The main evidence for axi-cel came from one single-arm Phase 1/2 study, supported by data from two small single-arm, dose-finding/proof-of-concept studies, and a patient level historical control study. The patient level historical control study SCHOLAR-1 is used in place of a literature review/meta-analysis, and given the heterogeneity between the patient populations for relevant comparator treatments (where the majority of patients have received only one prior line of therapy), the availability of patient-level data to account for differences between patient characteristics and key prognostic factors is considered to be more rigorous and allows a more appropriate comparison.

B.2.9. Indirect and mixed treatment comparisons

Full details on the methods of the SLR are presented in Appendix D. Due to the large amounts of heterogeneity between the studies identified in the SLR and the ZUMA-1 study, which included much more heavily pre-treated patients compared to the majority of the SLR studies which were mostly patients after first-line treatment, direct comparison between these studies was not considered appropriate. Instead, the SCHOLAR-1 study was conducted using data from four sources for which patient-level data were available: MD Anderson Cancer Centre (MDACC) database;

Mayo Clinic and University of Iowa (MC/IA) Specialised Program of Research Excellence (SPORE) database; the National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) randomised Phase 3 study LY.12; and the French Lymphoma Academic Research Organisation (LYSARC) randomised phase 3 Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study. This would allow patients to be included that more closely matched the patient population of ZUMA-1 and would allow for adjustment to be made to account for any differences between patients and therefore allow for a more appropriate comparison.

Full details on the methodology of the SCHOLAR-1 study and the comparison to ZUMA-1 are presented in Appendix D. The analysis uses the updated, 12-month data from ZUMA-1 for the patients from the Phase 2 part of the study (N = 101).

ZUMA-1 and SCHOLAR-1 demographic and baseline/disease characteristics

Demographic and disease characteristics among subjects in the SCHOLAR-1 evaluable set are presented in Table 11. Most patients had ECOG performance status ≤ 1 and Stage III–IV disease; ZUMA-1 did not include any ECOG ≥2 patients, but it did have a higher proportion of patients with Stage III-IV disease. Approximately one-third of evaluable patients in SCHOLAR-1 had high-intermediate to high-risk IPI risk classification, compared to almost half in ZUMA-1. ZUMA-1 also contained a higher proportion of patients with PMBCL and TFL. Overall, around 20% of patients had relapsed ≤ 12 months following ASCT. More patients in SCHOLAR-1 had a history of being primary refractory, but slightly more patients in ZUMA-1 had a history of being refractory to two consecutive lines of therapy. It is also important to note that around [redacted] of patients in SCHOLAR-1 went on to receive ASCT after determination of refractory status (compared to only [redacted] in the ZUMA-1 trial). This needs to be taken into account when considering the SCHOLAR-1 results, as this could lead to an overestimation of survival outcomes for these patients. In addition, patients in the ZUMA-1 trial were more aggressively pre-treated compared to SCHOLAR-1 patients (40% of patients receiving 4 or more lines of therapy in ZUMA-1 compared to only 0.2% in SCHOLAR-1).

Table 11: Baseline characteristics in the ZUMA-1 and SCHOLAR-1 studies

	ZUMA-1 (N=101)	SCHOLAR-1				
		CORAL (N=170)	LY12 (N=219)	MAYO (N=82)	MDACC (N=165)	Overall (N=636)
Type of Data Source, n (%)						
Clinical Trial	101 (100)	170 (100.0)	219 (100.0)	0	0	389 (61.2)
Retrospective Database	NA	0	0	82 (100.0)	165 (100.0)	247 (38.8)
Region, n (%)						
Europe	0	170 (100.0)	0	0	0	170 (26.7)
North America	100 (99)	0	219 (100.0)	82 (100.0)	165 (100.0)	466 (73.3)
Sex, n (%)						
Female	33 (33)	53 (31.2)	85 (38.8)	31 (37.8)	60 (36.4)	229 (36.0)
Male	68 (67)	117 (68.8)	134 (61.2)	51 (62.2)	105 (63.6)	407 (64.0)
Age (years)[a]						
n	101	170	219	82	165	636
Median (Q1, Q3)	58.0	54.0 (42.0, 60.0)	54.4 (44.6, 59.9)	60.0 (49.0, 65.0)	56.0 (47.0, 65.0)	55.0 (45.0, 61.0)
Min, Max	23, 76	19, 65	24, 70	20, 80	20, 81	19, 81
Age Category						
<65	77 (76)	168 (98.8)	204 (93.2)	59 (72.0)	122 (73.9)	553 (87.0)
≥65	24 (24)	2 (1.2)	15 (6.9)	23 (28.1)	43 (26.1)	83 (13.1)
ECOG PS, n (%)						
0-1	101 (100)	142 (83.5)	194 (88.6)	59 (72.0)	69 (41.8)	464 (73.0)
2-4	0	26 (15.3)	25 (11.4)	20 (24.4)	16 (9.7)	87 (13.7)
Unavailable or Missing	0	2 (1.2)	0	3 (3.7)	80 (48.5)	85 (13.4)
IPI Risk Classification[a], n (%)						
Low risk (0-1 points)	27 (27)	55 (32.4)	78 (35.6)	18 (22.0)	8 (4.8)	159 (25.0)

	ZUMA-1 (N=101)	SCHOLAR-1				
		CORAL (N=170)	LY12 (N=219)	MAYO (N=82)	MDACC (N=165)	Overall (N=636)
Low-intermediate risk (2 points)	26 (26)	50 (29.4)	65 (29.7)	25 (30.5)	12 (7.3)	152 (23.9)
High-intermediate to High risk (>=3 points)	48 (48)	57 (33.5)	76 (34.7)	39 (47.6)	38 (23.0)	210 (33.0)
Missing or incompletely assessed	0	8 (4.7)	0	0	107 (64.8)	115 (18.1)
Disease Stage[b], n (%)						
I - II	15 (15)	55 (32.4)	73 (33.3)	16 (19.5)	30 (18.2)	174 (27.4)
III - IV	86 (85)	114 (67.1)	146 (66.7)	65 (79.3)	135 (81.8)	460 (72.3)
Missing	0	1 (0.6)	0	1 (1.2)	0	2 (0.3)
Number of Chemotherapy Regimens						
n	101	122	194	65	137	518
Median (Q1, Q3)	NA	3.0 (3.0, 3.0)	6.0 (4.0, 7.0)	4.0 (3.0, 5.0)	4.0 (3.0, 4.0)	4.0 (3.0, 5.0)
Min, Max	NA	2, 3	2, 26	2, 8	3, 5	2, 26
First Refractory Subgroup, n (%)[b]						
Primary Refractory	2 (2)	48 (28.2)	112 (51.1)	20 (24.4)	0	180 (28.3)
Refractory to 2nd or later therapy	78 (77)	78 (45.9)	46 (21.0)	42 (51.2)	149 (90.3)	315 (49.5)
Relapse after ASCT	21 (21)	44 (25.9)	61 (27.9)	20 (24.4)	16 (9.7)	141 (22.2)
Last Refractory Subgroup, n (%)[c]						
Primary Refractory	2 (2)	6 (4)	87 (95)	8 (9)	0 (0)	101 (20)
Refractory to 2nd or later therapy	78 (77)	115 (68)	5 (5)	49 (60)	147 (89)	316 (62)
Relapse after ASCT	21 (21)	49 (29)	0 (0)	24 (30)	18 (11)	91 (18)

	ZUMA-1 (N=101)	SCHOLAR-1				
		CORAL (N=170)	LY12 (N=219)	MAYO (N=82)	MDACC (N=165)	Overall (N=636)
Ever primary refractory – n (%)	26 (26)	48 (28.2)	113 (51.6)	20 (24.4)	76 (46.1)	257 (40.4)
Ever refractory to any 2 consecutive lines of therapy, n (%)	54 (53)	78 (45.9)	75 (34.2)	44 (53.7)	124 (75.2)	321 (50.5)
Stem Cell Transplant Prior to Determination of Refractory Status, n (%)	NA	44 (25.9)	61 (27.9)	22 (26.8)	19 (11.5)	146 (23.0)
Stem Cell Transplant After Determination of Refractory Status, n (%)	NA	91 (53.5)	36 (16.4)	12 (14.6)	41 (24.8)	180 (28.3)
Disease Type, n (%)						
DLBCL	77 (76)	170 (100.0)	183 (83.6)	73 (89.0)	126 (76.4)	552 (86.8)
PMBCL	8 (8)	0	12 (5.5)	0	2 (1.2)	14 (2.2)
TFL	16 (16)	0	22 (10.0)	0	5 (3.0)	27 (4.2)
Other, Unknown, or Missing	0	0	2 (0.9)	9 (11.0)	32 (19.4)	43 (6.8)
Total Number of Lines of Chemotherapy & ASCT Received, n (%)						
1	2 (2)	48 (28.2)	112 (51.1)	20 (24.4)	0	180 (28.3)
2-3	59 (58)	78 (45.9)	46 (21.0)	41 (50.0)	149 (90.3)	314 (49.4)
>=4	40 (40)	0	0	1 (1.2)	0	1 (0.2)

Notes: a, age at determination of refractory status for SCHOLAR-1 and age a study entry for ZUMA-1; b, three subjects were confirmed to have IPI 5 (2 patients in MAYO and 1 patient in MDACC); c, for the ZUMA-1 study it is unclear whether these data are related to their first treatment or their last treatment.
Source:

ZUMA-1 and SCHOLAR-1 results

ORR and CR

Table 12 presents a summary of the ORR, CR and PR rates in SCHOLAR-1 and ZUMA-1. There were 523 patients who were evaluable in the response analysis set. The pooled estimates from SCHOLAR-1, using a random-effects model, resulted in an ORR of 26%, CR of 7% and PR of 17.5%. These were significantly lower than the results from ZUMA-1 (82%, 54% and 28%, respectively), indicating that treatment with axi-cel results in significantly greater proportions of patients being able to achieve a response.

Table 12: ORR and CR in ZUMA-1 and SCHOLAR-1

	ZUMA-1 (N=101)	SCHOLAR-1				
		CORAL (N=170)	**LY12 (N=219)**	**MAYO (N=82)**	**MDACC (N=165)**	**Overall (N=636)**
ORR to subsequent therapy[a]	n=101	n=170	n=106	n=82	n=165	n=523
Responders, n (%)	83 (82)	53 (31.2)	28 (26.4)	21 (25.6)	33 (20.0)	135 (25.8)
95% Exact CI	(73, 89)	(24.3, 38.7)	(18.3, 35.9)	(16.6, 36.4)	(14.2, 26.9)	(22.1, 29.8)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	25.7 (20.9, 31.3)
CR to subsequent therapy[a]	n=101	n=170	n=106	n=82	n=165	n=523
Responders, n (%)	55 (54)	26 (15.3)	2 (1.9)	6 (7.3)	11 (6.7)	45 (8.6)
95% Exact CI	(44, 64)	(10.2, 21.6)	(0.2, 6.6)	(2.7, 15.2)	(3.4, 11.6)	(6.3, 11.3)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	7.0 (3.2, 14.5)
PR to subsequent therapy[a]	n=101	n=170	n=106	n=82	n=165	n=523
Responders, n (%)	28 (28)	27 (15.9)	26 (24.5)	15 (18.3)	22 (13.3)	90 (17.2)
95% Exact CI	(19, 38)	(10.7, 22.3)	(16.7, 33.8)	(10.6, 28.4)	(8.5, 19.5)	(14.1, 20.7)
DerSimonian-Laird Estimator	NA	NA	NA	NA	NA	17.5 (13.3, 22.7)

Key: CI, confidence interval; CR, complete response; NA, not applicable; ORR, overall response rate.
Notes: a, Treatment with axi-ce in ZUMA-1, first therapy after refractory determination in SCHOLAR-1.
Source:

Survival

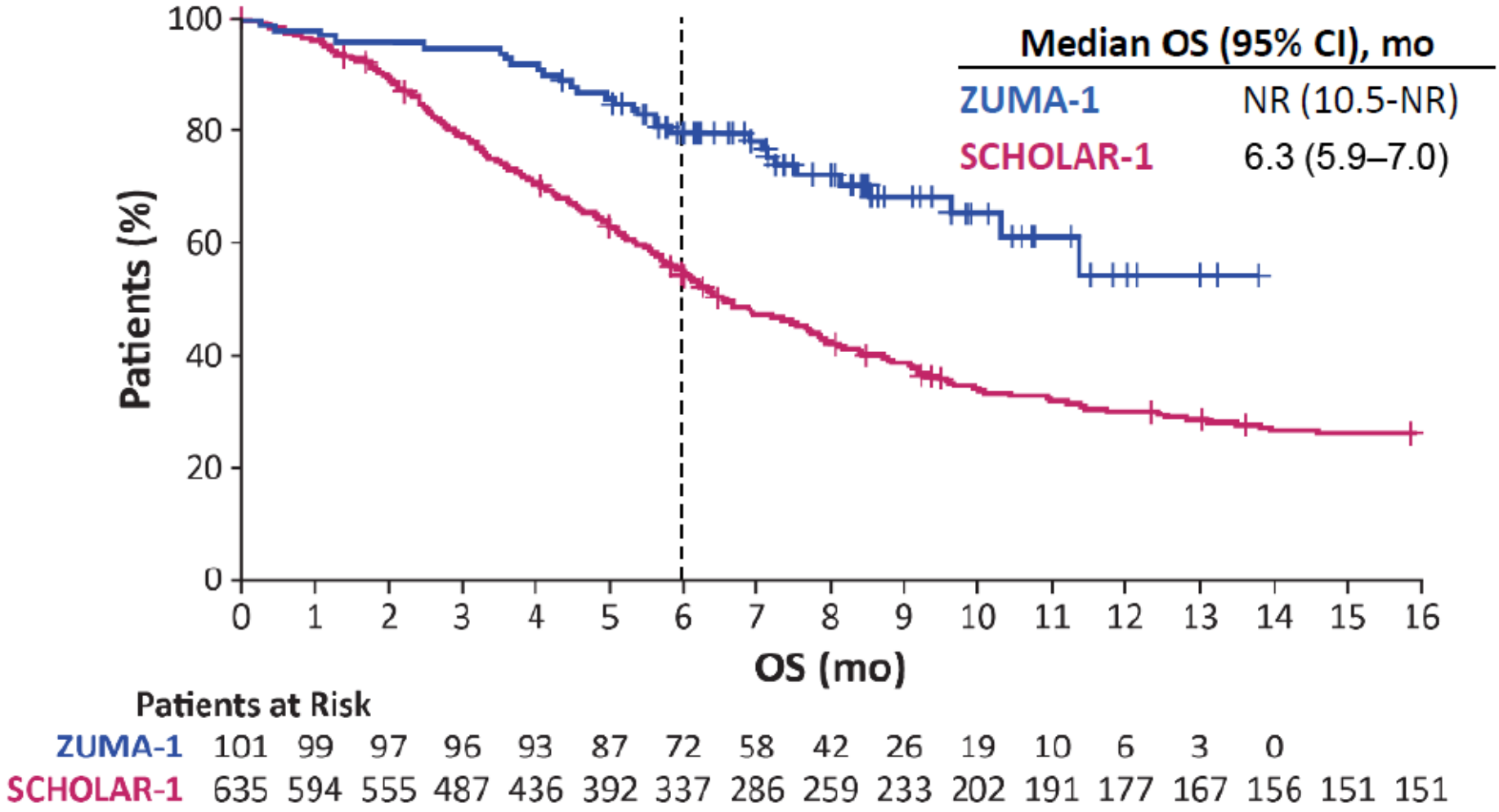
A summary of survival in the 603 survival evaluable subjects is provided in Table 13. The median OS in SCHOLAR-1 was 6.3 months, with 6-month, 1-, and 2-year OS rates of 53%, 28% and 20%. This is significantly lower than the 6-month (80%) and 1-year (55%) OS rates in ZUMA-1 (n=101), indicating that axi-cel treatment results in significantly greater survival for patients. This difference in survival for axi-cel patients is clearly demonstrated in the KM curves comparing ZUMA-1 and SCHOLAR 1 (Figure 11).

Table 13: OS in ZUMA-1 and SCHOLAR-1

	ZUMA-1 (N=101)	SCHOLAR-1				
		CORAL (N=170)	**LY12 (N=219)**	**MAYO (N=82)**	**MDACC (N=165)**	**Overall (N=636)**
Survival Status at Last Follow-up	n=101	n=170	n=196	n=72	n=165	n=603
Alive (Censored)	71 (70.0)	34 (20.0)	39 (19.9)	6 (8.3)	19 (11.5)	98 (16.3)
Dead	30 (30.0)	136 (80.0)	157 (80.1)	66 (91.7)	146 (88.5)	505 (83.7)
Median, mo (95% CI)	NE (10.4, NE)	6.5 (5.8, 8.7)	6.6 (5.7, 8.1)	5.0 (4.1, 6.0)	6.6 (5.7, 7.8)	6.3 (5.9, 7.0)
KM Estimates (95% CI)						
6-Month	80 (71, 87)	55 (47, 62)	55 (48, 62)	39 (28, 50)	54 (46, 62)	53 (49, 57)
1-year	55 (36, 70)	30 (23, 37)	31 (24, 37)	18 (10, 27)	28 (21, 35)	28 (25, 32)
2-year	NE	22 (16, 28)	23 (17, 29)	10 (05, 19)	17 (12, 24)	20 (16, 23)
Median, mo	NE	6.5 (5.8, 8.7)	6.6 (5.7, 8.1)	5.0 (4.1, 6.0)	6.6 (5.7, 7.8)	6.3 (5.9, 7.0)

Key: CI, confidence interval; KM, Kaplan-Meier; mo, months; NE, not evaluable.
Source:

Figure 11: Comparison of OS between ZUMA-1 (mITT, Phase 2 primary analysis) and SCHOLAR-1



Key: CI, confidence interval; mITT, modified intent-to-treat; mo, months; OS, overall survival.

Survival by response

A summary of OS by response, with survival derived from time of response for responding patients in SCHOLAR-1, is presented in Table 14. This analysis was conducted in the subset of SCHOLAR-1 patients in the survival RR analysis set who have non-missing response and response dates (n=372 subjects). This subset is used because survival time is landmarked from the time of response and hence a response date is required. As indicated, responding subjects experience longer survival than non-responding subjects, with subjects who attain CR experiencing 14.9 months median overall survival, and 1- and 2-year survival rates of 56% and 40%, respectively. This supports the message from the Maurer study, that there are a proportion of patients who achieve CR who are able to maintain this response long-term and be considered cured. The results from the ZUMA-1 study have higher survival rates at 6- and 12-months for CR patients, but the main benefit is from the increasing proportion of patients that are able to achieve CR with axi-cel therapy.

Table 14: OS by response in ZUMA-1 and SCHOLAR-1

	ZUMA-1 (mITT; Phase 2)			**SCHOLAR-1**		
	CR	**PR**	**Non-responder**	**CR**	**PR**	**Non-responder**
N	55	28	18	18	63	291
Alive (censored)	48 (87)	16 (57)	7 (39)	9 (50)	16 (25)	32 (11)
Dead	7	12	11	9	47	259
Median OS, mo	NE (10.4, NE)	NE (5.7, NE)	5.7 (3.7, NE)	14.9	6.9	4.6
6-mo OS	98%	64%	49%	83%	63%	41%
1-year OS	65%	53%	NE	56%	44%	20%
2-year OS	NE	NE	NE	40%	34%	14%
Hazard ratio	NA	NA	NA	Reference	1.8	3.2
p-value	NA	NA	NA		0.1135	0.0008

Key: CR, complete response; mo, months; NA, not applicable; NE, not evaluable; OS, overall survival; PR, partial response;
Source:

Standardised comparison of ZUMA-1 and SCHOLAR-1

Due to the significant heterogeneity discussed previously between ZUMA-1 and SCHOLAR-1 standardised comparisons of response and survival between the two studies were conducted and summarised below.

Standardised comparisons of response (by ECOG status)

Standardising based on refractory subgroup and ECOG provides standardised estimates of response and complete response in SCHOLAR-1 of [redacted], respectively. The standardised comparisons indicate approximately [redacted] in the incidence of response and CR between ZUMA-1 and SCHOLAR-1, with odds ratios for response and complete response of [redacted]. This demonstrates that patients treated with axi-cel are statistically significantly more likely to achieve response or CR than patients treated with SoC.

Table 15: Standardised comparison of ORR and CR in ZUMA-1 and SCHOLAR-1 (including standardisation for ECOG status)

	ZUMA-1 mITT (N=101)	SCHOLAR-1 Response (N=508)	Standardised[a] difference (95% CI)	Standardised[a] ratio (95% CI)	Odds ratio (p-value[b])
ORR[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; ORR, overall response rate.
Notes: a, standardised according to pre-specified stratification factors; b, CMH test stratified based on pre-specified stratification factors; c, for the purpose of comparisons, the response rate in ZUMA-1 is landmarked from the time of SCT for subjects in the SCT strata and therefore is different than that reported for the primary endpoint of ZUMA-1.
Source: ZUMA-1 versus SCHOLAR-1 data on file

Standardised comparisons of survival (by ECOG status)

Standardising based on refractory subgroup and ECOG provides standardised median OS for the SCHOLAR-1 study of 5.8 months, with 3-, 6-, and 12- month survival rates of [redacted], respectively. The standardised difference in median survival time was not estimable because the ZUMA-1 median survival is not

yet reached. The standardized ratios of 3-, 6-, and 12-month survival rates are [redacted], respectively, and the hazard ratio from the Cox model stratified by the covariates used was [redacted]. This indicates that there is a statistically significantly lower risk of death for patients treated with axi-cel.

Table 16: Standardised comparisons of survival in ZUMA-1 and SCHOLAR-1 (including standardisation for ECOG status)

	ZUMA-1 mITT (N=101)	SCHOLAR-1 Survival (N=479)	Standardised difference/ratio (95% CI)
Median OS, months	[redacted]	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]	[redacted]
Stratified Cox model			[redacted]

Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; OS, overall survival.
Source: ZUMA-1 versus SCHOLAR-1 data on file

Standardised comparisons of response (by subsequent ASCT)

Standardising based on refractory subgroup and subsequent ASCT provides standardised estimates of response and complete response in SCHOLAR-1 of [redacted], respectively. The standardised comparisons indicate approximately [redacted] in the incidence of response and CR between ZUMA-1 and SCHOLAR-1, with odds ratios for response and complete response of [redacted]. This demonstrates that patients treated with axi-cel are statistically significantly more likely to achieve response or CR than patients treated with SoC.

Table 17: Standardised comparison of ORR and CR in ZUMA-1 and SCHOLAR-1 (including standardisation for subsequent ASCT)

	ZUMA-1 mITT (N=101)	SCHOLAR-1 Response (N=508)	Standardised[a] difference (95% CI)	Standardised[a] ratio (95% CI)	Odds ratio (p-value[b])
ORR[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; ORR, overall response rate.

Notes: a, standardised according to pre-specified stratification factors; b, CMH test stratified based on pre-specified stratification factors; c, for the purpose of comparisons, the response rate in ZUMA-1 is landmarked from the time of SCT for subjects in the SCT strata and therefore is different than that reported for the primary endpoint of ZUMA-1.
Source: ZUMA-1 versus SCHOLAR-1 data on file

Standardised comparisons of survival (by subsequent ASCT)

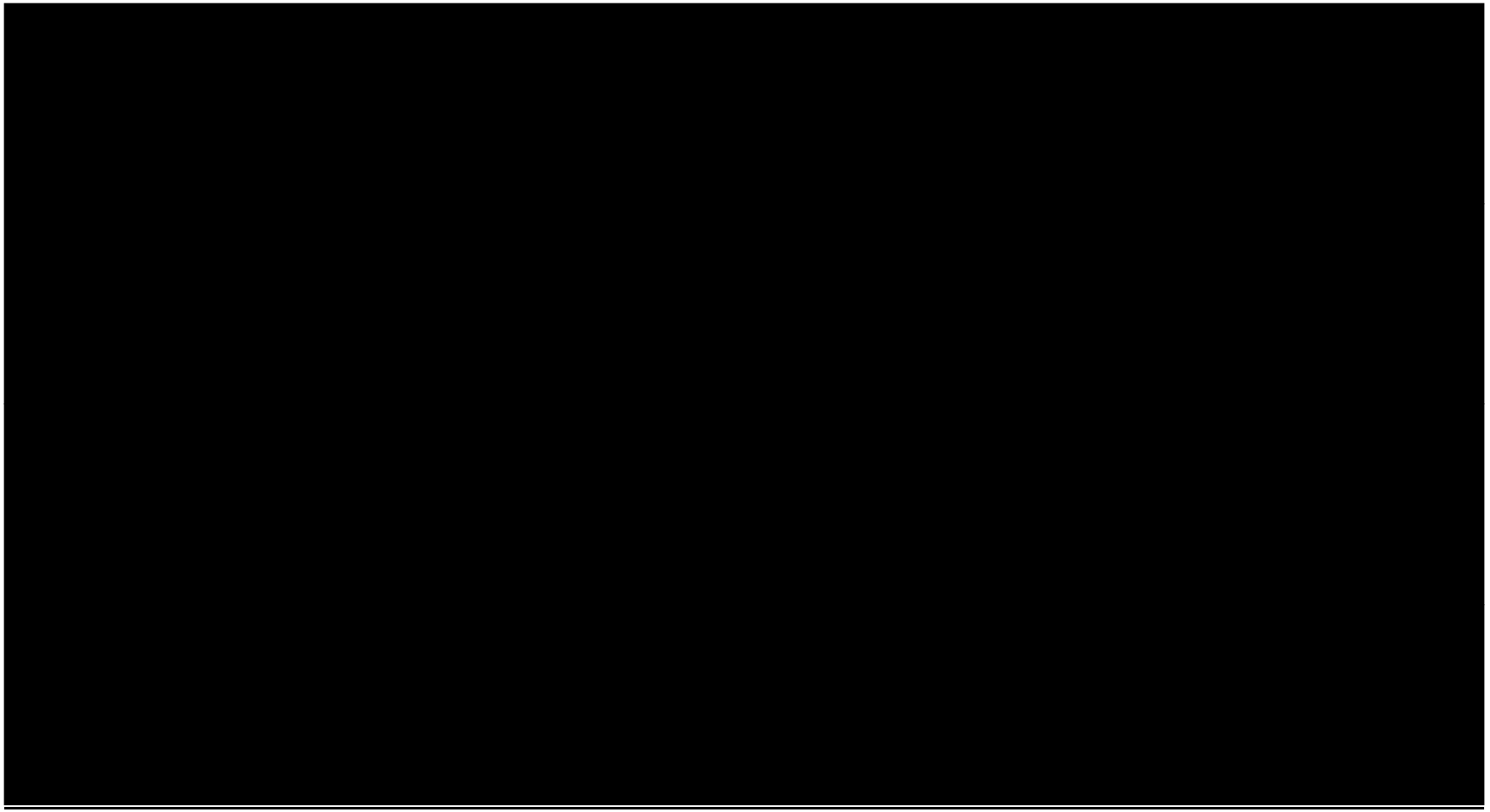
Standardising based on refractory subgroup and ECOG provides standardised median OS for the SCHOLAR-1 study of [redacted], with 3-, 6-, and 12- month survival rates of [redacted], respectively. The standardised difference in median survival time was not estimable because the ZUMA-1 median survival is not yet reached. The standardized ratios of 3-, 6-, and 12-month survival rates are [redacted], respectively, and the hazard ratio from the Cox model stratified by the covariates used was [redacted]. This indicates that there is a statistically significantly lower risk of death for patients treated with axi-cel. Figure 12 presents the KM curve for SCHOLAR-1 versus ZUMA-1 from this analysis and shows a significant improvement in survival for axi-cel patients.

Table 18: Standardised comparisons of survival in ZUMA-1 and SCHOLAR-1 (including standardisation for subsequent ASCT)

	ZUMA-1 mITT (N=101)	**SCHOLAR-1 Survival (N=479)**	**Standardised difference/ratio (95% CI)**
Median OS, months	[redacted]	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]	[redacted]
Stratified Cox model			[redacted]

Key: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat; OS, overall survival.
Source: ZUMA-1 versus SCHOLAR-1 data on file

Figure 12: Overall Survival ZUMA-1 versus SCHOLAR-1 (SCHOLAR-1 Survival-RR Analysis set, ZUMA-1 mITT Analysis Set)



Source: ZUMA-1 versus SCHOLAR-1 data on file

Uncertainties in the indirect and mixed treatment comparisons

The comparison between SCHOLAR-1 and ZUMA-1 makes the best use of the evidence that is available, as by using the patient-level data from SCHOLAR-1, the inclusion criteria could be matched to ZUMA-1. However, there remain a number of key limitations that should be considered when interpreting this evidence, which may have biased results against ZUMA-1. Although the inclusion criteria for the studies were matched, there remains a large amount of heterogeneity between the study populations. It is important to note that the population of ZUMA-1 are a heavily pre-treated population; [redacted] of patients had received four or more prior lines of therapy, compared to only [redacted] in SCHOLAR-1. Heavily pre-treated patients are likely to have already exhausted all other treatments, have few options remaining to them, and would be expected to have poor outcomes. In addition, [redacted] of patients went on to receive subsequent ASCT, compared to [redacted] of patients in ZUMA-1. Therefore, the outcomes in SCHOLAR-1 may not be fully reflective of the SoC outcomes that would be expected in a comparable ZUMA-1 population. In an analysis standardised for patients receiving subsequent ASCT, the outcomes in SCHOLAR-1 were poorer and this resulted in a more favourable comparison between axi-cel and SoC.

It is also important to consider that ZUMA-1 is an open-label single-arm study, which is being compared to a historical cohort consisting of data from two RCTs and two observational, database studies. Such analyses can always be criticised, however the naïve comparison of SCHOLAR-1 compared to ZUMA-1 still shows the significant benefit of axi-cel treatment to these patients, and the analyses attempting to adjust for the imbalances between the patient populations indicates that these benefits are likely to be even greater in reality.

B.2.10. Adverse reactions

The two most commonly encountered toxicities with CAR T-cell therapies are cytokine release syndrome (CRS) and neurotoxicity. CRS is characterised by high fever, hypotension, hypoxia, and/or multiorgan toxicity; neurotoxicity manifests as a toxic encephalopathic state with symptoms of confusion and delirium, and occasionally seizures and cerebral oedema. These toxicities are manageable in most patients, although some require monitoring and treatment in the intensive-care setting, and fatalities can occur, as emphasised by the clinical trial experiences

reported to date. Accurate assessment and prompt management of toxicities can mitigate the adverse outcomes. The overall goal of management is to maximise the benefit from potentially curative cellular therapy while minimising the risk of life-threatening complications, particularly CRS and neurotoxicity.

Furthermore, clinical evidence from ZUMA-1 has revealed that with increasing clinician experience in the use of axi-cel (and in monitoring and treating these AEs), there is a demonstrable decrease in the incidence of these events, and this experience is likely to be of great benefit to the wider clinical community.[5]

Due to the limited clinical experience with axi-cel within the UK, the manufacturer is working with NHS England in order to identify a small number of centres with relevant expertise in managing the side effect profile associated with cell based therapy.

CAR-T-cell-therapy-associated TOXicity (CARTOX) Working Group has been formed in order to develop a consistent approach to the monitoring, grading, and management of toxicities.[59, 60] This group includes representatives from multiple institutions and multiple medical disciplines, including haematological oncology, solid-tumour oncology, stem-cell transplantation, neurology, critical care, immunology, and pharmaceutical sciences. The CARTOX Working Group has now collectively developed recommendations and a practical guide for monitoring, grading, and management of CRS and neurotoxicity in adult patients.[59, 60]

As the majority of AEs associated with CAR T therapy occur soon after infusion, and this is what was observed in the ZUMA-1 study, only detailed safety data are available from the primary analysis (median follow-up 8.7 months). Additional AEs that occurred after this point, for the updated analysis (median follow-up 15.4 months) are presented to support this case.

Summary of safety data from ZUMA-1, primary analysis

A summary of the safety events from the primary analysis (at a median follow-up of 8.7 months) of the Phase 2 part of ZUMA-1 is provided in Table 19. Across the combined 101 treated participants, 96 (95%) experienced a Grade 3 or higher AE. The most commonly occurring AEs are presented in Table 20.

Table 19: Summary of key safety events from ZUMA-1 Phase 2 (mITT population)

	Overall
Patients treated, n	101
Average duration of follow-up (months)	8.7
Patients with an AE, n (%)	101 (100)
Patients with Grade ≥3 AE, n (%)	96 (95)
Patients with an SAE, n (%)	[redacted]
Patients with Grade ≥3 SAE, n (%)	[redacted]
Deaths, n (%)	[redacted]
• Death from PD	[redacted]
• Death due to AE	[redacted]
• Other	[redacted]
Deaths due to treatment-related AEs	[redacted]
Deaths within 30 days of axi-cel transfusion	[redacted]
Deaths after receiving other cancer therapy	[redacted]

Key: AE, adverse events; axi-cel, axicabtagene ciloleucel; mITT, modified intent-to-treat; PD, progressive disease; SAE, serious adverse events.
Source: Neelapu et al., 2017[7]; ZUMA-1 CSR[5]

Table 20: Most frequent Grade ≥3 treatment emergent adverse events occurring in ≥10% of patients and SAEs occurring in ≥2 patients in ZUMA-1 Phase 2 (mITT population)

	Overall (N = 101)
Grade ≥3 AE, n (%)	96 (95)
Neutropenia/neutrophil count decreased	[redacted]
• Neutropenia	[redacted]
• Neutrophil count decreased	[redacted]
Leukopenia/WBC count decreased	[redacted]
• Leukopenia	[redacted]
• White blood cell count decreased	[redacted]
Anaemia	[redacted]
Febrile neutropenia	[redacted]
Neurological events	[redacted]
Thrombocytopenia	[redacted]
Encephalopathy	[redacted]
Lymphocyte count decreased	[redacted]
Hypophosphataemia	[redacted]
Hypotension	[redacted]
Platelet count decreased	[redacted]

Pyrexia	[redacted]
CRS	[redacted]
Hyponatraemia	[redacted]
Hypoxia	[redacted]
Grade 5 AE, n (%)	[redacted]
Any SAE, n (%)	[redacted]
Encephalopathy	[redacted]
Pyrexia	[redacted]
Confusional state	[redacted]
Febrile neutropenia	[redacted]
Lung infection	[redacted]
Atrial fibrillation	[redacted]
B-cell lymphoma	[redacted]
Ejection fraction decreased	[redacted]
Urinary tract infection	[redacted]
Acute kidney injury	[redacted]
Aphasia	[redacted]
Cardiac arrest	[redacted]
Hypotension	[redacted]
Hypoxia	[redacted]
Pneumonia	[redacted]
Somnolence	[redacted]
Agitation	[redacted]
Atrial flutter	[redacted]
Headache	[redacted]
Lactic acidosis	[redacted]
Neutropenia	[redacted]

Key: AE, adverse events; CRS, cytokine release syndrome; mITT, modified intent-to-treat; WBC, white blood cell.
Source: Neelapu et al., 2017[7]; ZUMA-1 CSR[5]

Deaths

Among the 10 patients who underwent leukapheresis, but were not treated with axi-cel, eight died: six patients died due to PD; one patient died from myelodysplastic syndrome (MDS) that occurred 1 year after starting other off-study therapy, and one patient died from tumour lysis syndrome (TLS) that was considered related to conditioning chemotherapy. Further details regarding these patients are presented below.

Among the 101 patients treated with axi-cel, 30 died. Two deaths occurred within 30 days after the axi-cel infusion. One of these two deaths was an AE (pulmonary embolism) deemed unrelated to conditioning chemotherapy or axi-cel; the other event was a death due to PD. Twenty-five of the 30 patients died from disease progression. Two patients died after PD and initiation of other cancer therapy. Three patients had fatal AEs, which are discussed in more detail below.

Changes in AE rates between the interim and primary analysis of ZUMA-1

Throughout the ZUMA-1 study clinician experience in the recognition and management of toxicities increased remarkably as observed from the marked reduction in the incidence of severe CRS and neurotoxicity in the latter part of the study. Compared to patients recruited from the study start until the primary analysis, a there was a [redacted] and [redacted] in patients recruited after the interim analysis. Importantly, there were [redacted] (Table 21).

Table 21: Change in incidence of key adverse events between the interim analysis and the primary analysis of ZUMA-1 Phase 2

Grade of AE, n (%)	Interim analysis (N = 62)	Between interim and primary analyses (N=39)	Primary analysis (N = 101)	Reduction in AEs
Grade ≥3 AE	[redacted]	[redacted]	[redacted]	[redacted]
• Grade ≥3 CRS	[redacted]	[redacted]	[redacted]	[redacted]
• Grade ≥3 neurological event	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥5 AE	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event, CRS, cytokine release syndrome.
Notes: a, fatal events: two axi-cel-related (haemophagocytic lymphohistiocytosis and cardiac arrest in the setting of CRS) and one unrelated (pulmonary embolism).

Cytokine release syndrome (CRS)

CRS, the most-common toxicity of cellular immunotherapy, is triggered by the activation of T-cells on engagement of their T-cell receptors (TCRs) or CARs with

cognate antigens expressed by tumour cells. The activated T cells release cytokines and chemokines as do bystander immune cells. CRS is a clinical constellation of symptoms including fever, nausea, fatigue, myalgias, malaise, hypotension, hypoxia, coagulopathy and capillary leak, and/or multiorgan toxicity. Besides the constitutional symptoms, some severe cases can experience significant hemodynamic instability and or other organ toxicity. Mild-to moderate CRS usually is self-limiting and can be managed with close observation and supportive care. Severe CRS must require intensive medical management with tocilizumab alone or with steroids. Patients at high risk of severe CRS include those with bulky disease, comorbidities, and those who develop early onset CRS within 3 days of cell infusion.[59, 60]

In ZUMA-1 study, overall, [redacted]

The most common CRS symptom of any grade [redacted]

All of the Grade <3 CRS events resolved within a median of 8 days and all CRS events did resolve, with the exception of the two Grade 5 events (hemophagocytic lymphohistiocytosis and anoxic brain injury following cardiac arrest), both of which followed ongoing CRS events that started within the first week after the cell infusion.

Neurological events

Neurotoxicity is another prominent toxicity of CAR-T cell therapy with published reports of 20–64%, including grade ≥3 in 13–52%.[59] It typically manifests as a toxic encephalopathy; the most common symptoms include encephalopathy, headache, delirium, anxiety, tremor, aphasia; other manifestations of neurotoxicity such as decreased level of consciousness, confusion, seizures and cerebral edema have also been observed in clinical trials of CAR-T cells. In general, the mild clinical signs are self-limited and resolve within days; more severe symptoms may require supportive care alone or with dexamethasone and can be complete resolved within 4

weeks. However, some deaths caused by this unexpected toxicity have been documented.[59]

The manifestation of neurotoxicity can be biphasic; the first phase occurs concurrently with high fever and other CRS symptoms, typically within the first 5 days after cellular immunotherapy, and the second phase occurs after the fever and other CRS symptoms subside, often beyond 5 days after cell infusion. The pathophysiological mechanism underlying CRES remains to be determined. Two potential explanations can be postulated – either through passive diffusion of cytokines into the brain or by trafficking of T cells into the CNS. Neurotoxicity is primarily managed with supportive care.[59, 60]

In ZUMA-1 trial, overall, [redacted]. The most common neurologic event of any grade [redacted]

[redacted]

As discussed above, as investigator's experience with axi-cel therapy and with monitoring and managing neurological events increased over the course of the ZUMA-1 study, [redacted] (Table 21).

Cerebral oedema

No cases of cerebral oedema were reported.

Cytopenias

Cytopenias were consistent with the known toxicities of the conditioning regimen of cyclophosphamide and fludarabine. Grade 4 neutropenia, thrombocytopenia, and anaemia occurred in [redacted] of patients, respectively. Prolonged (duration >30 days) Grade 4 neutropenia or thrombocytopenia *occurred in* [redacted] of patients each. It is important to note that [redacted]

[redacted]

The proposed prescribing information recommends monitoring of blood counts during treatment with axi-cel. In the ZUMA-1 trial, patient blood counts were monitored at 2 weeks, 4 weeks, 2 months, 3 months and then every 3 months up to 24 months, following axi-cel infusion. In clinical practice, patient blood counts would be monitored as per local standard practice, as is currently done for SoC chemotherapy treatments.

Infections

[redacted].

[redacted].

[redacted], defined as prior to conditioning chemotherapy and axi-cel infusion. [redacted]

[redacted]

The proposed prescribing information recommends that axi-cel should not be administered to patients with active systemic infections and that prophylactic anti-microbial agents should be administered according to standard institutional guidelines (and this is how patients were managed within the ZUMA-1 trial).

Grade 5 adverse events/Deaths

Overall, [redacted].

Patients unable to receive axi-cel

In total, 111 patients were enrolled in the Phase 2 part of the ZUMA-1 study and all 111 patients were leukapheresed. Eight patients (7%) were unable to progress to conditioning chemotherapy; two patients (2%) died due to progressive disease, four patients (4%) had AEs, and two patients (2%) had non-measurable disease. Therefore, 103 patients progressed to conditioning chemotherapy, and of these patients, 101 went on to receive axi-cel; one patient died due to tumour lysis syndrome, which was considered to be related to conditioning chemotherapy, and one other patient experienced an AE that prevented them from receiving axi-cel.

Summary of safety data from ZUMA-1, updated analysis (N = 108; median follow-up 15.4 months)

After the data cut-off for the primary analysis until the updated analysis, ten patients had serious AEs (including nine infections in eight patients). There were no new events associated with the CRS or neurological events related to axi-cel treatment. Forty-four patients (44%) died from causes that included disease progression (in 37 patients), AEs (in three patients, including two with the above-mentioned axi-cel–related events associated with CRS and one with pulmonary embolism that was not related to axi-cel), and other causes after disease progression and subsequent

therapies that were not related to axi-cel (in four patients). One death that was not associated with axi-cel was previously reported in Phase 1 of ZUMA-1.[55] There were no new deaths from AEs after the primary analysis. No cases of replication-competent retrovirus or axi-cel treatment-related secondary cancers were reported.

No other studies reported additional AEs.

B.2.11. Ongoing studies

Follow-up in the ZUMA-1, Phase 2 study is ongoing.[7]

No other studies investigating axi-cel in patients with R/R DLBCL, PMBCL or TFL are due to provide additional evidence within the next 12 months.

B.2.12. Innovation

Axi-cel is the first in a breakthrough class of CAR T-cell therapies and is an innovative approach that provides complete personalised immunotherapy. Axi-cel is given as a *single infusion* and *single treatment* rather than the recurrent cycles of traditional chemotherapy and their associated toxicity. It offers a significant benefit in the potential treatment landscape for R/R DLBCL, PMBCL and TFL patients, who are ineligible to transplant and associated with a median life expectancy of 3.3 to 6.3 months.[6, 16, 17, 41] Due to elimination of malignant B-cell in the treatment group , axi-cel has been shown to have a durable complete response of 40% and median life expectancy has not yet been reached at 15.4 months. The American Society of clinical Oncology (ASCO) named CAR-T cell therapy the advance of the year.[61]

As described in Section B.1.3, current treatment options for patients with R/R DLBCL, PMBCL and TFL ineligible for ASCT are extremely limited and generally consist of palliative care, with poor outcomes and expected survival as low as 3.3 months.[6] As described in Section B.2.6 and Section B.2.9, patients treated with axi-cel achieve much higher rates of overall response compared to current SoC (82% compared to 26%), with a durable complete response (40% of patients remained in complete response at a median follow-up of 15.4 months).[5] Survival data in the pivotal ZUMA-1 study so far suggests that axi-cel will significantly improve survival outcomes for these patients, for whom few other treatment options remain. Current literature suggests that patients with DLBCL who achieve event-free survival at 24

months following first-line immunochemotherapy treatment have a subsequent OS equivalent to that of the age- and sex-matched general population, which means these patients can be considered to be cured.[48] Long-term follow-up data of patients from the NCI study[57] demonstrated that following axi-cel treatment, patients who achieve CR can experience a durable, long-term response with associated increases in survival; 44% were in ongoing CR between 38+ and 56+ months after axi-cel infusion, and three out of these four patients had recovery of normal B-cells. These data suggest that axi-cel has the potential to increase the OS of R/R DLBCL, PMBCL and TFL patients towards that of the age- and sex-matched general population.

Risks of therapy are known and include CRS and neurologic events that have an early onset, generally within 2 weeks after the therapy, and are mostly reversible (>95%). Alongside the understanding that tocilizumab use does not affect efficacy, strategies have been further developed to identify these AEs earlier and manage them more aggressively, so that the rates of severe CRS and neurologic events have decreased overtime.

Other oncology treatments, such as current chemotherapies and even newer immunotherapies, involve long-term, multiple and regular clinical visits. The potential for patients receiving axi-cel to achieve long-term, durable response and potentially be cured avoids multiple future hospital visits for additional treatments and disease-related monitoring. Therefore, axi-cel treatment visits will have less impact on patients HRQL, and given that the treatment is intended for patients who would otherwise be considered as being at end-of-life (see Section B.2.13), anything that reduces their time in hospital or their number of clinic visits can be considered to be a massive benefit to the patients.[1, 2] These quality of life benefits are unlikely to have been captured in the HRQL/QALY data used in the economic analysis.

In clinical practice, axi-cel will be given as a single-time administration. This means that patient adherence is effectively 100%. Patient compliance is also expected to be high, with 92% of patients identified as suitable to receive axi-cel in the ZUMA-1 study going on to receive treatment.[5] In the Juliet study[62] for the closest alternative CAR T therapy, tisagenlecleucel, this was only 60%. This highlights the consistency and effectiveness of the manufacturing process for axi-cel. As there is the potential

for patients receiving axi-cel to achieve long-term, durable response and potentially be cured, there would be reduced ongoing direct costs expected for these patients after axi-cel administration and AEs have been satisfactorily managed; there will likely be a monitoring period of 1–2 years after axi-cel administration[5], at which point, according to published data, a patient could be considered cured.[1, 2, 48]

Overall, axi-cel has demonstrated a positive benefit-risk profile and offers a new and effective treatment option for patients with relapsed or refractory aggressive B-cell NHL. The intended patient population is well defined and has high unmet medical need, with no curative options, no standard therapy, and short expected survival. The unprecedented and consistent treatment effect observed with axi-cel is a complete step change for these patients and supports recommendation for the use of axi-cel for patients with relapsed/refractory aggressive B-cell NHL who are ineligible for ASCT.

B.2.13. Interpretation of clinical effectiveness and safety evidence

Summary and discussion of the available evidence to support axi-cel

From the ZUMA-1 study results, axi-cel is a highly effective treatment option for patients with R/R DLBCL, PMBCL and TFL who are ineligible to receive ASCT.[7] In the updated analysis (median follow-up 15.4 months), 82% of patients achieved a response, with a durable complete response (40% of patients remained in complete response). Median OS was not reached at 12 months (95% CI: 12.0, not reached) and the OS at 18 months was 52%. This is a significant improvement on the 3.3–6.6 months expected OS with current SoC.[6, 16, 17, 41] For patients achieving CR, 83.1% were still alive at 12 months, highlighting the benefit of axi-cel treatment for these patients. Median PFS in ZUMA-1 was 5.8 months (95% CI: 3.3, not reached) with 41% of patients still progression-free at 15 months. The KM curves for OS and PFS also have long, flat tails, with few events occurring (i.e. few incidents of progression or deaths) towards the end of the curves. This indicates the potential for long term disease free survival and potential cure.

In this disease there is potential for long term survival in those that achieve CR.[14, 48] The evidence from ZUMA-1 indicates that the benefit of axi-cel will be in increasing

the number of patients who are able to reach and remain in CR and are therefore able to experience these long-term survival benefits.

The ZUMA-1 population was a heavily pre-treated patient population, with 69% of patients having received 3 or more prior therapies and therefore the outcomes may underestimate the efficacy in the licensed indication where patients have been less heavily treated.

Axi-cel patients treated in ZUMA-1 are compared to a patient-level pooled analysis of SoC in patients with refractory DLBCL, PMBCL and TFL in SCHOLAR-1, where the ORR was 26%, 7% of patients achieved CR, and the median OS was 6.3 months.[6] In a standardised comparison of ZUMA-1 and SCHOLAR-1 (accounting for patients with ECOG 2-4 in SCHOLAR-1), the median OS in SCHOLAR-1 was only [redacted], suggesting a [redacted] in the risk of death for axi-cel patients. In a standardised comparison of ZUMA-1 and SCHOLAR-1 (accounting for patients receiving subsequent ASCT), the median OS in SCHOLAR-1 was only [redacted], suggesting a [redacted] in the risk of death for axi-cel patients.

The safety profile of CAR T therapy is well described and includes CRS, neurological events, infections and cytopenias. In the ZUMA-1 study 95% of patients experiencing a grade ≥3 AEs (the most important were [redacted]). Established treatment protocols are now in place for the management of CRS, neurological events and cytopenias, and as a result, in the second part of the trial the majority of these events were manageable and reversible within the first month after infusion (see Section B.2.10). Management of these AEs is already available as part of standard practice within NHS England.[1, 2] Axi-cel is also likely to be administered in specialist centres in the UK, which will result in even greater increases in experience in the long-term. This increased experience and shared knowledge is likely to be of additional benefit for clinicians throughout the UK,[1, 2] allowing them to better manage the toxicities associated with CAR T therapies and potentially lead to reductions and improvements in management of these AEs, both when CAR T therapies are introduced with further reductions over time.

Strengths and limitations of the evidence base

There are a number of strengths of the evidence to support axi-cel. ZUMA-1 was a relatively large clinical trial (given the orphan nature of the population of interest) in a population directly relevant to the decision problem, including reasonable numbers of patients of all relevant subtypes (DLBCL, PMBCL and TFL) and with compelling results in a condition with significant unmet medical needs, no curative options, no standard therapy and short expected survival. The results from ZUMA-1 were consistent across all patient subgroups and supports axi-cel as a viable treatment option for the entire population likely to be specified in the marketing authorisation (as per the SmPC). Clinical opinion confirmed that the population treated in ZUMA-1 was reflective of the population anticipated to be treated with CAR T therapy in NHS England.[1, 2] The outcomes used in the trial are consistent with those that would be captured as part of standard practice in NHS England, and clinical opinion confirmed that the results seen in ZUMA-1 would be expected to be the same for patients treated in the UK.[1, 2]

Due to the curative nature of the treatment and the high proportion of patients in the ZUMA-1 trial still alive and in ongoing CR at a median follow-up of 15.4 months, median OS has yet to be reached. This creates some uncertainty in terms of fully assessing the benefits of axi-cel, with the potential to underestimate the efficacy of treatment. The fact that 52% of patients with limited other treatment options, poor expected survival and high unmet need are still alive at 18 months (compared to expected survival of 3.3–6.6 months with SoC) is a significant benefit. The NCI studies[9, 56, 57] provide support to the long-term duration of response observed in ZUMA-1, with 47% in ongoing CR between 7+ and 24+ months and 44% in ongoing CR between 38+ and 56+ months, respectively. UK clinicians agreed that they would expect the long-term DoR data seen in ZUMA-1 to translate to substantial improvements in survival for these patients.[1, 2]

ZUMA-1 was conducted as a single-arm study, which makes comparison to SoC difficult. However, as patients with aggressive B-cell NHL that is refractory or relapsed after two prior therapies have no other curative options and no specified SoC, a single-arm study was considered the most appropriate. Simon et al.[63]

suggest the following criteria for judging whether a single-arm study can support traditional approval, which the data for axi-cel support:

- The drug mechanism of action is supported by strong scientific rationale and/or preclinical data
  - The mechanism of action of axi-cel is via T-cell mediated killing of CD19+ target cells. Pharmacokinetic studies in ZUMA-1 and the NCI study demonstrate levels of anti-CD19 CAR T-cells are associated with objective response. Immune checkpoint inhibitors[64, 65] and blinatumomab are FDA approved therapies that activate or re-direct T-cells to treat cancer. Data from NCI 09-C-0082, the longest ongoing study of anti-CD19 CAR T-cells in B-cell malignancies have demonstrated the potential for anti-CD19 CAR T-cells to induce responses in patients with advanced B-cell malignancies.[9, 56, 57, 66]

- The drug is intended for a well-defined patient population
  - The indicated population to be treated, represents a homogeneous population with respect to outcome, with no curable options or SoC. In clinical practice, these patients are managed with salvage therapies, with limited response and poor survival (ORR, CR and OS in SCHOLAR-1 of 26%, 7%, and 6.3 months, respectively [primary analysis] and 20%, 6%, and 3.9 months, respectively [standardised analysis]).

- The drug produces substantial, durable tumour responses that clearly exceed those offered by any existing available therapies
  - The results presented in Section B.2.6 and B.2.9 and summarised at the beginning of Section B.2.13 show that axi-cel demonstrates substantial and durable tumour response that clearly outweigh outcomes currently experienced by patients treated with SoC.

- The benefits outweigh the risks
  - The benefits of axi-cel outweigh the risks. Axi-cel is administered as a single dose following conditioning chemotherapy, and the majority of AEs, which can be severe, occur within 30 days of infusion, are well defined, generally reversible, and manageable, with no apparent long-term consequences other than B-cell aplasia. The rates of severe CRS and neurologic events decreased

over the course of the trial. (See Section B.2.10 and the summary at the beginning of B.2.13).

Limited HRQL data are available for patients with R/R DLBCL, PMBCL and TFL. The analysis performed on the safety management cohort of ZUMA-1 contains the first set of health utility values that will be published for this population. However, this analysis only contains small patient numbers, and therefore, the results are difficult to interpret. Discussion with UK clinical experts confirmed the assumption that CR implies the disease no longer adversely impacts patient's HRQL;[1] therefore, the substantial proportion of patients achieving a durable CR when treated with axi-cel are also likely to benefit from associated significant improvements in HRQL. Clinical experts also agreed that after 2 years in CR a patient at this stage of disease could be considered cured,[1] which supports the other available evidence in this area.[48] Therefore, it can be assumed that patients who remain in CR for 2 years and beyond would return to a similar level of HRQL as patients in the general population.

There are a number of difficulties in comparing axi-cel to SoC. Given the lack of availability of studies in a comparable population to ZUMA-1 and the large amounts of heterogeneity between ZUMA-1 and the studies identified in the clinical SLR, the approach was taken to use studies for which patient level data were available, to match the inclusion criteria to ZUMA-1 (SCHOLAR-1). However, although this comparison matched on inclusion criteria and is the most appropriate comparison to consider, there remains a large amount of heterogeneity between the study populations, which may have biased the results against ZUMA-1. The population of ZUMA-1 are a heavily pre-treated population; [redacted]. Heavily pre-treated patients are likely to have already exhausted all other treatments, have few options remaining to them, and would be expected to have much poorer outcomes. Therefore, the outcomes in SCHOLAR-1 may not be fully reflective of the SoC outcomes that would be expected in a comparable ZUMA-1 population. Also, [redacted] of patients in SCHOLAR-1 went on to receive subsequent ASCT, compared to [redacted] patients in ZUMA-1. This is likely to have improved outcomes for SCHOLAR-1 patients. In an analysis standardised for patients receiving subsequent ASCT, the outcomes in SCHOLAR-1 were poorer and this resulted in a more favourable

comparison between axi-cel and SoC (see Section B.2.9). However, the naïve comparison of SCHOLAR-1 compared to ZUMA-1 still shows the significant benefit to these patients of axi-cel treatment, and the analyses attempting to adjust for the imbalances between the patient populations indicates that these benefits are likely to be even greater in reality.

Generalisability

The ZUMA-1 trial was conducted in 24 centres; 23 across the US and one in Israel. As this represents a large geographical area, and manufacturing of axi-cel was so successful (92% of patients identified to receive axi-cel went on to receive treatment) and was delivered to patients within such a short time frame (median: 17.0 days; range: 14–51 days) no issues are anticipated in providing axi-cel to patients in the UK. However, as there were no UK centres, no UK patients were enrolled in the study. The median age of patients in the ZUMA-1 trial was 58, which is similar to the median age for these patients in clinical practice, which is 61 for patients with DLBCL and TFL.[14] PMBCL patients are generally younger, with a median age of 35,[23-25] and this could have pulled down the median age in ZUMA-1. UK clinical experts agreed that the patients treated in ZUMA-1 were likely to be reflective of the UK patients who would be considered for treatment with CAR T therapy and they believed that the ZUMA-1 trial population overall was generally reflective of patients who would be seen in clinical practice.[1] Therefore, they also assumed that the treatment outcomes seen for patients in ZUMA-1 would be what they would expect for patients treated in NHS England.[1]

Axi-cel as an end-of-life therapy

Table 22 presents the evidence to support axi-cel as an end-of-life therapy, in line with the NICE criteria. In summary, with current SoC, median OS for R/R DLBCL, PMBCL and TFL patients is as low as 3.3 months and is therefore within the 24 months normally specified by NICE. Median OS was not reached in the ZUMA-1 study, but with a lower 95% confidence interval of 12.0 months and an 18-month OS rate of 52%, it seems that axi-cel is likely to offer an extension to life of greater than the 3 months specified by NICE. Therefore, axi-cel should be considered as an end-of-life therapy, in that it is a treatment option for patients who would otherwise be considered as being at end-of-life; however, it should be seen as a definitive,

curative therapy for those patients who are able to achieve CR and maintain this response beyond 2 years. The number of patients eligible to receive axi-cel every year is limited (approximately 970 patients in 2018).

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	• Canadian database study in R/R DLBCL patients ineligible for ASCT, median OS: 3.9 months[16] • CORAL study in R/R DLBCL patients who received third-line therapy but not ASCT, median OS: 3.3 months[17] • SCHOLAR-1 study of SoC in patients with refractory DLBCL, PMBCL or TFL, median OS: 6.3 months[6] • SCHOLAR-1 study matched to the ZUMA-1 trial population, median OS: 3.9 months The references above indicate an extremely limited life expectancy with SoC for the indicated patient population; within the 24 months suggested to be considered as an end-of-life therapy.	Section B.1.3 (page 16)
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	Median OS for SoC in the SCHOLAR-1 study was 6.3 months (95% CI 5.9, 7.0). Median OS for axi-cel in the ZUMA-1 study was not reached; however, the lower 95% confidence interval was 12.0 months with an 18-month OS rate of 52%, suggesting that, if current survival trends continue, the improvement in survival with axi-cel compared to SoC was >5.7 months (with possible median survival >18 months). When a standardised comparison of ZUMA-1 and SCHOLAR-1 was conducted to account for imbalances in the patient populations, the median OS in SCHOLAR-1 was 4.0 months, suggesting that, if current survival trends continue, axi-cel would improve OS by at least 8 months.	Section B.2.9 (page 52)
Key: ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; NHS, National Health Service; OS, overall survival; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapsed or refractory; SoC, standard of care; TFL, transformed follicular lymphoma.		

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology appraisal).
- See section 3.1 of the user guide for full details of the information required in appendix G.

A systematic review of the published literature was conducted to identify all relevant economic evaluations/modelling studies for the treatment of adult patients with R/R diffuse large B-cell lymphoma (DLBCL).

The search was conducted on 27 September 2017 using the following electronic databases:

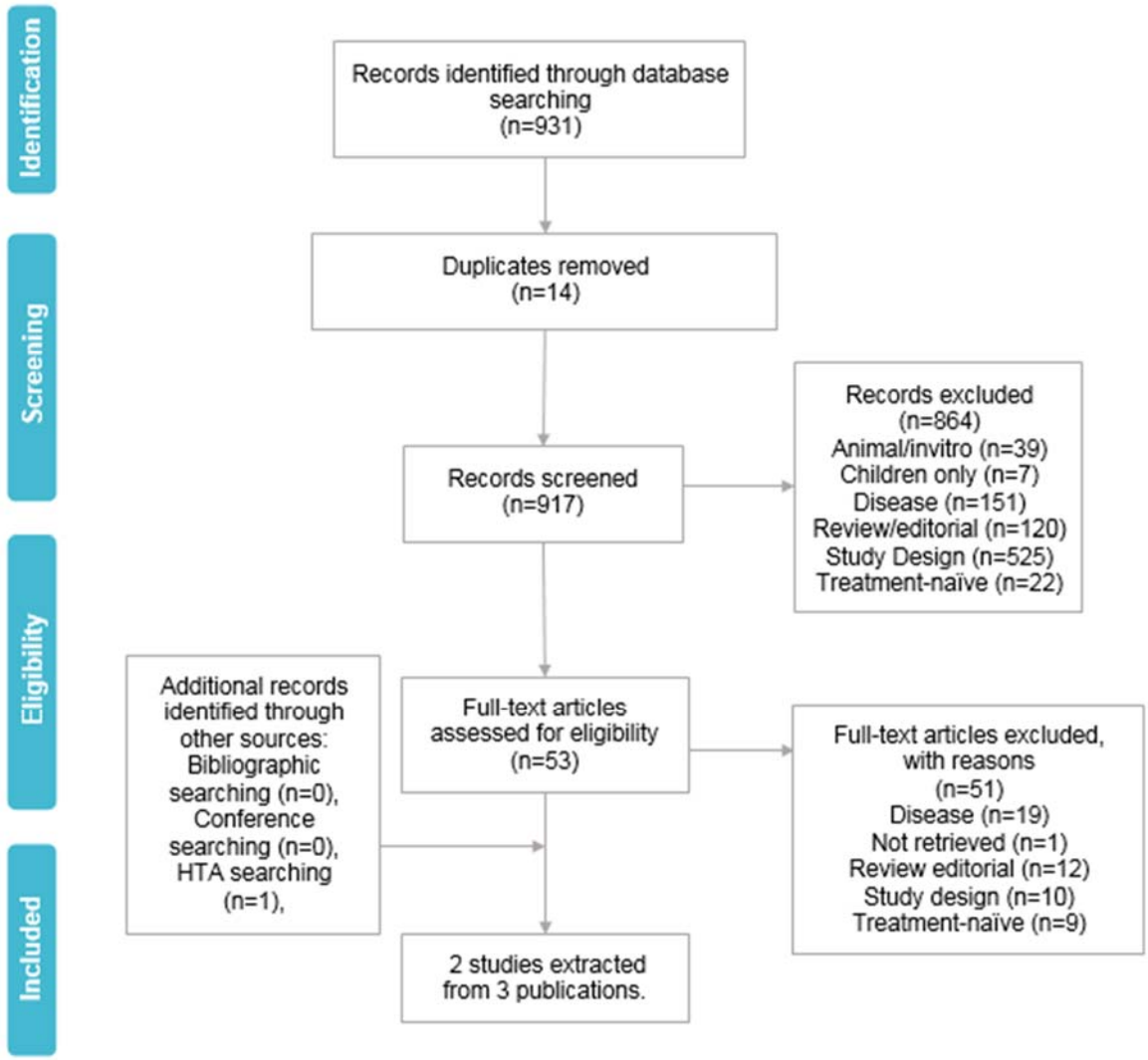
- MEDLINE and Embase (using Embase.com)
- MEDLINE In-Process (using Pubmed.com)
- EconLit (using Ebsco.com)
- The Cochrane Library (using wiley.com), including the following:
  - National Health Service Economic Evaluation Database
  - Health Technology Assessment Database

Additionally, conference proceedings from the last 2 years (2016–2017) and data available on HTA websites were searched to identify recently completed or ongoing studies of interest.

A total of 931 potentially relevant papers or abstracts were identified for this review. Fourteen duplicate records were excluded. After preliminary screening of abstracts, 864 records were excluded, and 53 records were included for secondary screening. After secondary screening of full text articles, 51 studies were excluded. One study was identified from HTA or conference searches. Due to the publication of multiple articles for the same study, 2 studies were extracted from 3 publications.

Figure 13 presents the PRISMA flow diagram of studies identified for the cost-effectiveness review.

Figure 13: PRISMA flow diagram for cost-effectiveness studies



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HTA, health technology assessments.

A summary of the published cost-effectiveness studies is presented in Table 23.

Table 23: Summary list of published cost-effectiveness studies

Study	Year	Model settings	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Kymes et al.[67]	2012	• Perspective: Societal perspective • Time horizon: Life time • Cycle length: 1 year	The model is made up of 8 health states: • 1st apheresis • 2nd apheresis • 3rd apheresis • 4th apheresis • rescue • transplant • recurrence • death	• G-CSF: 5.05 • G-CSF + plerixafir: 6.80	• G-CSF: $67,730 • G-CSF + plerixafir: $93,180	G-CSF + Plerixafor: $14,574
NICE [TA306][45]	2014	• Perspective: Payer's (NHS) perspective • Time horizon: Life time (23 years) • Cycle length: 1 week	The model consists of 4 health states: • Stable/PFS, on 3rd or 4th line treatment • Stable/PFS, discontinued 3rd or 4th line treatment • Progressive/relapsed disease • Death	• TPC: 0.83 • Pixantrone: 1.25	• TPC: £52,953 • Pixantrone: £62, 836	Pixantrone: £23,800

Key: ICER, incremental cost-effectiveness ratio; G-CSF, granulocyte colony-stimulating factor; PFS, progression-free survival; QALY, quality-adjusted life years; TPC, treatment of physician's choice.

Full details of the systematic review methods and results are provided in Appendix G.

B.3.2. Economic analysis

A de novo model was built to assess the cost-effectiveness of axi-cel in the treatment of adult patients with R/R DLBCL, primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL) who are ineligible for autologous stem cell transplant (ASCT).

Identified previous cost-effectiveness models did not assess CAR T therapies and may not be appropriate to model axi-cel, which has a very different mechanism of action and superior efficacy compared to current standard of care (see Section B.2). Therefore, a de novo model was developed.

More recently, NICE commissioned the Centre for Reviews and Dissemination/Centre for Health Economics, University of York (the York team) to explore the suitability of current NICE technology assessment guidelines for the assessment and appraisal of regenerative medicines and cell therapy products (e.g. CAR T therapy). As a result, the York team published a report detailing the findings, which also included two examples of de novo cost-effectiveness models for CAR T therapy for the treatment of acute lymphocytic leukaemia (ALL) as a "bridge" to stem cell transplant (SCT) or with "curative intent".[68] This report and the de novo models developed will be referred to as the York study in this document. Although the cost-effectiveness models were based on hypothetical data, these models, especially the model for the CAR T therapy with "curative intent", are highly relevant to this analysis. Therefore, the de novo model developed for this analysis has drawn heavily on the York study.

Patient population

As outlined in Section B.1.1, in accordance with the anticipated European licence, axi-cel is indicated for [redacted]

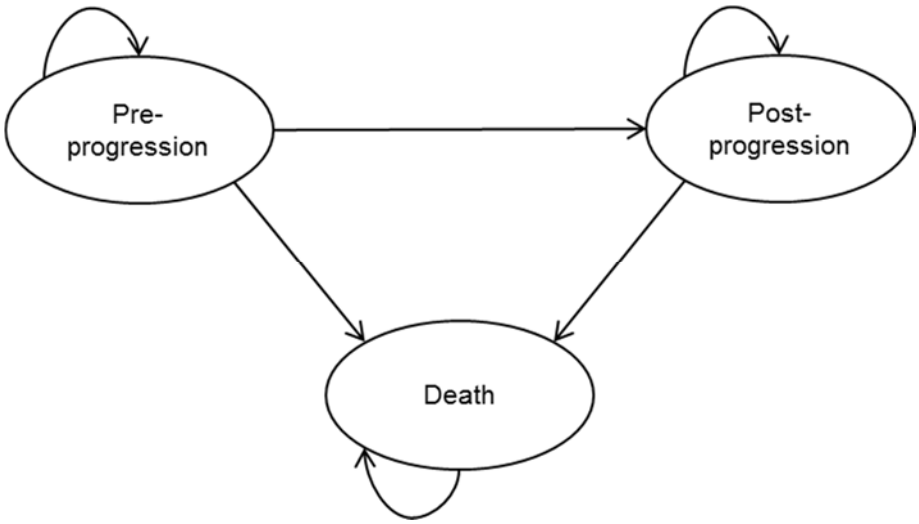
The chosen population is in line with what was discussed in the decision problem and the scope, and reflects the population of ZUMA-1, from which efficacy and safety data for axi-cel are derived.

Model structure

A partitioned survival model with three health states (pre-progression, post-progression and death) was selected as the model structure. The three-state partitioned survival model is widely used in oncology modelling, including NICE submissions[69], and is also the method used by the York study for the modelling of CAR T therapy with "curative intent".[68] A state transition approach is not used for this analysis because the lack of PFS data in the SCHOLAR-1 study (which provides efficacy data for the comparator arm), and hence it is not possible to directly estimate pre-progression survival or post-progression survival, which are required for the state transition model for the comparator arm. Furthermore, the state transition approach assumes that OS is dependent on PFS (i.e. post progression survival is explicitly used to model the transition probabilities from progressed to death), which is not in line with the expected long-term survivors in the axi-cel arm.

All patients enter the model in the pre-progression health state, having progressed on previous treatment(s) for either DLBCL, PMBCL or TFL. Patients remain in the pre-progression health state until they experience disease progression or die. Once patients enter the post-progression state, where they remain until death. The model structure is presented below (Figure 14).

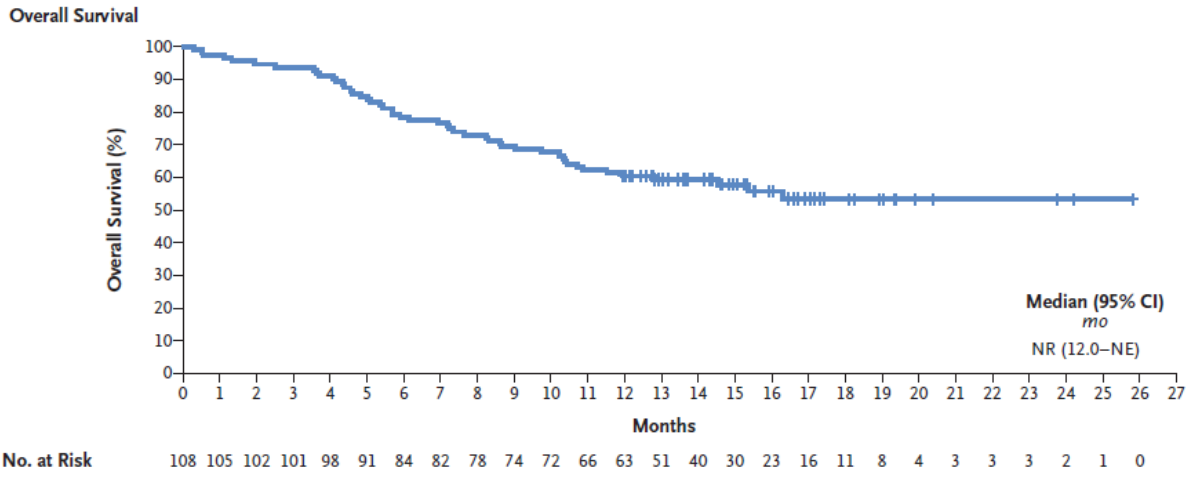
Figure 14: Model structure

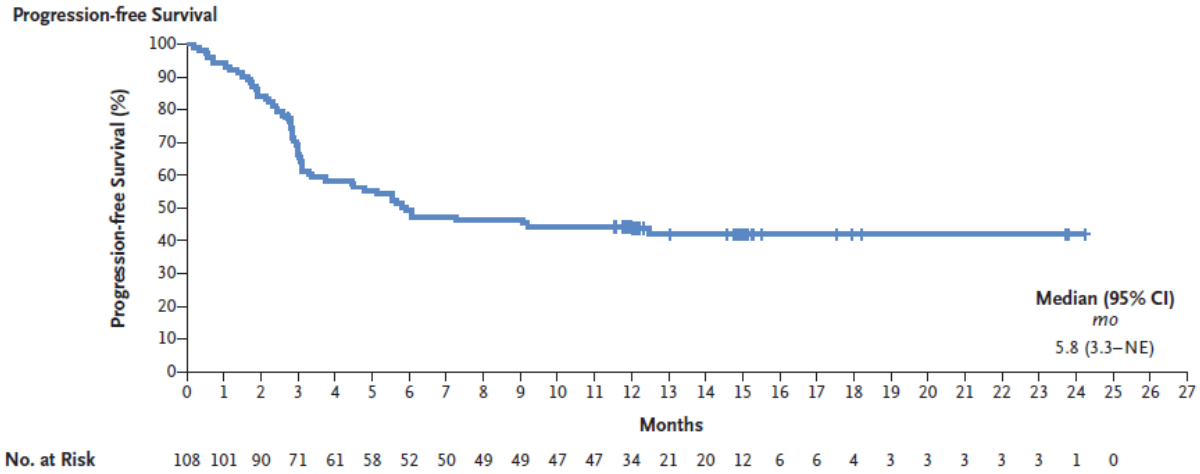


In a partitioned survival model, OS and PFS are modelled independently and the proportions of patients who are progression-free, progressed and dead over time are derived directly from the OS and PFS curves which are calculated as “PFS”, “OS – PFS”, and “1-OS”, respectively.[69]

The OS and PFS KM data for axi-cel based on the latest ZUMA-1 combined Phase 1 and 2 data cut (August 2017) are presented in Figure 15.[7] The corresponding hazard plots are presented in Figure 16. Despite the relatively short follow-up period and small number of patients at risk, it seems a plateau began to emerge in the PFS data from around 6 months, and a similar trend for OS also seems to be evident after around 16 months. The flat tails of OS and PFS are suggestive of a proportion of patients experiencing long-term remission and survival.

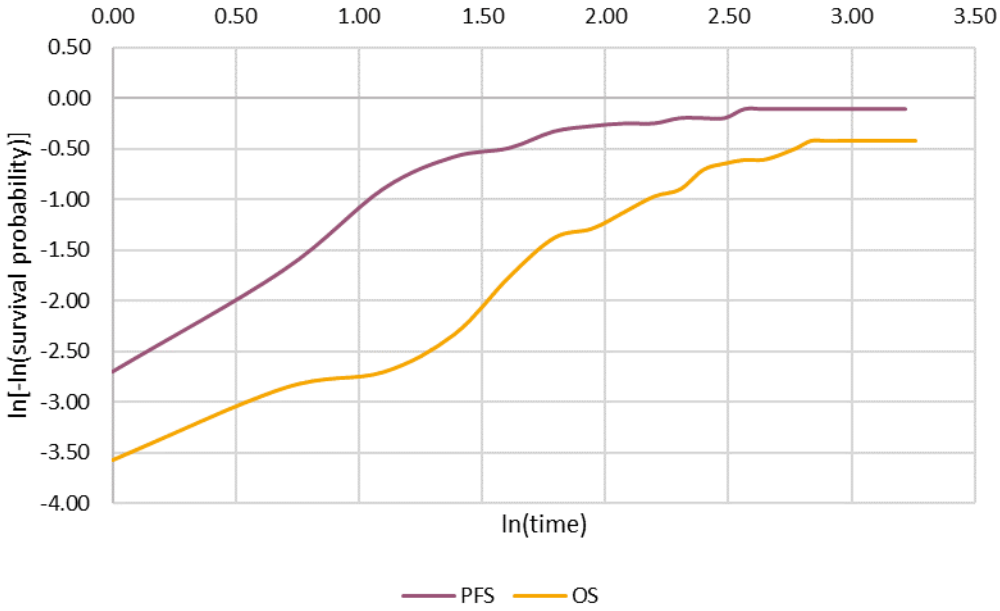
Figure 15: OS and PFS in ZUMA-1 combined Phase 1 and 2 (August 2017 data cut)





Key: PFS, progression-free survival; OS, overall survival.
Note: OS and PFS data are from the 12-month data cut.

Figure 16: OS and PFS in ZUMA-1 combined Phase 1 and 2: cumulative hazard plots



Key: PFS, progression-free survival; OS, overall survival.

Modelling OS for axi-cel

The modelling of OS for axi-cel is based on the patient level data collected in the latest combined Phase 1 and 2 ZUMA-1 data cut (August 2017).[7] All survival analyses for axi-cel were conducted using the modified intent-to-treat (mITT) population from combined Phase 1 and 2 of ZUMA-1 (N = 108; i.e. those patients

who received at least 1 x 10^6 anti-CD19 CAR T-cells/kg body weight). This population will be referred to as Phase 1/2 ZUMA-1 in subsequent sections.

As stated above, the partitioned survival approach is used whereby OS is fitted independently (from PFS). The steps and processes suggested in TSD 14 were followed for the choice of appropriate modelling and extrapolation methods.[70] Specifically, the visual fit, statistical fit and clinical plausibility are all considered when assessing the plausibility of different approaches/models for OS.

Apart from the standard single parametric curves suggested in TSD 14, the more complex method of a mixture cure model[71, 72] was also applied to model OS for axi-cel. Regarding the statistical model's name, "cure" relates to the assumption that a proportion of patients will experience long-term remission and thus will have a mortality rate equivalent to the age and sex matched population. The mixture cure model has been used as the base case method because: (i) there is a strong biomedical rationale for believing a proportion of those patients treated with axi-cel will have an excellent long-term prognosis (with a risk of mortality similar to the general population, and (ii) the standard parametric curves did not provide a plausible estimate of the OS for axi-cel arm (see Section B.3.3). A mixture cure model is based on clinical rationale and has the potential to more accurately model the OS for axi-cel, especially the tail of the curve, due to the likelihood for a significant proportion of patients being long-term survivors in the axi-cel arm.

A detailed description of the methodology for mixture cure modelling is presented in Appendix L. A similar novel approach was also tested in the York study, where spline models were used to provide more options for the modelling of OS for CAR T therapy.[68] Notably, the spline model in the York study resulted in the most plausible extrapolation of OS (based on hypothetical OS data that have a plateau in the tail) and provided the best statistical fit based on Akaike/Bayesian information criteria (AIC/BIC). Spline models are not used in this analysis as the extrapolations based on spline models rely most strongly on data observed towards the end of the curve due to the fitting of knots, which allow the curve to account for changes in hazard. In the case where data are sparse towards the end of the KM, then the suitability of extrapolations would require careful consideration as these would be informed mostly by the end of the curve. The spline models also do not have a strong clinical

rationale compared to the mixture cure model in this case. The details of the mixture cure model are described in Section B.3.3.

The mixture-cure models fitted to ZUMA-1 data have been published.[73] The updated analysis presented here used a more recent ZUMA-1 data cut-off (August 2017 data cut-off) and explored more parametric options for mixture-cure models. Furthermore, the latest UK general population mortality was used in the model to estimate mortality for "cured" patients.

Modelling OS for the comparator

The modelling of OS for the comparator is based on the patient level data that was collected in the SCHOLAR-1 study.

Subjects in SCHOLAR-1 may be refractory to therapy at multiple times throughout the treatment course. Therefore, refractory subgroup was classified in 2 ways. The first was based on the refractory status at the first time in the treatment course the subject was determined to be refractory ("first refractory categorisation"). The second was based on the refractory status at the last time in the treatment course the subject was determined to be refractory ("last refractory categorisation"). The "first refractory categorisation" maximises the subject cases included in the SCHOLAR-1 analysis. The latter is consistent with how analyses of the ZUMA-1 study were conducted and therefore more appropriate to be used for comparisons of SCHOLAR-1 with the ZUMA-1 study. Based on "last refractory categorisation", 593 SCHOLAR-1 evaluable patients were used in this analysis, among which 562 patients were evaluable for survival.

For the model base case, the SCHOLAR-1 data were adjusted by removing patients with an ECOG score of 2–4. This adjustment was performed because only patients with ECOG 0–1 were recruited in ZUMA-1 trial based on the trial protocol.

Additional to the preferred base case, three further options of SCHOALR-1 data were presented as scenario analyses. The base case and scenarios of SCHOLAR-1 data used in the model are summarised in Table 24.

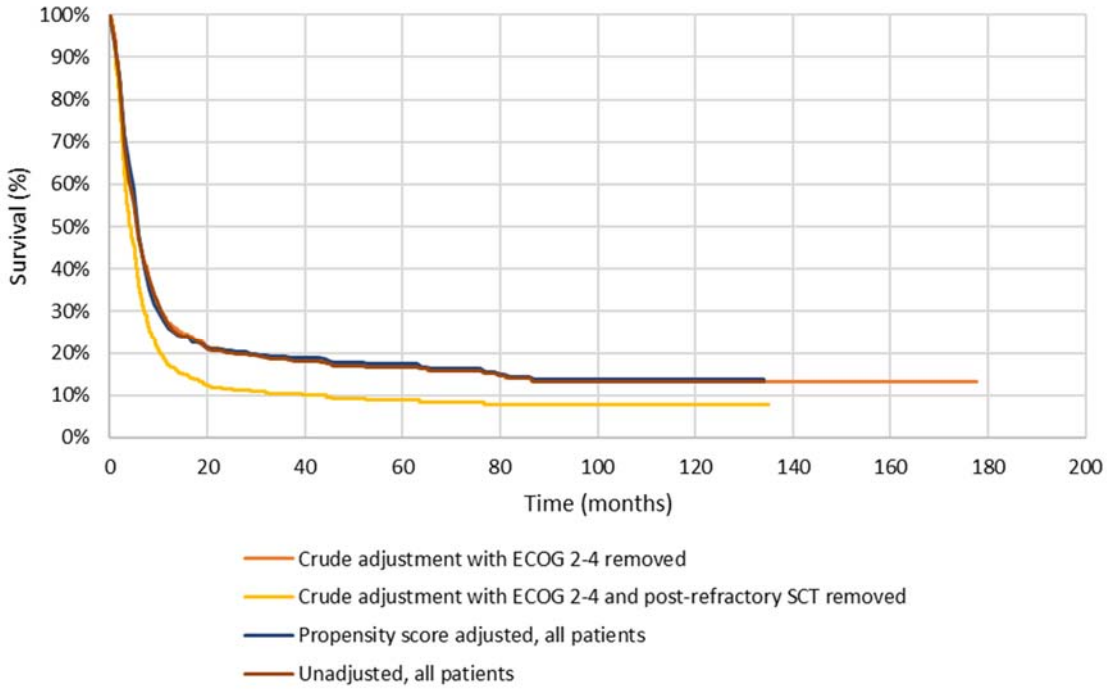
Table 24: SCHOLAR-1 data source scenarios

SCHOLAR-1 data source	Description	Justification	Limitation
Base case: crude adjustment with ECOG 2–4 removed	Subjects with ECOG 2–4 at baseline were removed from the SCHOLAR-1 dataset.	Inclusion criteria of ZUMA-1 only allows ECOG 0–1 patients; The propensity score adjustment performed on all SCHOLAR-1 patients shows little difference compared to unadjusted data (see Figure 17); It is not clear from literature if statistical adjustment (e.g. propensity score) would provide a more robust comparison compared with no adjustment	No statistical adjustment (e.g. propensity score analysis) was performed
Scenario 1: Unadjusted, all patients	No methods of adjustment were made to the SCHOLAR-1 dataset.	This option is provided as the "raw" SCHOLAR-1 data where no adjustments have been made (i.e. no statistical adjustments or removal of subjects).	No crude or statistical adjustments are performed
Scenario 2: Propensity score adjusted, all patients	Propensity score adjustment was performed in which weights were generated for each individual SCHOLAR-1 to adjust for the differences in baseline characteristics between SCHOLAR-1 and ZUMA-1. Further detail on the methodology of this approach is provided in the appendices.	This follows guidance provided in TSD17, which describes methods to reduce the bias of estimating relative treatment efficacy based on single arm trials or observational studies.[74]	The propensity score adjustment was performed to match SCHOLAR-1 data to ZUMA-1 Phase 2 patients (n=101) only; ECOG 2–4 patients were not removed from SCHOLAR-1
Scenario 3: Adjustment with ECOG 2–4 and post-refractory SCT removed	Subjects with ECOG 2–4 at baseline and those who had received post-refractory SCT were removed from the SCHOLAR-1 dataset.	In ZUMA-1, only [redacted] of patients [redacted] received allogeneic SCT post treatment compared to almost [redacted] in SCHOLAR-1. The removal of post-refractory SCT patients in SCHOLAR-1 may improve the	No statistical adjustment was performed; It is not clear if post-refractory SCT patients should be removed from SCHOLAR-1

		comparability between ZUMA-1 and SCHOLAR-1	

The KMs for the different SCHOLAR-1 data sources are presented in Figure 17. The figure shows that removing ECOG 2–4 patients or propensity score adjustment appear to have a minimal impact on KM survival of the unadjusted overall SCHOLAR-1 patients. The only adjustment that resulted in significantly different (worse in this case) KM survival is the adjustment with both ECOG 2–4 and post-refractory SCT patients removed. This is likely due to the removal of patients with long-term survival by excluding patients with successful SCT after the refractory treatment. Because a relatively high proportion of patients in SCHOLAR-1 are given SCT compared to ZUMA-1 ([redacted] respectively), this highlights the bias in the SCHOLAR-1 data due to the improved survival benefit of SCT.

Figure 17: Overall survival in BSC: comparison of SCHOLAR-1 datasets



For the base case, an adjustment was made by removing ECOG 2–4 patients, and no formal statistical adjustment (e.g. propensity score analysis) was performed. Propensity score analysis was only performed on the overall SCHOLAR-1 patients (i.e. not removing ECOG 2–4) and only matched to the ZUMA-1 Phase 2 patients (n=101). However, Figure 17 shows that the propensity score adjustment makes

very little difference to the corresponding unadjusted data. Therefore, it is expected that the propensity score analysis would only make a small difference when applied to a subset of SCHOLAR-1 patients (removing ECOG 2–4) and when matched to combined Phase 1 & 2 ZUMA-1 (n=108). Therefore, the most appropriate base case is considered the crude adjustment with ECOG 2–4 patients removed.

The patient level data (unadjusted or adjusted) for the base case and scenarios are used to fit parametric survival curves to model and extrapolate OS for the comparator arm. The use of patient level data to fit various types of standard and more advanced parametric curves for the BSC arm is one advantage of this analysis compared to other single arm studies where only aggregate data are available for the comparator arm(s). The steps and processes suggested in TSD 14 for the choice of appropriate modelling and extrapolation methods were followed.[70] Specifically, the visual fit, statistical fit and clinical plausibility are all considered when assessing the plausibility of different approaches/models for OS.

Apart from the standard single parametric curves suggested in TSD 14, the more complex method of a mixture cure model[71, 72] was also applied to model OS for BSC, which is consistent to how the axi-cel arm is modelled.

Modelling PFS for axi-cel

The modelling of PFS for axi-cel is based on the patient level data collected in the latest combined Phase 1 & 2 ZUMA-1 data cut (August 2017, n=108), using the partitioned survival approach. In general, PFS has much less impact on the estimated LYs, QALYs and ICERs compared to the OS. There is also more certainty regarding the modelling of PFS compared to OS due to the relative maturity of PFS data (see Figure 15).

To apply the partitioned survival approach, PFS is fitted independently, and the steps and processes suggested in TSD 14 were followed for the choice of appropriate modelling and extrapolation methods.[70] The standard single parametric curves (exponential, Weibull, Gompertz, log-normal, log-logistic, generalised gamma) were fitted, and the curve used in the base case was chosen based on statistical fit, visual inspection and clinical plausibility.

Modelling PFS for the comparator

Progression status was not collected in SCHOLAR-1; therefore, the following 3 options were included in the model for the modelling of PFS for the comparator:

- Apply a time-dependent ratio to the comparator OS to derive PFS, where the time-dependent ratio is derived directly from the modelled OS and PFS for axi-cel (base case)
- Assuming PFS=0 for the comparator (scenario analysis)
- Assuming PFS is the same as OS for the comparator (scenario analysis)

Modelling utility and cost and resource use

Health-related quality of life (HRQL) data were collected in a safety management cohort of ZUMA-1 (87 EQ-5D-5L observations from 34 patients), as detailed in B.3.4. This was used as the base case source for model utilities. Values for patients receiving second- and subsequent-line treatment for renal cell carcinoma (RCC)[75] were used in the scenario analyses. These were 0.76 for the pre-progression health state and 0.68 for the post-progression health state, and were used in the base case in the pixantrone company submission.[45]

To model cost and resource use, costs that were considered in the York report were used.[68] For drug and administration costs, the following sources were used: eMit, NHS reference costs, MIMS, South East London Cancer Network and Thames Valley Strategic Clinical Networks. For model resource use, NICE TA306, the Personal Social Services Research Unit (PSSRU), NHS reference costs and the National Audit Office End of Life Care report were used.

General model settings

The cost-effectiveness analysis assumes a lifetime time horizon (44 years). This approach is considered to be appropriate, given that axi-cel is associated with reduced mortality and expected long-term survivors and NICE guidance states that the time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.

The model uses a cycle length of 1 month. This is anticipated to capture all the relevant changes in the modelled cohort, considering the median OS in the BSC arm

is expected to be approximately 6 months. Half-cycle correction is implemented using the life table method.[76]

Costs and efficacy were discounted at 3.5% in the model base case, based on NICE method guidance[77] and the York study.[68] Due to the potential for axi-cel to provide long-term survival (the model estimates a mean undiscounted OS of >10 years) and HRQL benefits, and given that the total acquisition cost of axi-cel is incurred within the first model cycle, an alternative discount rate of 1.5% was used in a scenario analysis. This scenario analysis is especially relevant if the NICE committee decides that axi-cel qualifies for the use of a 1.5% discount rate based on the NICE method guide (section 6.2.19).[77]

Intervention technology and comparators

Intervention

The intervention, axi-cel, is implemented in the model as per the expected marketing authorisation, which is expected in June 2018, and is reflective of the decision problem described in B.1.1. Axi-cel has been granted Priority Medicines (PRIME) regulatory support for DLBCL in the European Union (EU) and has been designated an orphan product.

Axi-cel is a therapy in which a patient's T-cells are engineered to express a chimeric antigen receptor (CAR), which recognises the antigen CD19 expressed on the surface of B-cell lymphomas and eliminates the target cells. The process of generating and administering the engineered T-cells is described in Section B.1.2.

Axi-cel is administered as a single intravenous infusion in the hospital setting. All patients receive lymphodepleting low-dose conditioning chemotherapy of 500 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine during the 3 days prior to the infusion of anti-CD19 CAR T-cells.

Comparator

The comparator considered in this economic evaluation is BSC as a blended comparator including several therapy options, which are assumed to have the same efficacy and safety. This is in line with the NICE treatment pathway, which recommends that salvage therapy with multi-agent chemotherapy be offered to

individuals who are not eligible for ASCT. The use of BSC as a single comparator was also deemed appropriate based on interviews with UK clinicians.

In light of the recommendation from NICE (TA306) for the use of pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma[45], interviews with UK clinicians were carried out to establish the level of use of pixantrone in clinical practice. The UK clinicians interviewed stated that they did not use pixantrone due to disappointing clinical experience.[78] Therefore, following clinical validation, pixantrone was not included as a potential treatment in the BSC arm or as a separate comparator in the model.

During clinician interviews, several treatment regimens were identified, with no universal standard of care. The Oxford University Hospitals (OUH) NHS Foundation Trust derived a list of regimens used in UK clinical practice. These identified regimens are assumed to have equal efficacy to the regimens used in SCHOLAR-1 (which is used as the source of BSC efficacy) and were validated in the clinical ad-board. The regimens include:

- Gemcitabine and methylprednisolone (GEM)
- Gemcitabine, methylprednisolone and cisplatin (GEM-P)
- Rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone (RGCVP)
- Rituximab, vinblastine and prednisolone (RVP)

B.3.3. Clinical parameters and variables

Clinical data from the Phase 1/2 trial, ZUMA-1, and a multi-cohort retrospective analysis of two randomised studies and two registries, SCHOLAR-1, were used to inform the model base case. Specifically, patient level data from ZUMA-1 were used to inform the efficacy of axi-cel, and patient level data from SCHOLAR-1 were used to derive efficacy for the BSC arm, due to the absence of a comparator arm in ZUMA-1. However, a limitation of SCHOLAR-1 is that it does not contain PFS data.

Data utilised from the trials include:

- OS

- PFS (ZUMA-1 only)
- Body surface area (for drug dosing)
- AE rates (ZUMA-1 only)

The data sources for each clinical parameter are detailed in Table 25.

Table 25: Data sources of clinical parameters used in the model

Model input	Data source
Axi-cel OS	Phase 1/2 ZUMA-1 (n=108), August 2017 data cut-off
Axi-cel PFS	Phase 1/2 ZUMA-1 (n=108), August 2017 data cut-off
BSC OS	See Table 24
Adverse event rates	Phase 2 ZUMA-1 (n=101), January 2017 data cut-off
Proportion of patients who underwent leukapheresis and did not receive axi-cel	Phase 1/2 ZUMA-1 (n=108), August 2017 data cut-off
Proportion of patients who underwent conditioning chemotherapy and did not receive axi-cel	Phase 1/2 ZUMA-1 (n=108), August 2017 data cut-off
Proportion of axi-cel patients who underwent retreatment	Phase 1/2 ZUMA-1 (n=108), August 2017 data cut-off

Efficacy data

For the BSC arm, survival data from SCHOLAR-1 are relatively mature (>85% dead at the end of follow-up [approximately 15 years after diagnosis]). In contrast, survival data derived from ZUMA-1 for axi-cel are immature (48% dead at the end of the 2-year follow-up), and therefore, the appropriate extrapolation of the data was vital to allow the long-term treatment effects to be estimated.

Overall survival – axi-cel arm

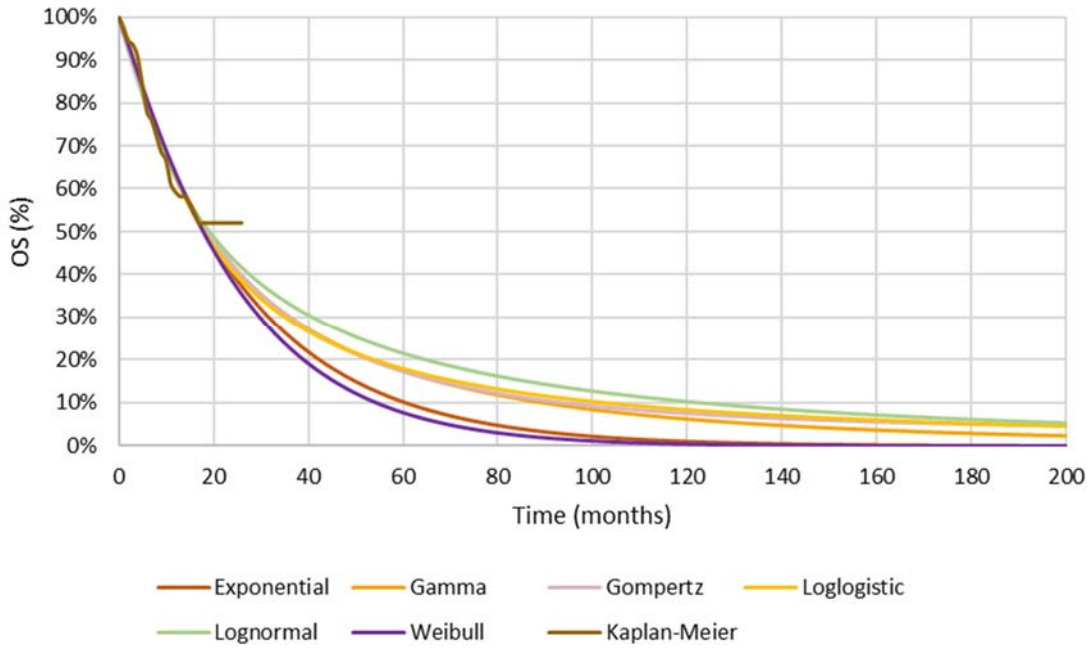
Standard single parametric curves for partitioned survival approach

A partitioned survival model (PSM) with standard single parametric curves has been widely used in oncology modelling and was employed in the York report. A variety of single parametric survival curves were fit and applied to the axi-cel OS data in the model using the coefficient data presented in Table 26. These are presented graphically in Figure 18.

Table 26: Overall survival for axi-cel: PSM with single parametric curves coefficients

Distribution	Parameter	Mean
Exponential	Constant	-3.27
Gamma	Constant	3.05
	ln(sigma)	0.25
	Kappa	0.31
Gompertz	Constant	-0.01
	Gamma	-3.18
Loglogistic	Constant	0.24
	ln(gamma)	2.89
Lognormal	Constant	2.95
	ln(sigma)	0.37
Weibull	Constant	0.07
	ln(p)	3.22

Figure 18: Overall survival for axi-cel: KM with single parametric curves



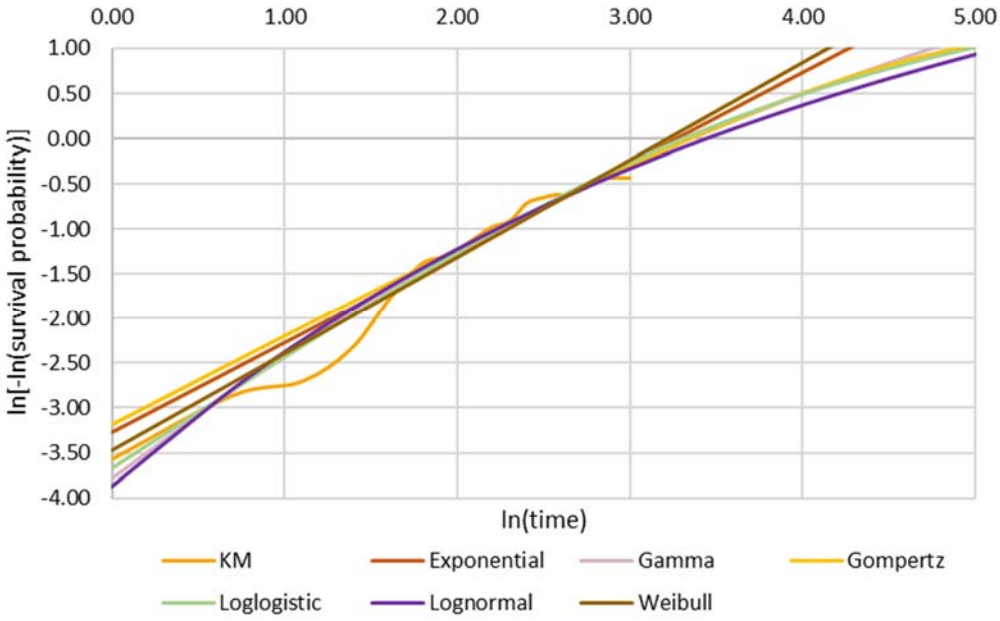
The goodness of fit statistics, in terms of AIC and BIC, are presented in Table 27 for each curve fit option.

Table 27: Overall survival for axi-cel: PSM with single parametric curves goodness of fit statistics

Model	AIC	BIC
Exponential	412.10	414.79
Weibull	413.80	419.16
Gompertz	413.93	419.29
Loglogistic	411.92	417.29
Lognormal	412.54	417.90
Generalised gamma	414.23	422.28
Key: AIC Akaike information criterion; BIC, Bayesian information criterion.		

Plots of modelled cumulative hazard over time and observed cumulative hazard over time are presented in Figure 19.

Figure 19: Overall survival for axi-cel: PSM with single parametric curves log-cumulative hazard plot



Key: KM, Kaplan–Meier.

Based on AIC and BIC statistics, the loglogistic and exponential curve fits provide the best statistical fit. However, none of the standard parametric curves provide a plausible extrapolation of the long-term survival for axi-cel arm. Based on the mechanism of action of axi-cel and expert opinion from clinicians, it is expected that the tail seen towards the end of the observed KM for axi-cel (based on the Phase 1/2

ZUMA-1 data) would continue and plateau as these are likely long-term survivors and would have the same mortality as the gender- and age-matched general population. Furthermore, by Year 10, the estimated OS based on all standard parametric curves are lower than the observed OS for the comparator arm based on the SCHOLAR-1 data; which is deemed clinical implausible given the significant survival benefit for axi-cel compared to SCHOLAR-1 data observed during the ZUMA-1 trial period. Therefore, standard single parametric curves were not deemed clinically plausible, and were therefore not considered further in this analysis.

Mixture cure models for partitioned survival approach

As described previously, a mixture-cure model was used as an alternative method to model OS for the axi-cel treatment arm to be used in the partitioned survival approach. The mixture cure model was estimated using the Phase 1/2 ZUMA-1 patient level data for which a logistic regression was used to model the probability that patients experienced long-term remission, and parametric models were used to estimate the survival for those without long-term remission. In the model, patients with long-term remission were assumed to have the age- and gender-matched background mortality, derived from population life tables.[76] Expert clinical opinion suggests that patients with long-term remission can be assumed to have the same mortality as age- and gender-matched general population. The model has the option to assume additional mortality risk (compared to the general population) for long-term remission patients over and above the general population mortality, and these were tested in the scenario analyses.

Given the expectation and clinical opinion that a proportion of patients experience long-term remission based on Phase 1/2 ZUMA-1 KM data (see Figure 15), and given the plateau shown in the relatively mature SCHOLAR-1 data for BSC patients (Figure 17), the mixture cure model is deemed a more appropriate method for accounting for these long-term survivors. The rationale and methodology behind mixture cure models is further discussed in Appendix L.

The logistic regression model estimated the “cure fractions” (proportion of patients in long-term remission), and three standard parametric models were fitted to estimate survival on the proportion of patients not experiencing long-term remission: Weibull,

gamma and lognormal. The parameter information for each of these is presented in Table 28.

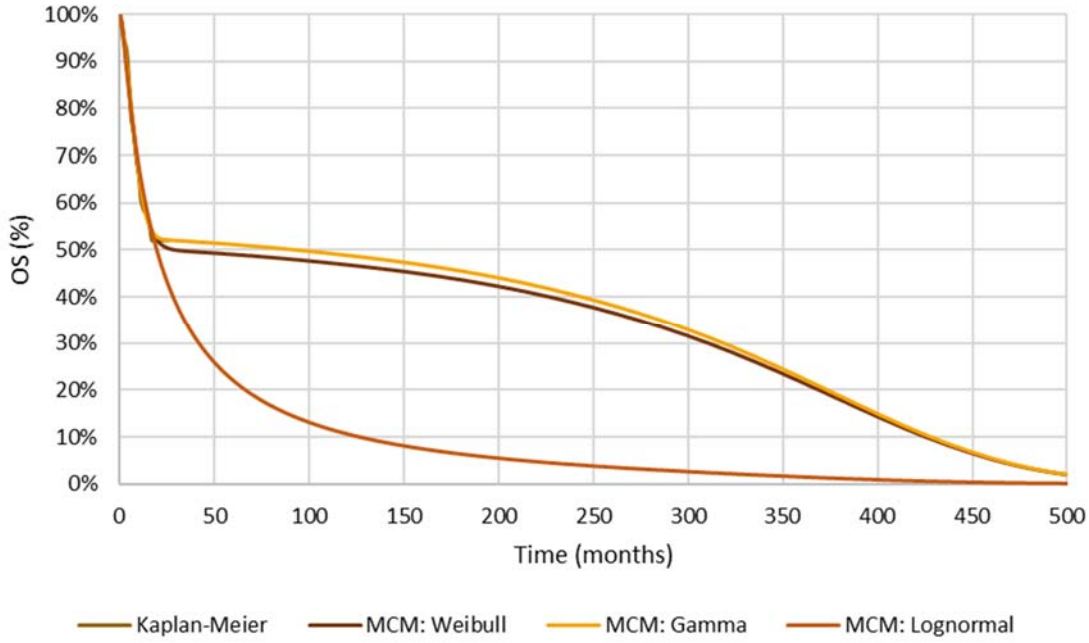
It should be noted that the estimated cured fractions differ dependent on the parametric curve chosen to represent the patients not in long-term remission, as it is the combination of the estimated cure fraction, general population mortality for patients in long-term remission and the estimated survival (Weibull, gamma and lognormal) for patients not in long-term remission that jointly produces the overall OS for the axi-cel arm.

Table 28: Overall survival for axi-cel: mixture-cure model coefficients

Distribution	Parameter	Mean
Weibull	pi	0.02
	Implied “cure fraction”	0.50
	Constant	0.42
	ln(gamma)	0.42
Gamma	pi	0.108
	Implied “cure fraction”	0.53
	Constant	-0.23
	ln(sigma)	-0.61
	Kappa	1.41
Lognormal	pi	-4.27
	Implied “cure fraction”	0.01
	Constant	0.47
	ln(sigma)	0.37

Combining the estimated cure fraction, the general population mortality (for “cured” patients) and the fitted parametric curves for “not cured”, Figure 20 shows the overall estimated OS for each mixture-cure model compared to the observed OS KM.

Figure 20: Overall survival for axi-cel: KM with mixture cure model parametric curves



Key: MCM, mixture cure model.

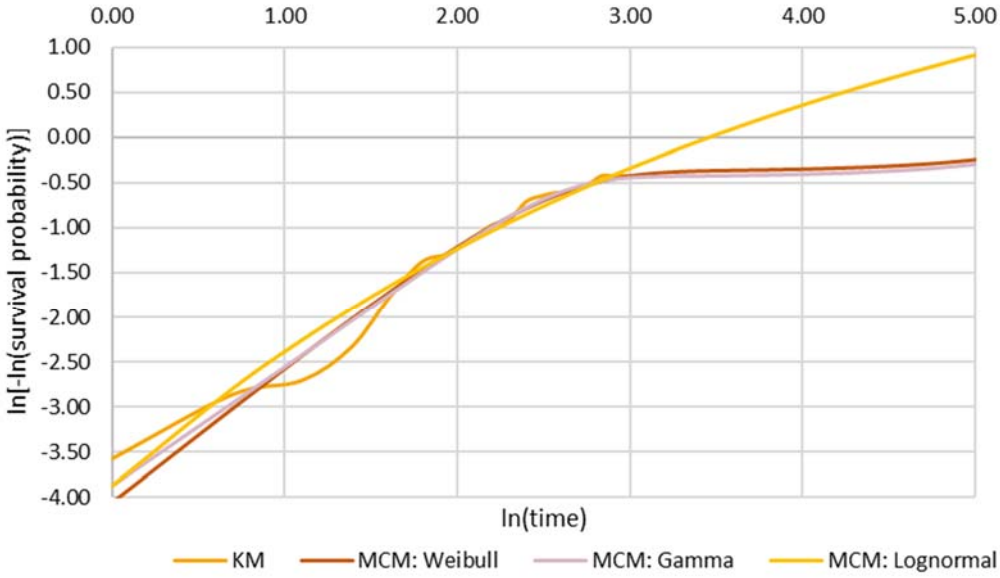
Statistical goodness of fit of each distribution is presented in Table 29 using AIC and BIC statistics.

Table 29: Overall survival for axi-cel: mixture cure model goodness of fit statistics

Model	AIC	BIC
Lognormal	173.83	181.87
Weibull	170.51	178.56
Gamma	171.93	182.66
Key: AIC Akaike information criterion; BIC, Bayesian information criterion.		

Figure 21 shows plots of modelled cumulative hazard over time and observed cumulative hazard over time.

Figure 21: Overall survival for axi-cel: mixture-cure model log-cumulative hazard plot



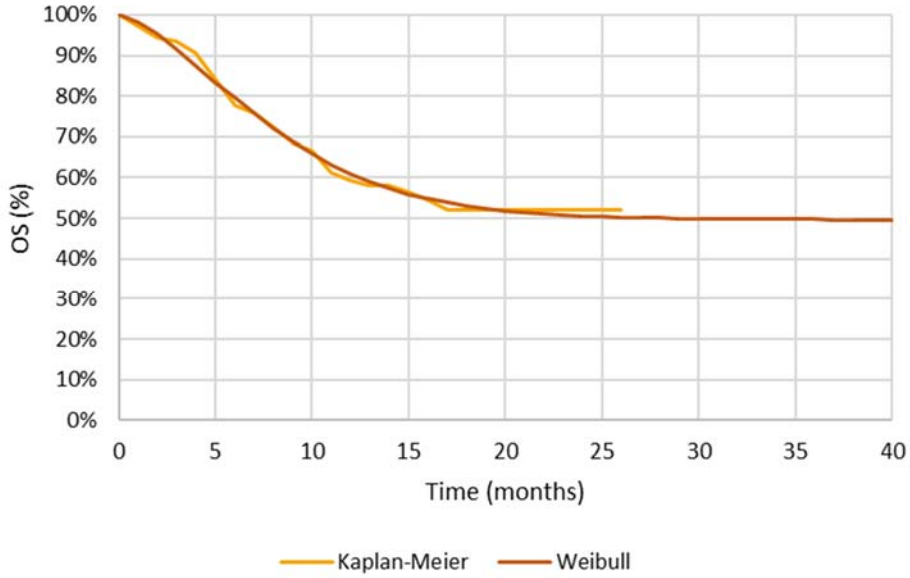
Key: KM, Kaplan–Meier; MCM, mixture cure model.

The comparison of modelled OS with observed OS and modelled cumulative hazard over time with observed cumulative hazard over time suggested that Weibull and gamma mixture-cure models provided plausible OS and hazard predictions compared to the observed KM.

The estimated cure fraction for the lognormal mixture-cure model is close to 1% (see Table 28), and consequently, there is not much difference between the lognormal mixture-cure model and the standard lognormal model. The rationale to assess standard parametric curves applies, and hence, the lognormal mixture-cure model is deemed clinically implausible and excluded from further analyses.

Considering statistical fit, visual inspection and the clinical rationale for a substantial proportion of the treated population having long-term remission, the Weibull mixture-cure model was used in the base case analysis of OS for axi-cel and is presented below in Figure 22.

Figure 22: Overall survival for axi-cel: mixture-cure method



Key: MCM, mixture cure model.

The gamma mixture-cure model is tested in a scenario analysis.

Overall survival – BSC arm

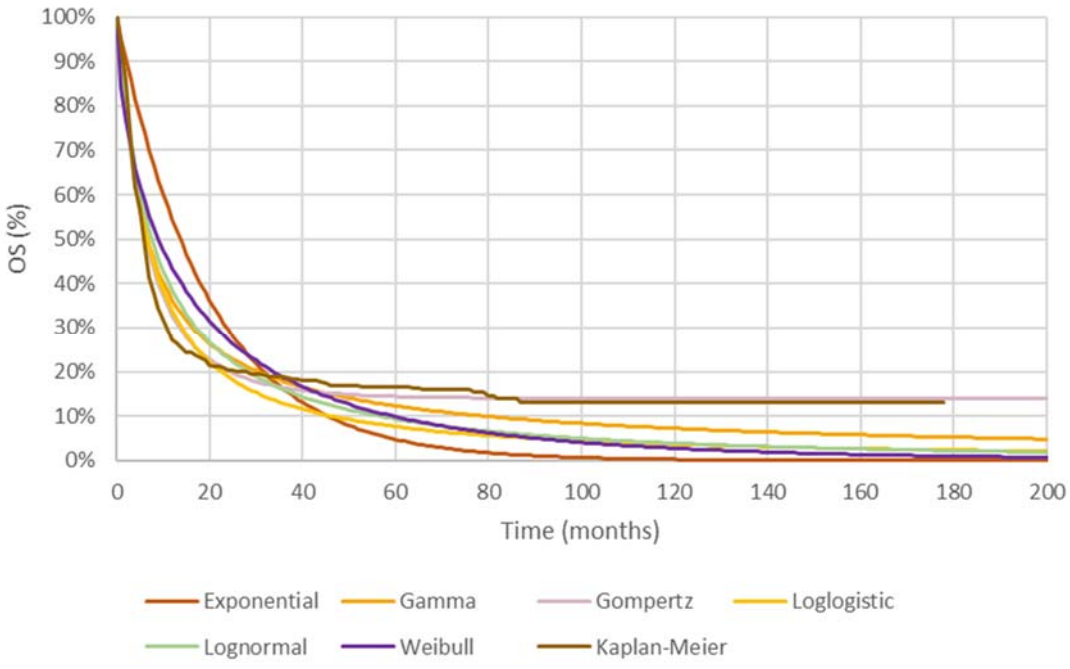
Standard Parametric survival curves for OS for BSC

Using the SCHOLAR-1 patient level data with ECOG 2–4 removed, standard single parametric survival curves were fitted for the modelling of OS for the comparator arm (see Table 30 and Figure 23 for coefficients estimated for each parametric curve and the fitted curves compared to adjusted SCHOLAR-1 OS).

Table 30: Overall survival for BSC: curve fit coefficients

Distribution	Parameter	Mean
Exponential	Constant	-2.51
Gamma	Constant	1.29
	ln(sigma)	0.27
	Kappa	-0.49
Gompertz	Constant	-0.07
	Gamma	-1.68
Loglogistic	Constant	0.33
	ln(gamma)	1.51
Lognormal	Constant	1.60
	ln(sigma)	0.30
Weibull	Constant	-0.37
	ln(p)	2.27

Figure 23: Overall survival for BSC: PSM with single parametric curves log-cumulative hazard plot



AIC and BIC statistics for each curve fit are presented in Table 31.

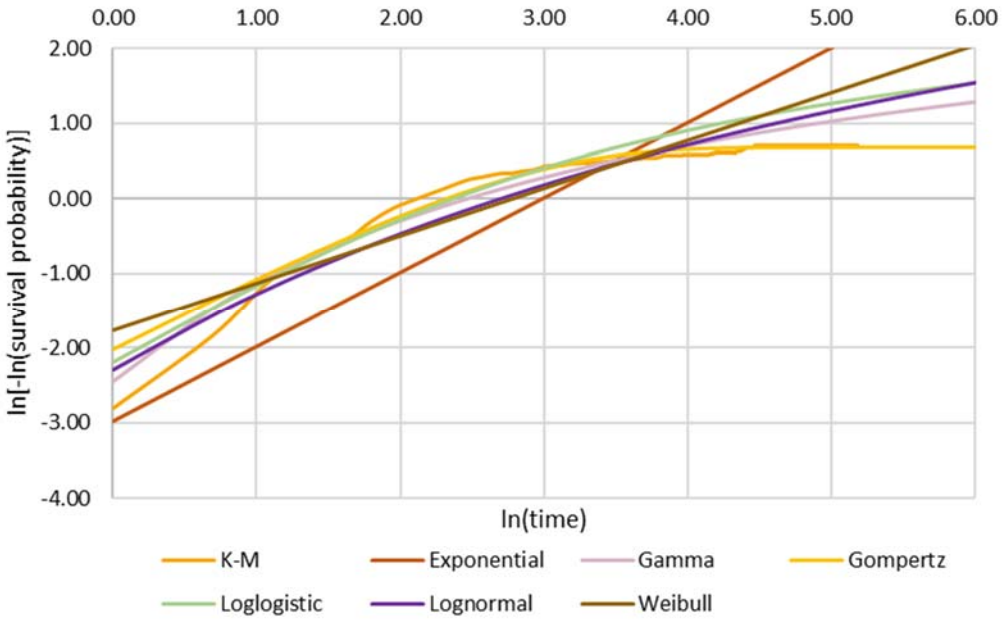
Table 31: Overall survival for BSC: goodness of fit statistics

Model	AIC	BIC
Exponential	3472.15	3476.42
Weibull	3277.14	3285.67
Gompertz	3069.09	3077.63
Lognormal	3128.19	3136.72
Loglogistic	3112.97	3121.50
Generalised gamma	3083.80	3096.60

Key: AIC Akaike information criterion; BIC, Bayesian information criterion; BSC, best supportive care.

Plots of modelled cumulative hazard over time and observed cumulative hazard over time are presented in Figure 24.

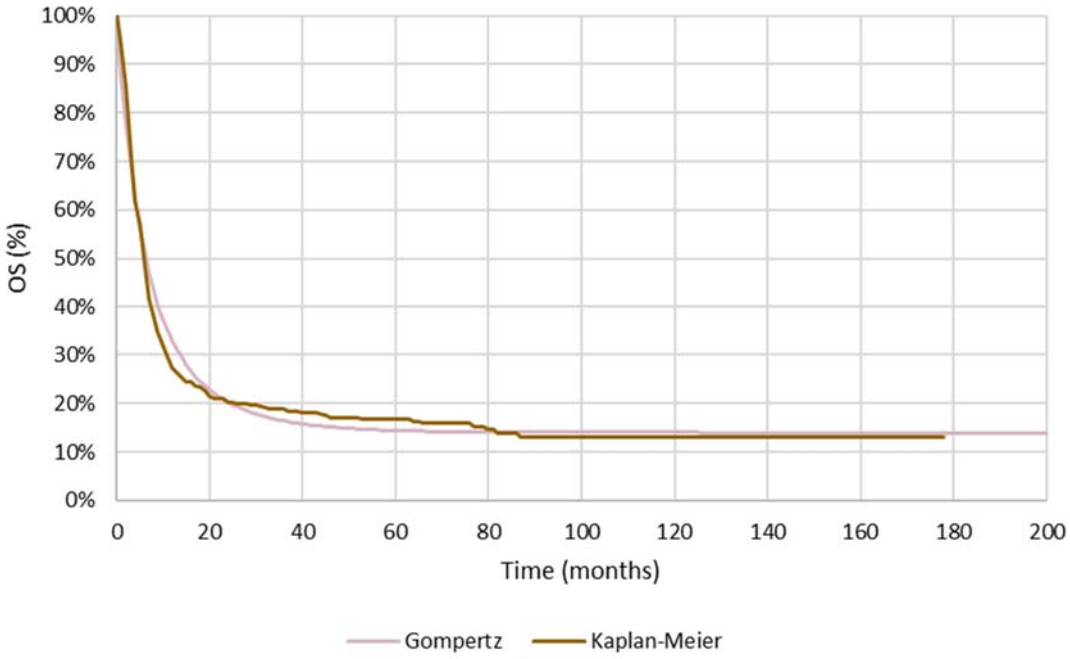
Figure 24: Overall survival for BSC: PSM with single parametric curves log-cumulative hazard plot



Key: K-M, Kaplan–Meier.

Based on AIC and BIC statistical fit, Gompertz is the best fit curve. This is also supported by visual inspection and clinical opinion. Therefore, the Gompertz curve was chosen as the most suitable single parametric curve as it has a good visual fit, reasonably good AIC/BIC statistics and better represents the long-term survivors as observed in the SCHOLAR-1 data. This is presented in Figure 25.

Figure 25: Overall survival for BSC: PSM with single parametric curves selected distribution



For each of the alternative SCHOLAR-1 data sources that are explored as part of the scenario analysis, the Gompertz distribution was also chosen as the best fit to the SCHOLAR-1 OS data based on visual inspection and AIC/BIC statistics.

Mixture cure models for OS for BSC

Consistent with the approach used to model axi-cel OS, a mixture cure model was estimated using the SCHOLAR-1 patient level data with ECOG 2–4 removed and followed the same methodology as for the axi-cel arm.

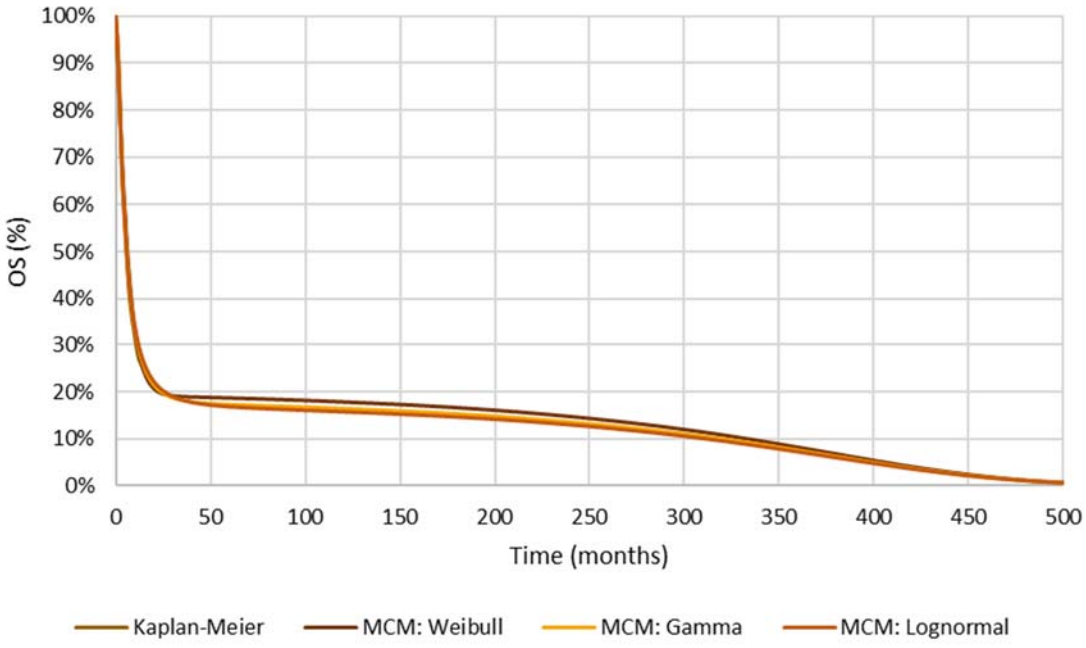
The logistic regression model estimated the “cure fractions” and three parametric models were fitted to estimate survival on the proportion of patients not experiencing long-term remission: Weibull, gamma and lognormal. The parameter information for each of these is presented in Table 32.

Table 32: Overall survival for BSC: mixture-cure model coefficients

Distribution	Parameter	Mean
Weibull	pi	-1.43
	Implied “cure fraction”	0.19
	Constant	0.74
	ln(gamma)	0.17
Gamma	pi	-1.54
	Implied “cure fraction”	0.18
	Constant	-0.89
	ln(sigma)	-0.04
	Kappa	0.28
Lognormal	pi	-1.59
	Implied “cure fraction”	0.17
	Constant	-1.00
	ln(sigma)	0.00

Combining the estimated cure fraction, the general population mortality (for “cured” patients) and the fitted parametric curves for “not cured”, Figure 26 shows the fit of all the distributions to the observed OS KM.

Figure 26: Overall survival for BSC: KM with mixture cure model parametric curves



Key: MCM, mixture cure model.

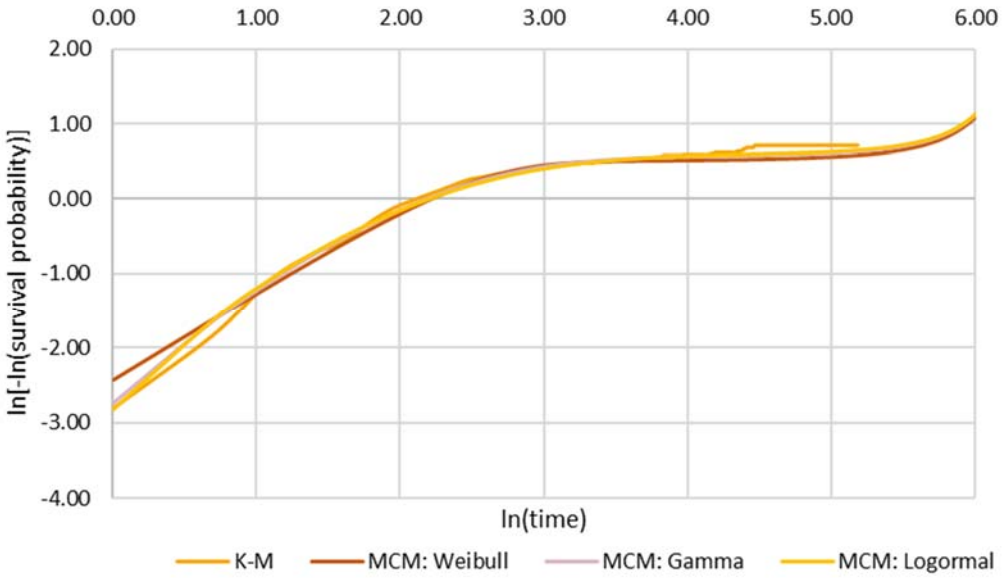
The goodness of fit of the curve fits used for the “not cured” proportion are presented in Table 33 using AIC and BIC statistics.

Table 33: Overall survival for BSC: mixture cure model goodness of fit statistics

Model	AIC	BIC
Lognormal	244.64	254.06
Weibull	259.21	268.63
Gamma	245.58	258.15
Key: AIC Akaike information criterion; BIC, Bayesian information criterion.		

Figure 27 shows plots of modelled cumulative hazard over time and observed cumulative hazard over time.

Figure 27: Overall survival for BSC: mixture-cure model log-cumulative hazard plot



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

The comparison of modelled OS and observed OS and modelled cumulative hazard over time and observed cumulative hazard over time suggest that all parametric models fit the KM very well and are tested in scenario analyses. The mixture-cure models are not used in the base case as the standard (simpler) Gompertz parametric model has a good statistical and visual fit.

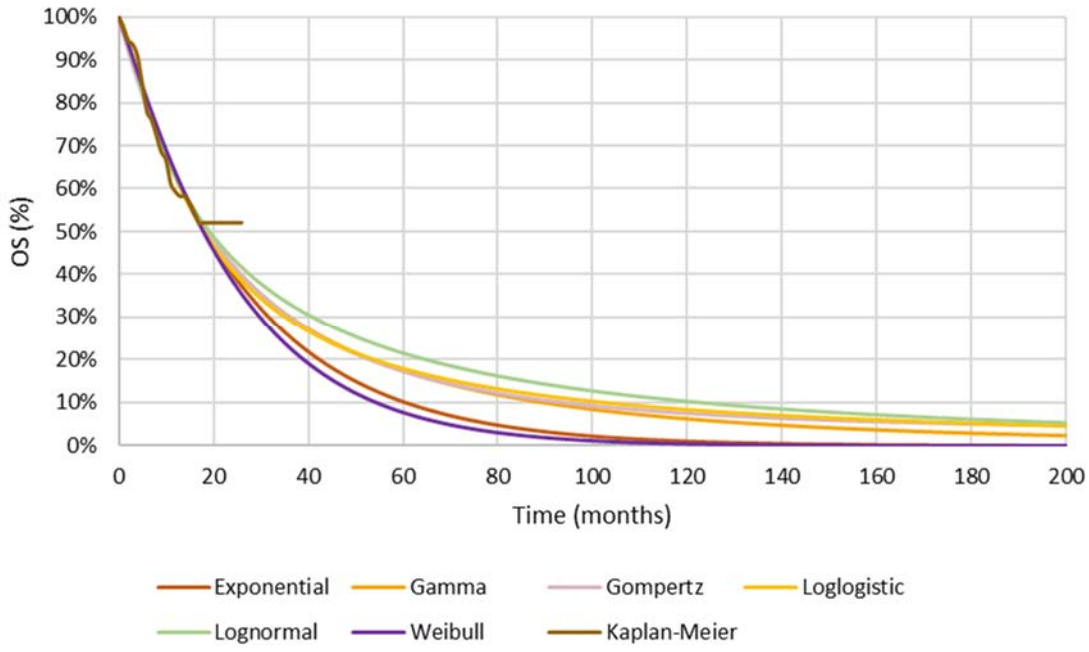
Progression-free survival – axi-cel arm

As discussed previously, a partitioned survival approach was used to model PFS for the axi-cel arm. A variety of single parametric survival curves were fit and applied to the axi-cel PFS data in the model using the coefficient data presented in Table 34. The curve fits are presented graphically in Figure 28.

Table 34: Progression-free survival for axi-cel: curve fit coefficients

Distribution	Parameter	Mean
Exponential	Constant	-2.62
Gamma	Constant	1.36
	ln(sigma)	0.54
	Kappa	-1.17
Gompertz	Constant	-0.18
	Gamma	-1.81
Loglogistic	Constant	0.01
	ln(gamma)	2.08
Lognormal	Constant	2.14
	ln(sigma)	0.50
Weibull	Constant	-0.27
	ln(p)	2.71

Figure 28: Progression-free survival for axi-cel: KM with single parametric curves



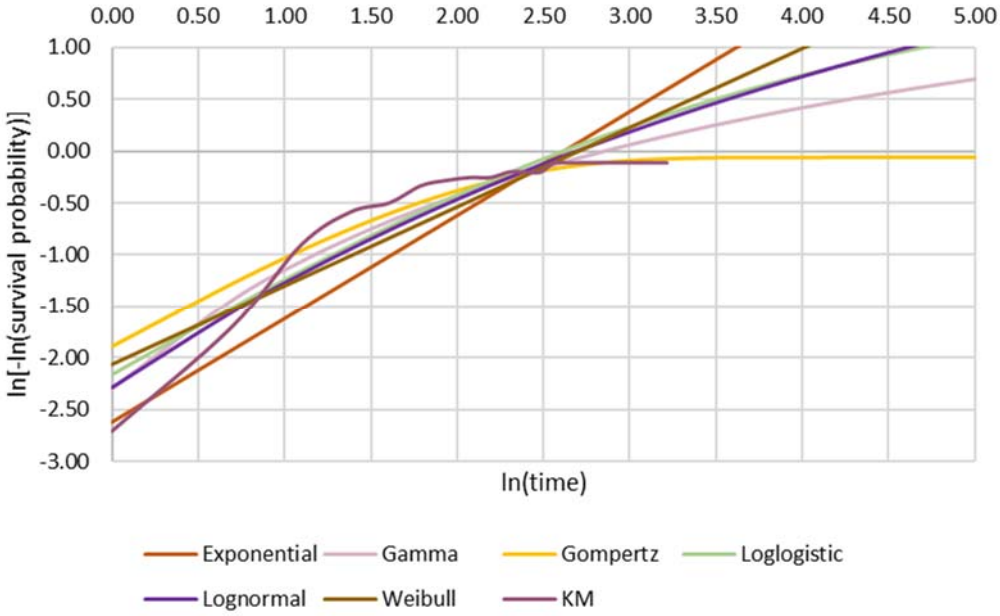
The AIC and BIC goodness of fit statistics for each parametric curve fitted to axi-cel PFS are presented in Table 35.

Table 35: Progression-free survival for axi-cel: PSM with single parametric curves goodness of fit statistics

Model	AIC	BIC
Exponential	450.48	453.16
Weibull	445.78	451.15
Gompertz	425.87	431.23
Loglogistic	435.77	441.13
Lognormal	432.17	437.54
Generalised gamma	427.74	435.79
Key: AIC Akaike information criterion; BIC, Bayesian information criterion.		

Plots of modelled cumulative hazard over time and observed cumulative hazard over time are presented in Figure 29.

Figure 29: Progression-free survival for axi-cel: PSM with single parametric curves log-cumulative hazard plot

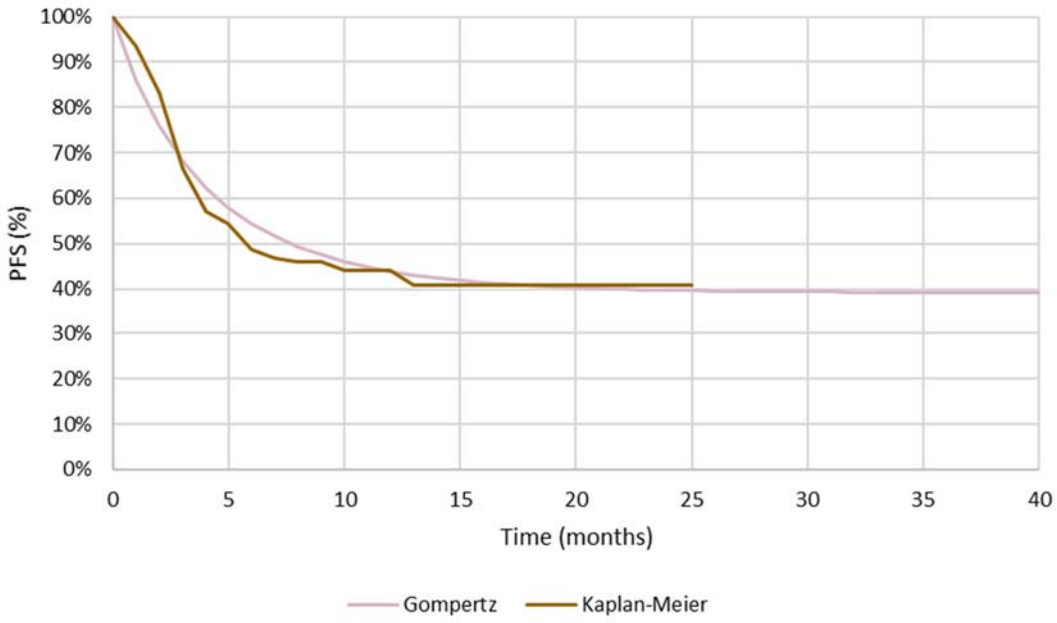


Key: KM, Kaplan–Meier .

From the goodness of fit statistics, the Gompertz curve fit demonstrates the best statistical fit while also having a good visual fit and was used in the model base case. The log cumulative hazard plot further demonstrates that the Gompertz curve provides the most plausible fit to the observed data, particularly toward the end of the observed PFS.

Figure 30 presents the base case curve fit alongside the KM for axi-cel.

Figure 30: Progression-free survival for axi-cel: PSM with single parametric curves selected distribution

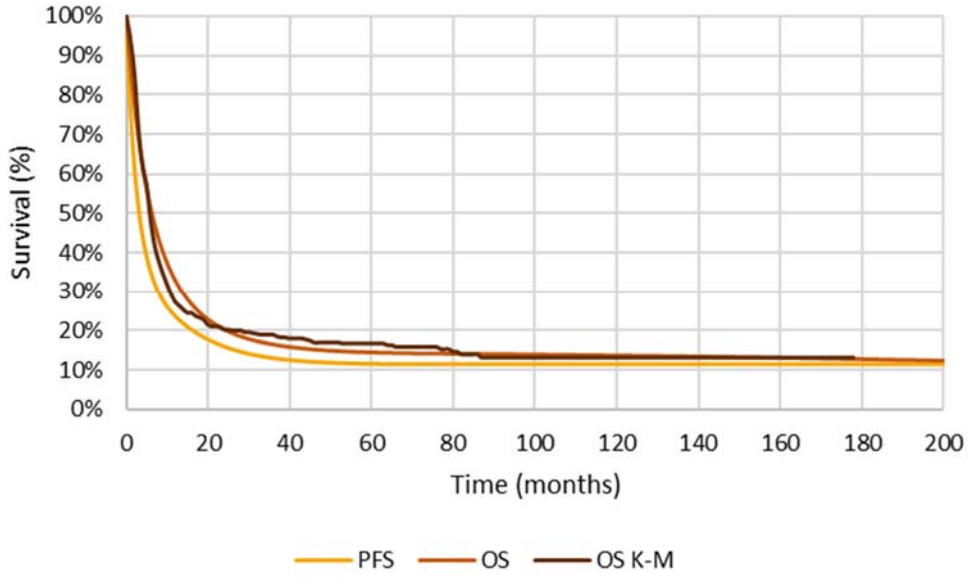


Alternative curve fits were explored as part of the scenario analysis.

Progression-free survival – BSC arm

Due to the lack of PFS data from SCHOLAR-1, PFS for BSC was estimated by assuming that the same ratio between PFS and OS at each time point in the axi-cel arm can be applied to the BSC arm. Applying this ratio to the OS data of the BSC arm allowed for a PFS curve to be constructed, as shown in Figure 31. It is acknowledged that this is a limitation of the SCHOLAR-1 data but is thought to be the most appropriate method to overcome the lack of PFS data for the comparator.

Figure 31: Progression-free survival for BSC, constructed from BSC overall survival



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

The assumption that 100% of time spent alive in the BSC arm is spent in the progression-free state or that 100% of time spent alive in the BSC arm is spent in the progressed state were tested in scenario analyses.

Time on treatment and retreatment

Time on treatment was not explicitly reported in the SCHOLAR-1 study and is not relevant to the ZUMA-1 trial, as axi-cel is given as a one-off infusion. For the modelled BSC regimens, the number of treatment cycles and the days per cycle for each component of each regimen are taken from the South East London Cancer Network[79] and the Thames Valley Strategic Clinical Networks.[80] These are presented in Table 36.

Table 36: Cycles per course and days per cycle

Regimen	Number of cycles per course	Days per cycle
GEM	3	Gemcitabine – 3 Methylprednisolone – 5
GEM-P	3	Gemcitabine – 3 Methylprednisolone – 5 Cisplatin – 1
RGCVP	6	Rituximab – 1 Gemcitabine – 2 Cyclophosphamide – 1 Vincristine – 1 Prednisolone – 5
RVP	3	Rituximab – 1 Vinblastine – 2 Prednisolone – 1

In the ZUMA-1 trial, although axi-cel was given as a one-off infusion, some patients were retreated in line with the trial protocol (10/108 subjects were retreated based on the August 2017 data cut; 9 patients from Phase 2 and 1 patient from Phase 1 trial). Although the expected market authorisation does not allow retreatment of axi-cel, for this analysis, these retreated patients were not removed or censored (at the time of re-treatment) for the PFS or OS endpoints. Based on the ZUMA-1 trial protocol, patients had to have progressed on axi-cel to be eligible for retreatment; therefore, censoring was not required for PFS. For OS, censoring at the time of re-treatment with axi-cel was not done to be consistent with subsequent treatments across all ZUMA-1 study patients, i.e. whether patients underwent retreatment or a new anticancer therapy following the initial axi-cel treatment. Based on best overall responses per investigator, among the 9 retreated patients from the Phase 2 trial, [redacted] patients had complete and partial response, respectively; [redacted] patient had stable disease and [redacted] patients had progressed disease. It is therefore assumed that including the retreated patients in ZUMA-1 would have minimal impact on the OS for the axi-cel arm.

To account for additional costs of these axi-cel retreated patients in the model, additional costs for conditioning chemotherapy, cell infusion and monitoring were applied to the 9.3% retreated population (i.e. 10/108). As the quantity of axi-cel

initially manufactured is sufficient for the delivery of up to two treatments based on the ZUMA-1 trial protocol, no additional leukapheresis or axi-cel acquisition costs are applied to the re-treated patients.

Body surface area (BSA)

The dosing of the conditioning chemotherapy (500 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine) is based on patient BSA, as are most of the BSC regimens. Therefore, estimation of the distribution around patient BSA for the patient population was required and was derived from the Phase 2 ZUMA-1 trial (n=101).

The optimal combinations of vial sizes (achieve lowest drug cost by assuming no vial sharing) were calculated for each range of BSA (see Table 37 and Table 38 for conditioning chemotherapy and BSC regimens, respectively). The proportions of patients belonging to each range of BSA were calculated using the ZUMA-1 patient-level data.

Table 37: Optimal combinations of vial sizes for conditioning chemotherapy by BSA

	Fludarabine		Cyclophosphamide	
BSA (m^2)	≤ 1.6	> 1.6	≤ 2.0	> 2.0
% of patients	12%	88%	48%	52%
Optimal combination of doses	1 x 50 mg	2 x 50 mg	1 x 1000 mg	1 x 1000 mg, 1 x 500 mg
Key: BSA, body surface area.				

Table 38: Optimal combinations of vial sizes for BSC by BSA

Chemotherapy	BSA (m^2)	% of patients	Optimal combination of doses
Gemcitabine	≤ 2.0	52%	2 x 1,000 mg
	2.0–2.2	29%	2 x 1,000 mg, 1 x 200 mg
	2.2–2.4	14%	2 x 1,000 mg, 2 x 200 mg
	> 2.4	5%	3 x 1,000 mg
Cisplatin	≤ 1.5	5%	1 x 100 mg, 1 x 50 mg
	1.5–2.0	48%	2 x 100 mg
	2.0–2.1	13%	2 x 100 mg, 1 x 10 mg
	2.1–2.2	16%	2 x 100 mg, 2 x 10 mg
	2.2–2.3	10%	2 x 100 mg, 3 x 10 mg

Chemotherapy	BSA (m^2)	% of patients	Optimal combination of doses
	2.3–2.5	7%	2 x 100 mg, 1 x 50 mg
	> 2.5	2%	3 x 100 mg
Rituximab	≤ 1.6	10%	6 x 100 mg
	1.6–1.866	21%	1 x 500 mg, 2 x 100 mg
	1.866–2.133	42%	8 x 100 mg
	2.133–2.4	23%	1 x 500 mg, 4 x 100 mg
	2.4–2.666	4%	2 x 500 mg
	> 2.666	1%	1 x 500 mg, 6 x 100 mg
Cyclophosphamide	≤ 2.0	52%	1 x 1,000 mg, 1 x 500 mg
	2.0–2.666	47%	2 x 1,000 mg
	> 2.666	1%	2 x 1,000 mg, 1 x 500 mg
Vincristine	≤ 2.143	74%	1 x 2 mg, 1 x 1 mg
	> 2.143	26%	2 x 2 mg
Vinblastine	≤ 1.666	12%	1 x 10 mg
	> 1.666	88%	2 x 10 mg
Key: BSA, body surface area; BSC, best supportive care.			

Adverse event rates

For axi-cel patients, AE rates were captured in the ZUMA-1 trial. The AE model inputs were based on the Phase 2 ZUMA-1 trial January 2017 data cut-off (n=101). Specifically, the following AEs were modelled:

- Grade 3 or higher axi-cel-related AEs occurring in ≥10% of subjects in ZUMA-1
- Grade 3 or higher conditioning chemotherapy-related AEs occurring in ≥10% of subjects in ZUMA-1
- Grade 3 or higher treatment-emergent cytokine release syndrome (CRS) occurring in ZUMA-1

No Grade 3 or higher leukapheresis-related AEs occurred in ≥10% of subjects in ZUMA-1. Grade 3 or higher leukapheresis-related AEs that occurred in <10% of patients include anaemia, decreased white blood cell count, decreased platelet count, decreased lymphocyte count, decreased neutrophil count and vomiting. Only one Grade 4 leukapheresis-related AE occurred (platelet count decreased).

The incidence of modelled Grade 3+ axi-cel related AEs by AE type are presented in Table 39, while the incidence of AEs due to conditional chemotherapy are presented in Table 40.

Table 39: Incidence of Grade 3+ axi-cel-related AEs occurring in ≥10% subjects (N=101)

Adverse events (AEs)	Number (%)
Encephalopathy	21 (21%)
Febrile neutropenia	17 (17%)
Hypotension	11 (11%)
Neutropenia	[redacted]
Pyrexia	12 (12%)

Table 40: Incidence of Grade 3+ conditioning chemotherapy-related AEs occurring in ≥10% subjects (N=101)

Adverse events (AEs)	Number (%)
Anaemia	41 (41%)
Febrile neutropenia	29 (29%)
Hypophosphatemia	[redacted]
Leukopenia	15 (15%)
Lymphocyte count decreased	[redacted]
Neutropenia	[redacted]
Neutrophil count decreased	[redacted]
Platelet count decreased	[redacted]
Thrombocytopenia	[redacted]
White blood cell count decreased	27 (27%)

No AE data were collected in the SCHOLAR-1 trial. Therefore, as a conservative assumption, no AEs were modelled for the BSC arm. The rates of AE incidence affect both the quality of life and cost aspects of the model, which are discussed further in Sections B.3.4 and B.3.5, respectively.

B.3.4. Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

HRQL data were collected in a safety management cohort of ZUMA-1. The key limitations of the EQ-5D data are that it is from a relatively small sample (87 observations from 34 patients), and EQ-5D-5L was used instead of EQ-5D-3L, which is preferred by NICE for technology appraisals.[81] As suggested by NICE, the crosswalk algorithm proposed by van Hout et al. (2012)[82] was used to convert EQ-5D-5L to EQ-5D-3L, and the resulting data are used to derive utilities for progression-free and progressed patients in the model base case (see Table 43).

Alternative utilities identified from the literature were used in scenario analyses.

Health-related quality-of-life studies

In appendix H describe how systematic searches for relevant health-related quality-of-life data were done.

Identification of studies

A systematic review of the published literature was conducted to identify all relevant utility and HRQL studies for the treatment of adult patients with R/R DLBCL.

The search was conducted on 07 September 2017 using the following electronic databases:

- MEDLINE and Embase (using Embase.com)
- MEDLINE In-Process (using Pubmed.com)
- EconLit (using Ebsco.com)
- The Cochrane Library (using wiley.com), including the following:
  - National Health Service Economic Evaluation Database
  - Health Technology Assessment Database

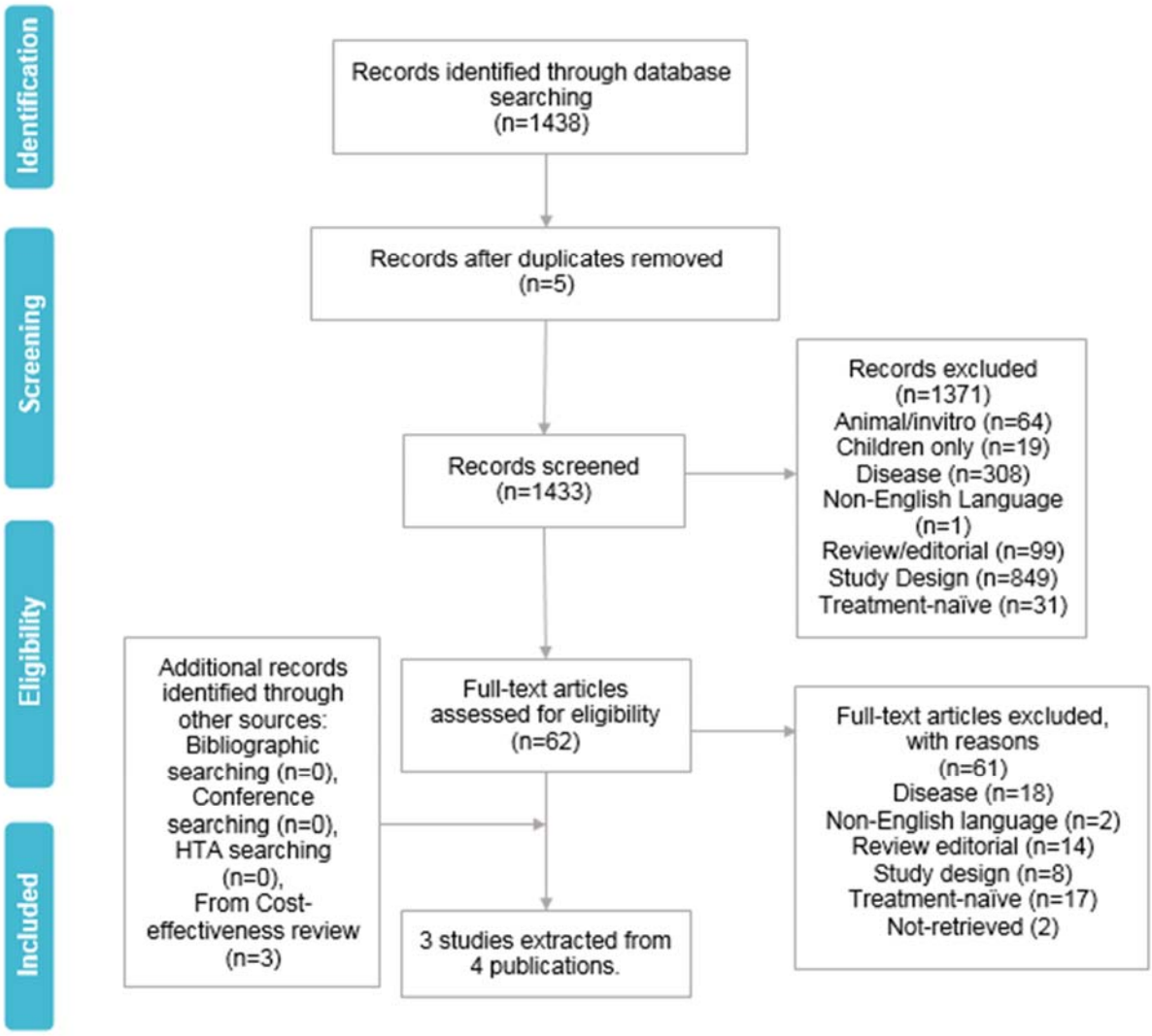
Additionally, conference proceedings from the last 2 years (2016–2017) and data available on HTA websites were searched to identify recently completed or ongoing studies of interest.

A total of 1,438 potentially relevant papers or abstracts were identified for this review. Studies were screened based on the information reported in their titles and/or abstracts. Of these, 5 were removed as duplicates, and 1,371 were excluded at the primary screening stage as they were not relevant to the research question.

Sixty-two articles were assessed in full for further evaluation. Of these, 61 were excluded, and 1 was included. Additionally, 3 studies were included from cost-effectiveness review. Therefore, 4 citations were included for this review. Due to the publication of multiple articles for the same study, 3 studies were extracted from 4 publications.

Figure 32 presents the PRISMA flow diagram of studies identified for the utility review.

Figure 32: PRISMA flow diagram for utility studies



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HTA, health technology assessments

Studies that met the inclusion criteria of the review

Of the three studies included, two were economic modelling studies from the US, and one was a UK HTA.

The study populations in all three studies consisted of DLBCL patients, although the line of therapy differed between studies. One study specifically considered relapsed DLBCL patients, one looked at DLBCL patients after first remission, and one only specified DLBCL.

Details of the data collected are presented in Table 41. A further description of the findings is provided in Appendix H.

Table 41: Characteristics and results of included utility studies

Study name	Treatment Type of setting	Country Type of study	Cohort size (response rates Health states	Method of elicitation and valuation	Utility data
Kymes et al., 2012[67]	G-CSF/ G-CSF + Plerixafor Relapsed DLBCL	USA Economic modelling study	20 (NR) <u>Health states</u> 1st aphresis 2nd aphresis 3rd apheresis 4th apheresis rescue transplant, recurrence, death	NR	<u>Utility value:</u> Day before transplant (Patients while undergoing apheresis): 0.75 14 days post-transplant (during high-dose chemotherapy and engraftment): 0.53 3 months post-transplant (post engraftment): 0.78
Knight et al., 2004[83]	CHOP/R-CHOP DLBCL patients	UK HTA	NR	NR	<u>Utility value of Non-responders /relapses:</u> CHOP: 0.38 R-CHOP: 0.38
Huntington et al., 2015[84]	NR DLBCL Patients after first remission	USA Economic modelling study	NR <u>Health states</u> Continued first remission, disease relapse treated with salvage immunochemotherapy, ASCT, second complete remission, refractory or relapsed disease treated with palliative immunotherapy, death	NR	<u>Utility values, range:</u> Second remission: 1.0, 0.90 to 1.0 Relapsed disease: 0.90, 0.80 to 0.95 Refractory disease: 0.80, 0.80 to 0.90 <u>Utility adjustments in model</u> False-positive surveillance scan: -0.02, 0.0 to -0.03 Salvage cytotoxic chemotherapy: -0.15, -0.10 to -0.30 Autologous SCT: -0.20, -0.10 to -0.30

Key: ASCT, autologous stem-cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; DLBCL, diffuse large B-cell lymphoma; G-CSF, granulocyte colony-stimulating factor; NR, not reported; R-CHOP, rituximab (MabThera) + cyclophosphamide, doxorubicin, vincristine, prednisolone.

Adverse reactions

AEs associated with axi-cel are detailed in Section B.3.3. These are expected to occur in the short term after the initial treatment of axi-cel; therefore, a one-off QALY decrement is applied in the first model cycle.

Utility decrements for anaemia, febrile neutropenia, neutropenia, platelet count decrease, pyrexia and thrombocytopenia were identified in the pixantrone submission to NICE.[45] As in the York study, it is conservatively assumed that those experiencing cytokine release syndrome (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).[68] Data on utility decrements for encephalopathy, hypophosphatemia, hypotension, leukopenia, decreased neutrophil count, and decreased white blood cell count were not identified. For each of these AEs, a disutility equal to the maximum of the identified non-CRS AE disutilities was assumed. This approach was also taken in the pixantrone submission to NICE.[68]

Total AE durations were calculated using patient-level data from ZUMA-1. Durations were calculated as the total number of days that each patient experiences a specific AE, even if that event was experienced more than once. This is consistent with the use of the proportion of patients experiencing each AE, rather than the rate of each event. AEs were ongoing in eight of 712 observations; given the small number of missing end dates, these observations were excluded. The impact of this approach is expected to be minimal.

AE disutilities and durations, and their respective data sources, are presented in Table 42.

Table 42: Adverse event disutilities

Adverse event	Utility decrement	Source	Duration (days)	Source
Anaemia	-0.12	Swinburn et al., 2010	14	Analysis of patient-level data from ZUMA-1
CRS	-0.76	Set to be equal in magnitude to the utility value in the progression-free health state. Assumption as in the York study[68]	4	
Neutropenia	-0.09	Nafees et al., 2008	47	
Platelet count decreased	-0.11	Tolley et al., 2013	50	
Thrombocytopenia	-0.11	Tolley et al., 2013	63	
Encephalopathy	-0.15	Assumed equal to the maximum of other, non-CRS AE disutilities in the absence of other data, as in the pixantrone submission to NICE	9	
Febrile neutropenia	-0.15		6	
Hypophosphatemia	-0.15		16	
Hypotension	-0.15		5	
Leukopenia	-0.15		21	
Lymphocyte count decreased	-0.15		64	
Neutrophil count decreased	-0.15		17	
Pyrexia	-0.11		2	
White blood cell count decreased	-0.15		40	
Key: AE, adverse event; CRS, cytokine release syndrome.				

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

In the model base case, health state utilities were based on EQ-5D data collected in a safety management cohort of ZUMA-1 (n=34, with 87 observations). Utilities derived from the NICE multiple technology appraisal of bevacizumab, sorafenib, sunitinib and temsirolimus in advanced/metastatic renal cell carcinoma[75], which was also used in NICE TA306, were used in a scenario analysis.

The model also assumes that if patients have remained in the PFS state for 2 years, they are classed as being in long-term remission and are thus assumed to have equal utility values as the age and gender matched general population after this point.[85] This assumption is supported by the findings of Maurer et al. (2014), where the survival of DLBCL patients treated with immunochemotherapy was compared to

that of the general population.[48] It was found that, in the DLBCL patients who were disease-free at 24 months, there was no significant difference in subsequent survival compared with that for the general population.

In scenario analyses, a percentage decrement to the age and gender matched general population utility values are applied.

Table 43: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval*	Reference in submission (section and page number)	Justification
Progression-free (base case)	[redacted]	[redacted]	Health-related quality-of-life data from clinical trials	Although the sample size is small, EQ-5D data from the pivotal trial (with the same patient population) are ideal.
Progressed disease (base case)	[redacted]	[redacted]		
Progression-free (scenario)	0.76	0.70–0.82	Health-related quality-of-life data used in the cost-effectiveness analysis	These values were deemed the most plausible in comparison to those identified in the literature. Also, these were accepted in TA306.
Progressed disease (scenario)	0.68	0.60–0.76		
Anaemia	-0.12	0.10–0.14	Adverse reactions	The same adverse event decrements were used as in TA306. For disutilities that could not be identified, a disutility equal to the maximum of the identified non-CRS adverse event disutilities was assumed. This approach was used in TA306. The assumption of assuming a utility of 0 for those experiencing CRS is in line with the NICE
Cytokine release syndrome	-0.76	0.65–0.87		
Neutropenia	-0.09	0.08–0.10		
Platelet count decreased	-0.11	0.09–0.13		
Thrombocytopenia	-0.11	0.09–0.13		
Encephalopathy	-0.15	0.13–0.17		
Febrile neutropenia	-0.15	0.13–0.17		
Hypophosphatemia	-0.15	0.13–0.17		
Hypotension	-0.15	0.13–0.17		
Leukopenia	-0.15	0.13–0.17		
Lymphocyte count decreased	-0.15	0.13–0.17		
Neutrophil count decreased	-0.15	0.13–0.17		
Pyrexia	-0.11	0.09–0.13		
White blood cell count decreased	-0.15	0.13–0.17		

State	Utility value: mean (standard error)	95% confidence interval*	Reference in submission (section and page number)	Justification
				regenerative medicines report.

Key: CRS, cytokine release syndrome.
Note: *The confidence intervals are calculated by assuming an arbitrary range of +/-15% from the mean.

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

In appendix I describe how relevant cost and healthcare resource data were identified.

Intervention and comparators' costs and resource use

Axi-cel treatment costs

For axi-cel, the costs included in the model were the costs of leukapheresis, conditioning chemotherapy, acquisition cost of axi-cel, and cell infusion and monitoring. For simplicity, all costs associated with axi-cel are assumed to be incurred in the first model cycle, including those associated with retreatment.

Leukapheresis

In Phase 1/2 of ZUMA-1, 119 subjects underwent leukapheresis, 110 subjects received conditioning chemotherapy, and 108 subjects received axi-cel. Of the nine subjects not treated with either conditioning chemotherapy or axi-cel:

- Two subjects died due to disease progression prior to treatment
- Four subjects experienced AEs that precluded treatment
- Two subjects had non-measurable disease prior to treatment
- One subject discontinued due to the need for immediate therapy for disease progression

The cost of leukapheresis was calculated as the weighted average of all healthcare resource groups (HRGs) for stem cell and bone marrow harvest in the NHS national

schedule of reference costs (Table 44).[86] This approach was also taken by the authors of the NICE regenerative medicines report.[68]

Table 44: Unit costs of leukapheresis

Currency code	Currency description	Number of cases	Unit cost
SA34Z	Peripheral Blood Stem Cell Harvest	2,854	£1,233.22
SA18Z	Bone Marrow Harvest	257	£1,857.22

The weighted average cost of leukapheresis was calculated to be £1,284.77. An uplifting factor of 1.102 (119/108) was used to adjust the unit leukapheresis cost and used in the model, to account for patients who undergo leukapheresis but do not proceed to receive axi-cel. Therefore, the model cost of leukapheresis is £1,415.63.

Conditioning chemotherapy

Conditioning chemotherapy includes intravenous infusions of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 on the 5th, 4th and 3rd days prior to infusion of axicabtagene ciloleucel. Unit costs for cyclophosphamide and fludarabine were taken from the NHS drug and pharmaceutical electronic market information tool (eMit)[87], and are presented in Table 45.

Table 45: Unit costs of conditioning chemotherapy

	Fludarabine (50 mg)	Cyclophosphamide (500 mg)	Cyclophosphamide (1,000 mg)
Cost/vial	£26.08	£10.00	£15.92

The costs of the conditioning chemotherapy were derived after calculating the optimal combination of the different vial sizes, considering the population BSA data based on patient level data from ZUMA-1 (Table 37). It was assumed that unused chemotherapy remaining in vials is wasted.

Conditioning chemotherapy is assumed to require a non-elective long-stay hospitalisation, in line with assumptions taken in the NICE regenerative medicines report.[68] The cost of a non-elective long-stay hospitalisation is calculated as the weighted average of non-elective long-stay HRGs for malignant lymphoma, including

Hodgkin's and Non-Hodgkin's, in the NHS national schedule of reference costs[86]; see Table 46.

Table 46: Malignant lymphoma non-elective long-stay HRGs

Currency code	Currency description	Number of cases	Unit cost
SA31A	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 15+	997	£8,655.88
SA31B	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 10–14	1,657	£6,542.94
SA31C	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 6–9	2,163	£4,949.32
SA31D	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 4–5	1,324	£3,967.74
SA31E	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 2–3	1,416	£3,236.25
SA31F	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 0–1	976	£3,265.05

The weighted average cost of hospitalisation for conditioning chemotherapy was calculated to be £5,062.63.

A multiplier of 1.019 (110/108) was used to adjust both the conditioning chemotherapy cost and the hospitalisation cost for conditioning chemotherapy to account for the two patients in ZUMA-1 who were treated with conditional chemotherapy but not axi-cel. Furthermore, the additional costs of conditioning chemotherapy for the retreated patients were also accounted for, as discussed in Section B.3.3. Therefore, the model cost of conditional chemotherapy, including hospitalisation, is £5,856.77.

Drug acquisition

The acquisition cost of axi-cel is assumed to be a one-off cost of [redacted] including all shipping, engineering and generation of the CAR T-cells.

A multiplier is not applied to the acquisition cost of axi-cel to account for patients who were recruited in ZUMA-1 but did not receive the axi-cel treatment. It is assumed the cost of the drug will only be reimbursed if axi-cel is administered to the patient.

Cell infusion and monitoring

The infusion of axi-cel and subsequent monitoring is assumed to incur the cost of an elective hospitalisation, in line with the assumption taken in the NICE regenerative medicines report.[68] However, the mean length of stay observed in the ZUMA-1 trial for axi-cel was 17.6 days, which is over a week longer than that reported for malignant lymphoma (including Hodgkin's and non-Hodgkin's) inpatient admissions in Hospital Episode Statistics[88], which is 10.4 days. To cost this in the model, the weighted average of elective inpatient HRGs for malignant lymphoma, including Hodgkin's and Non-Hodgkin's, in the NHS national schedule of reference costs[86] was used, plus the weighted average cost of 7.2 elective inpatient excess bed day HRGs.

Table 47: Malignant lymphoma elective inpatient HRGs

Currency code	Currency description	Number of cases	Unit cost
SA31A	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 15+	128	£15,250.10
SA31B	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 10–14	311	£7,933.49
SA31C	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 6–9	727	£5,647.01
SA31D	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 4–5	940	£3,673.41
SA31E	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 2–3	1,677	£3,049.10
SA31F	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 0–1	2,439	£2,472.99

Table 48: Malignant lymphoma elective inpatient excess bed day HRGs

Currency code	Currency description	Number of cases	Unit cost
SA31A	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 15+	432	£381.37
SA31B	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 10–14	387	£358.80
SA31C	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 6–9	442	£425.07
SA31D	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 4–5	302	£366.12
SA31E	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 2–3	597	£405.41
SA31F	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC score 0–1	654	£528.50

The weighted average cost of elective inpatient HRGs was calculated to be £3,716.28. The weighted average cost of elective inpatient excess bed day HRGs was calculated to be £422.79. The total cost for cell infusion and monitoring was therefore calculated to be £6,760.37 (i.e. 3716.28 + [7.2 x 422.79]).

BSC treatment costs

The BSC arm is applied as a blended comparator (BSC), which is comprised of four different regimens, as detailed in Section B.1.1. The model applies costs for each regimen, multiplied by their distribution of use in the UK. In the base case, without an identified better source of evidence, the four regimens are assumed to be distributed equally, i.e. 25% of each regimen is prescribed.

Drug acquisition

The treatments included in each regimen are a mixture of both orally administered and intravenously administered drugs, based on BSA, as presented in Table 49 and Table 50, respectively. For the chemotherapies where dosing is dependent on BSA, the optimal combinations of the vial sizes required for each range of BSA were calculated.

Table 49: Unit costs of chemotherapies that are not based on BSA

Chemotherapy	Mg/day	Mg/unit	Cost/unit
Prednisolone	100	5	£0.01
Methylprednisolone	1,000	1,000	£7.24

Table 50: Unit costs of chemotherapies based on BSA

Chemotherapy	Mg/m^2/day	Mg/unit	Cost/unit
Gemcitabine	1,000	200 mg	£2.76
		1,000 mg	£7.96
Cisplatin	100	10 mg	£1.99
		50 mg	£6.48
		100 mg	£8.45
Rituximab	375	100 mg	£349.25
		500 mg	£785.84
Cyclophosphamide	750	500 mg	£10.00
		1,000 mg	£15.92
Vincristine	1.4	1 mg	£3.74
		2 mg	£5.85
Vinblastine	6	10 mg	£15.40

Treatment duration data are detailed in Table 36 and BSA data are presented in Table 38.

Drug administration

The administration of BSC is assumed to incur the cost of a non-elective hospitalisation, as described previously for the cell infusion and monitoring costs in axi-cel.

Health-state unit costs and resource use

Medical resource use required is dependent on progression status and is thus modelled by applying different costs for each health state. The model considers costs associated with the following:

- Professional and social services (Table 51)
- Health care professionals (Table 52)
- Treatment follow-up (Table 53)

- Hospital resource use (Table 54)

Resource use in each health state was estimated from a survey of three key opinion leaders, commissioned by the manufacturer of pixantrone to support the pixantrone submission to NICE.[45] It is acknowledged that the population addressed by pixantrone differs to that of axi-cel, and that the estimates are only based on the opinions of three clinicians. This uncertainty is dealt with in the scenario analyses, in which medical resource use costs are doubled and halved to assess the impact of changes in these costs.

The pixantrone submission to NICE considered three health states to which the medical resource use is applied:

- PFS on 3rd (or 4th) line treatment
- PFS, discontinued 3rd or 4th line treatment
- PD

As discontinuation is not relevant to the axi-cel arm and is not modelled in the BSC arm, the model applies a crude average of the 'PFS on 3rd (or 4th) line treatment' and 'PFS, discontinued 3rd or 4th line treatment' states to derive the costs for the PFS health state.

In line with modelling utilities, it is assumed that patients remaining in PFS for at least 2 years are deemed to be in long-term remission. Consequently, these patients are assumed to no longer incur the costs of medical resource use after 2 years in PFS in the base case. Different cut-off points (beyond which medical resource use cost is not incurred) are explored in the sensitivity analyses.

Table 51: Resource use and costs associated with professional and social services

Resource	Resource use: PFS	Resource use: PPS	Unit cost	Duration	Source
Residential care	1.87	0	£124.00	28 days	PSSRU Unit Costs of Health and Social Care[89] Local authority own-provision residential care for older people: £155 establishment cost plus personal living expenses per permanent resident day Private sector residential care for older people: £93 establishment cost plus personal living expenses per permanent resident day Crude average = (£155 + £93)/2 = £124
Day care	0.70	1.87	£61.00	28 days	PSSRU Unit Costs of Health and Social Care[89] Local authority own-provision day care for older people: £61 per client attendance
Home care	2.92	9.33	£32.48	28 days	National Audit Office[90] Per diem cost of community care = £28 (assumed by the National Audit Office to be the same as the cost of home care) Inflation factor from 2007/08 to 2015/16 = 297.0/257.0 = 1.16 Inflated per diem cost of home care = 1.16 x £28 = £32.48
Hospice	0.41	12.13	£153.12	1 year	National Audit Office[90] Per diem cost of hospice inpatient care = £132 Inflation factor from 2007/08 to 2015/16 = 297.0/257.0 = 1.16 Inflated per diem cost of hospice care = 1.16 x £132 = £153.12
Total per cycle cost	£406.54	£607.89	-	-	-
Key: PFS, progression-free survival; PPS, post-progression survival.					

Table 52: Resource use and costs associated with healthcare professionals

Resource	Resource use: PFS	Resource use: PPS	Unit cost	Duration	Source
Hospital-based healthcare					
Oncologist	1.05	0.33	£162.84	28 days	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF01A, Non-Admitted Face to Face Attendance, Follow-up – Medical Oncology
Haematologist	0.49	1.00	£166.03	28 days	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF01A, Non-Admitted Face to Face Attendance, Follow-up – Clinical Haematology
Radiologist	0.83	0.00	£66.11	28 days	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF01A, Non-Admitted Face to Face Attendance, Follow-up – Interventional Radiology
Nurse	2.50	0.00	£37.98	28 days	NHS national schedule of reference costs[86] Other currencies, Currency Code N02AF, District Nurse, Adult, Face to Face
Palliative care team	0.00	1.33	£438.36	28 days	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF02A, Multiprofessional Non-Admitted Face to Face Attendance, Follow-up
Specialist nurse	0.42	2.50	£37.98	28 days	NHS national schedule of reference costs[86] Other currencies, Currency Code N02AF, District Nurse, Adult, Face to Face
Community-based healthcare					
GP	1.25	3.33	£31.00	28 days	PSSRU Unit Costs of Health and Social Care[89] Cost per surgery consultation lasting 9.22 minutes, including direct care staff costs, without qualification costs
District nurse	0.94	4.00	£37.98	28 days	NHS national schedule of reference costs[86] Other currencies, Currency Code N02AF, District Nurse, Adult, Face to Face

Resource	Resource use: PFS	Resource use: PPS	Unit cost	Duration	Source
CT scan	0.31	0.03	£107.52	28 days	NHS national schedule of reference costs[86] Diagnostic Imaging, weighted average of adult currency codes for computerised tomography (RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z, RD28Z)
Total per cycle cost†	£571.28	£1,255.90	-	-	-

Key: PFS, progression-free survival; PPS, post-progression survival.
Note: †, Calculated as the product of resource use and unit costs, multiplied by (365/12)/28 to give a monthly rather than 28-day cost.

Table 53: Resource use and costs associated with treatment follow-up

Resource	Resource use: PFS	Resource use: PPS	Unit cost	Duration	Source
Full blood counts	3.33	1.00	£3.10	28 days	NHS national schedule of reference costs[86] Directly Accessed Pathology Services, Currency Code DAPS05, Haematology
LDH	2.00	0.33	£3.10	28 days	NHS national schedule of reference costs[86] Directly Accessed Pathology Services, Currency Code DAPS05, Haematology
Liver function	3.33	1.00	£1.18	28 days	NHS national schedule of reference costs[86] Directly Accessed Pathology Services, Currency Code DAPS04, Clinical Biochemistry
Renal function	3.33	0.33	£1.18	28 days	NHS national schedule of reference costs[86] Directly Accessed Pathology Services, Currency Code DAPS04, Clinical Biochemistry
Immunoglobulin	0.67	0.33	£3.10	28 days	NHS national schedule of reference costs[86]

Resource	Resource use: PFS	Resource use: PPS	Unit cost	Duration	Source
					Directly Accessed Pathology Services, Currency Code DAPS05, Haematology
Calcium phosphate	0.67	1.00	£1.18	28 days	NHS national schedule of reference costs[86] Directly Accessed Pathology Services, Currency Code DAPS04, Clinical Biochemistry
Total per cycle cost	£29.60	£8.58	-	-	-
Key: PFS, progression-free survival; PPS, post-progression survival.					

Table 54: Resource use and costs associated with hospitalisation

Resource	Resource use: PFS	Resource use: PPS	Unit cost	Duration	Source
Inpatient days	3.17	2.70	£357.62	1 year	NHS national schedule of reference costs[86], ZUMA-1 CSR[5] and Hospital Episode Statistics[88] Weighted average cost of elective inpatient HRGs = £3,719.28 Average length of stay = 10.4 days Cost per inpatient day = £3,719.28/10.4 = £357.62
Junior haematologist visits	2.00	2.00	£166.03	1 year	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF01A, Non-Admitted Face to Face Attendance, Follow-up – Clinical Haematology
Senior haematologist visits	1.07	0.67	£166.03	1 year	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF01A, Non-Admitted Face to Face Attendance, Follow-up – Clinical Haematology

Resource	Resource use: PFS	Resource use: PPS	Unit cost	Duration	Source
Radiologist visits	0.03	0.03	£66.11	1 year	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF01A, Non-Admitted Face to Face Attendance, Follow-up – Interventional Radiology
Specialist nurse visits	2.53	2.07	£36.00	1 year	PSSRU Unit Costs of Health and Social Care[89] Nurse (GP practice) cost per hour, without qualification costs
Nurse visits	2.40	2.00	£36.00	1 year	PSSRU Unit Costs of Health and Social Care[89] Nurse (GP practice) cost per hour, without qualification costs
Oncologist visits	0.60	0.30	£162.84	1 year	NHS national schedule of reference costs[86] Consultant-led, Currency Code WF01A, Non-Admitted Face to Face Attendance, Follow-up – Medical Oncology
GP visits	0.13	0.07	£31.00	1 year	PSSRU Unit Costs of Health and Social Care[89] Cost per surgery consultation lasting 9.22 minutes, including direct care staff costs, without qualification costs
Total per cycle cost†	£160.38	£134.03	-	-	-

Key: PFS, progression-free survival; PPS, post-progression survival; PSSRU, Personal Social Services Research Unit.
Note: †, Calculated as the product of resource use and unit costs, divided by 12 to give a monthly rather than annual cost.

Adverse reaction unit costs and resource use

As AEs are only applied to the axi-cel treatment arm, in line with the York study[68], AE costs were applied as a one-off cost in the first model cycle.

Also, consistent with the York study[68], all AEs, barring CRS and B-cell aplasia, assume the cost of one excess bed day. This is because it is assumed that the costs of AEs are covered in the length of stay for axi-cel patients during cell infusion and monitoring, and costing each AE individually would result in double counting.

B-cell aplasia has not been considered in the economic model because the primary manifestation of B-cell aplasia, hypogammaglobulinemia, did not present as a Grade 3 or 4 AE in any patients in ZUMA-1. Hypogammaglobulinemia presented as a Grade 1 or 2 AE in 11 patients (11%) in ZUMA-1.

The method for costing CRS was taken from the NICE regenerative medicines report.[68] This assumes that the costs accrued for patients with Grade 3–4 CRS are the acquisition of cytokine inhibitor drugs and an intensive care unit (ICU) hospitalisation. The modelled cost of cytokine inhibitor drugs is £1,392.14, taken from the NHS national schedule of reference costs (currency code XD31Z, cytokine inhibitor drugs, band 1).[86] The cost of an ICU hospitalisation was calculated as the weighted average of HRGs for non-specific, general adult critical care in the NHS national schedule of reference costs.[86]

Miscellaneous unit costs and resource use

Allogeneic stem cell transplant

In ZUMA-1, [redacted] subjects out of 108 ([redacted]) underwent allogeneic SCT while in response to axi-cel, whereas no subjects underwent autologous SCT. The costs of allogeneic SCT is therefore applied to [redacted] of patients in the axi-cel arm of the model. In SCHOLAR-1, the proportion of subjects who underwent allogeneic SCT differs dependent on the data used. In the SCHOLAR-1 data that were used in the model base case (SCHOLAR-1, excluding ECOG 2–4), this was [redacted] of patients. For the other SCHOLAR-1 scenarios, this is presented in Table 55.

Table 55: Proportion of patients who underwent post-refractory SCT, using different SCHOLAR-1 data (scenario analyses)

SCHOLAR-1 data	% patients undergoing SCT
1. Unadjusted, all patients	[redacted]
2. Propensity score adjusted, all patients	[redacted]
3. Crude adjustment with ECOG 2–4 and post-refractory SCT removed	0%
Key: SCT, stem cell transplant.	

A weighted average of allogeneic SCT HRGs, taken from the NHS National Schedule of Reference Costs[86], was used to estimate the initial transplant cost. This is presented in Table 56.

Table 56: Allogeneic SCT HRGs

Currency code	Currency description	Number of cases	Unit cost
SA38A	Peripheral Blood Stem Cell Transplant, Allogeneic (Sibling), 19 years and over	204	£28,176.10
SA39A	Peripheral Blood Stem Cell Transplant, Allogeneic (Volunteer Unrelated Donor), 19 years and over	379	£33,485.89
SA40Z	Peripheral Blood Stem Cell Transplant, Allogeneic (Donor Type Not Specified)	518	£38,336.04

The weighted average cost of allogeneic SCT was calculated to be £34,783.96.

It is noted in the NICE regenerative medicines report that costs based on the admission period do not capture the full cost of allogeneic SCT over the patient's lifetime.[68] Therefore, the estimate of post-transplant costs that was used in the NICE regenerative medicines report was used in the model. This was from the UK Stem Cell Strategy Oversight Committee Report.[91] The cost per transplant patient in each follow-up period, weighted based on the proportion of patients alive in each period, is presented in Table 57.

Table 57: Costs of allogeneic SCT follow-up

Follow-up period	Weighted costs per transplant period	Inflated cost
Discharge to 6 months after transplant	£25,551	£26,413.67 (25,551 x [297.0/287.3] = 26,413.67)
6 to 12 months after transplant	£9,361	£9,677.05 (9,361 x [297.0/287.3] = 9,677.05)
12 to 24 months after transplant	£4,363	£4,510.31 (4,363 x [297.0/287.3] = 4,510.31)

The total cost of allogeneic SCT follow-up is therefore calculated to be £40,601.03. The cost of the initial transplant in addition to the costs of follow-up is calculated to be £75,384.99.

For simplicity, all costs associated with allogeneic SCT are assumed to be incurred in the first model cycle, including those associated with follow-up.

Training

As part of the costs associated with the axi-cel treatment arm, the per patient costs of training healthcare professionals in the use of axi-cel are included in the base case. To estimate a cost for this, a crude approach is taken based on:

- The expected cost per centre of training
- The expected annual number of patients per centre receiving axi-cel
- The expected number of years before healthcare professionals in each centre would need to be retrained

The per patient cost of training is calculated as:

$$\frac{Cost\ per\ centre}{Annual\ number\ of\ patients\ per\ centre\ x\ number\ of\ years\ before\ retraining}$$

The cost per centre is assumed to be 2 days of healthcare professional time. The expected number of patients in each centre and the number of years before retraining are assumed to be 10 and 2, respectively. The cost of 1 hour of medical consultant time is reported to be £104 in the NHS national schedule of reference costs, giving a total cost per centre of £1,664. This therefore equates to a cost per patient of £83.

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

Summary of base-case analysis inputs

Table 58: Summary of variables applied in the economic model base case

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution	Reference to section in submission
Model settings			
Cycle length	1 month	Not varied in SA	General model settings
Time horizon	44 years (so patients reach 100 at the end of model)	Varied in OWSA only	
Discount rate: costs	3.5%		
Discount rate: outcomes	3.5%		
Survival and progression: model inputs			
Axi-cel OS	See Table 28	Multivariate normal and normal	Efficacy data
BSC OS	See Table 30		
Axi-cel PFS	See Table 34		
BSC PFS	See explanation on Page 114		
Resource use			
Proportion receiving allogeneic SCT	[redacted]	Beta	Allogeneic stem cell transplant
Training: annual number of patients per centre	10.00	Not varied	Training
Training: years before retraining	2.00		
Costs			
Allogeneic SCT: cost	£75,384.99	Gamma	Allogeneic stem cell transplant
Medical resource use cost: PFS	£1,167.80		Health-state unit costs and resource use
Medical resource use cost: PPS	£2,006.40		
Training: cost per centre	£1,664.00	Not varied	Training
Cost of CRS	£2,754.82	Gamma	Adverse reaction unit costs and resource use
BSC: cost of administration	£5,062.63		BSC treatment costs
Axi-cel: cost of administration	£6,760.37		Axi-cel treatment costs

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution	Reference to section in submission
Hospitalisation cost for conditioning chemotherapy	£5,062.63		
Leukapheresis cost	£1,284.77		
Utilities and disutilities			
See detailed list in Table 43		Beta	Measurement and valuation of health effects
Adverse event proportions			
Axi-cel related adverse events	See Table 39	Beta	Adverse event rates
Conditional chemotherapy related	See Table 40		
Key: BSC, best supportive care; CI, confidence interval; CRS, cytokine release syndrome; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PPS, post-progression survival; SA, sensitivity analysis; SCT, stem cell transplant.			

Assumptions

Table 59 contains the key assumptions made in the de novo economic model.

Table 59: Key model assumptions

Assumption	Justification
A comparison of axi-cel and BSC can be made using two independent trials/studies: ZUMA-1 and SCHOLAR-1.	Given the single-arm trial design of ZUMA-1, unanchored indirect treatment comparison is the only option to assess relative treatment effect. To improve the comparability of the ZUMA-1 and SCHOLAR-1 trials, crude adjustment was made to remove patients in SCHOLAR-1 with a baseline ECOG score of 2–4. This matches the inclusion/exclusion criteria of ZUMA-1 and helps to improve the comparability between ZUMA-1 and SCHOLAR-1.
The ratio between OS and PFS in the axi-cel arm can be applied to the BSC OS to estimate progression.	Without PFS data in SCHOLAR-1, assumption is required to determine PFS for the comparator arm. Without further evidence regarding the PFS for the comparator, a more robust derivation of PFS is not possible. To explore the effect of this assumption on the outcomes, scenarios were tested where 100% patients are assumed to be progression free or 100% patients are assumed to be progressed. Assuming 100% are progression free has a minimal effect on the ICER (increase of <£1,000), whereas assuming 100% are progressed has a larger effect (decrease of around £8,000). This suggests that the base case method is conservative.

Age and gender matched generation population utility values in the PFS state are assumed from Month 24.	This considers the expected long-term remission following axi-cel, for which patients are likely to have the same quality of life as the general population. Scenario analyses tested a percentage decrement to the general population utility.
Medical resource use data were derived from the pixantrone submission, in which the resource use was estimated from a survey of three key opinion leaders.	Without further robust data on the resource use required in this population, it is acknowledged that the chosen methods are subject to uncertainty; therefore, the effect of different estimates on the model outcomes are explored in the scenario analyses and were found to have minimal impact.
No monitoring costs are assumed in the PFS state from Month 24.	This considers the expected long-term remission following axi-cel, for which patients are likely to not require further medical resource use (which includes costs for: professional and social services, health care professionals, treatment follow-up and hospital resource use).
All Grade 3 or 4 AEs for axi-cel, other than cytokine release syndrome and B-cell aplasia, do not incur treatment costs and only the cost of one excess bed day is applied.	The model applies initial hospitalisation costs for patient treated with axi-cel for a length of stay of 7.2 days longer than the average assumed for malignant lymphoma (in total 17.6 days and £6,760.37 one off cost). It is expected that the costs of treating the AEs will be captured within this initial hospitalisation for axi-cel. This is in line with the NICE regenerative medicines report.
The comparator regimens that make up the "blended comparator" for the BSC arm are assumed to be used in equal proportions in UK clinical practice	This is assumed in the absence of other data. As the same efficacy is used for all comparator regimens and the costs are low, it is not expected that this will have a large effect on the outcomes.
Key: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival.	

B.3.7. Base-case results

Base-case incremental cost-effectiveness analysis results

In appendix J please provide the following:

- Clinical outcomes from the model
  - Present the estimates of clinical outcomes included in the cost-effectiveness analysis (and compare with the clinical trial results).
  - See section 3.7 of the user guide for full details of the information required here.
- Disaggregated results of the base-case incremental cost effectiveness analysis

- Describe and tabulate the disaggregated results of the base-case incremental cost-effectiveness analysis.
- See section 3.7 of the user guide for full details of the information required here.

The discounted base-case results for axi-cel versus BSC are shown in Table 60. At the list price, axi-cel is associated with [redacted] incremental life years, [redacted] incremental QALYs, and incremental costs of [redacted] per patient, compared with BSC. The incremental cost-effectiveness ratio (ICER) is [redacted] per additional QALY gained.

Table 60: Base-case results without patient access scheme

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

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

Figure 33: Lifetime Markov trace for axi-cel

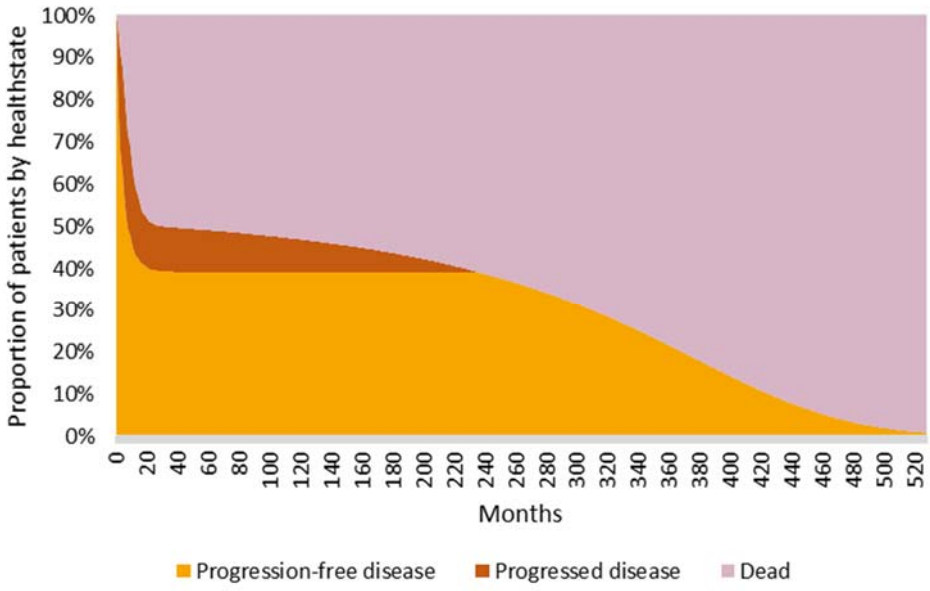
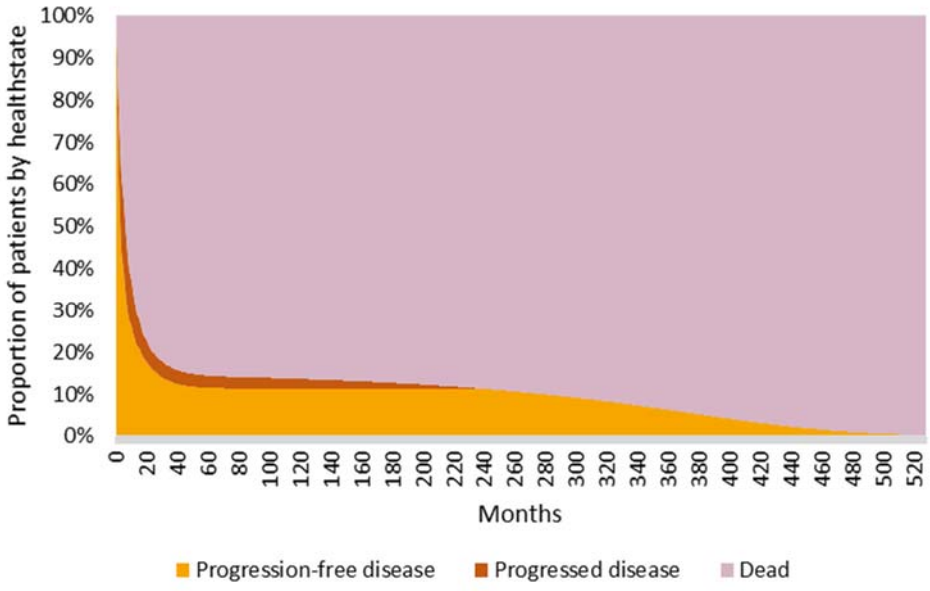


Figure 34: Lifetime Markov trace for BSC



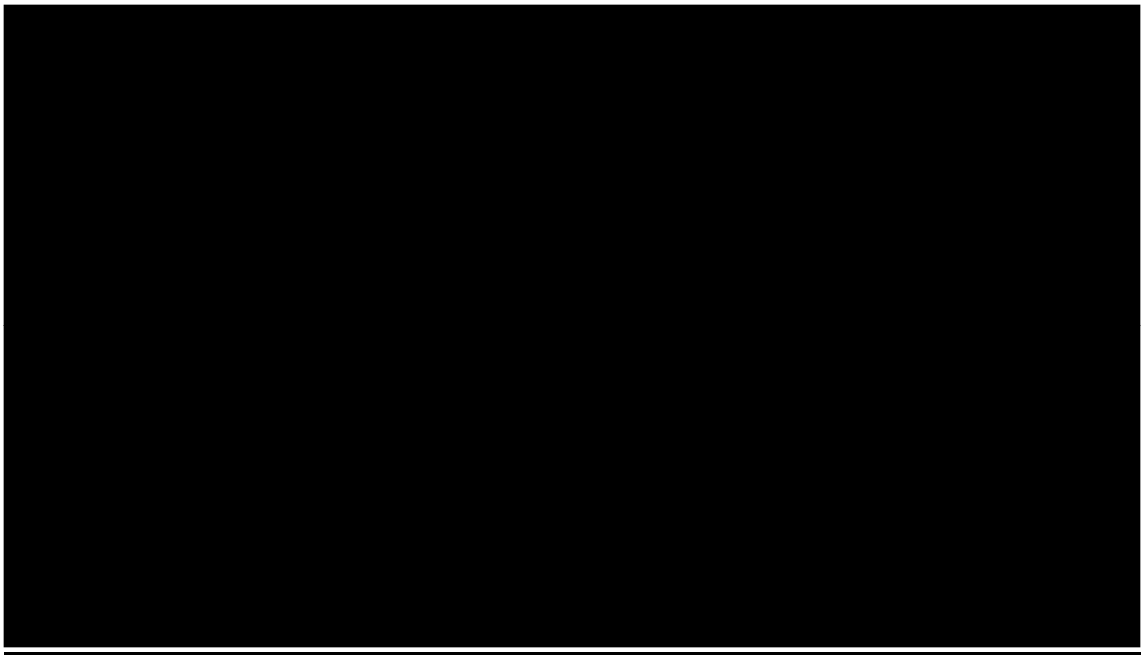
B.3.8. Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was carried out to explore the sensitivity in the deterministic base-case model results when all model parameters were varied simultaneously. Each parameter was varied according to its associated distribution 10,000 times, and mean model results were recorded. These mean model results were then used to inform a PSA scatter plot and a cost-effectiveness acceptability curve (CEAC). In line with what was discussed in Section B.2.13, a £50,000 threshold was used to reflect the end-of-life criteria.

The PSA scatter plots are presented in Figure 35.

[redacted]



The CEAC is presented in Figure 36. This shows that the probability of axi-cel being the most cost-effective treatment is 0.43% for a willingness-to-pay (WTP) threshold of £50,000.

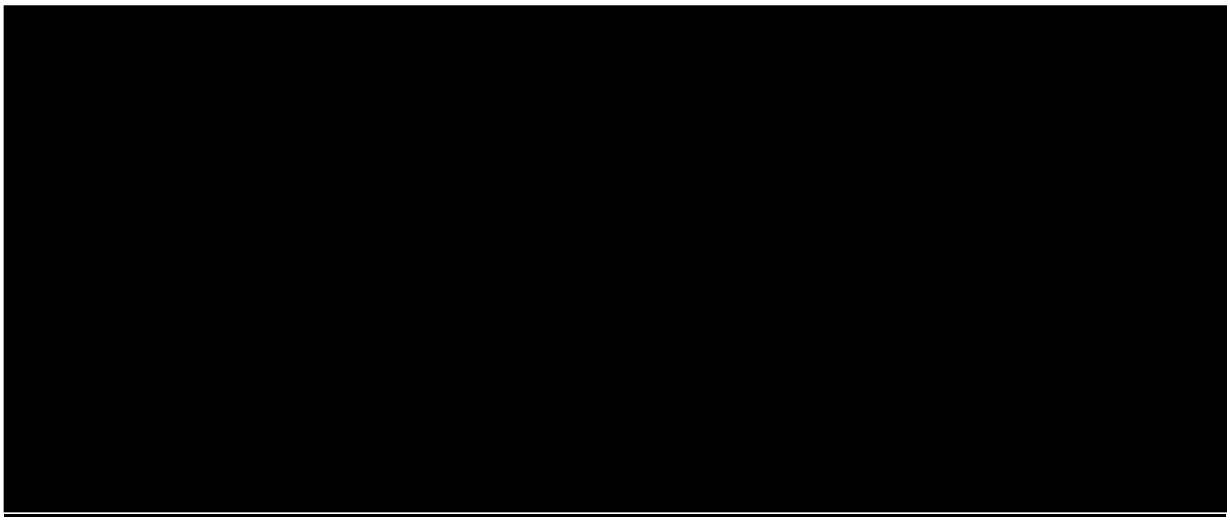
Figure 36: Cost-effectiveness acceptability curve

The average incremental costs over the simulated results were [redacted], and the average incremental QALYs were [redacted], giving a probabilistic ICER of £[redacted]. This is relatively congruent with deterministic changes in costs and QALYs of [redacted] and [redacted], respectively, and resulted in a difference in ICER of approximately 2%.

Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to explore the sensitivity in the deterministic base-case model results when one parameter is varied at a time. Each parameter was set to its lower and upper bound, and the deterministic model results were recorded. The top 10 influential parameters on the net monetary benefit (NMB) at a willingness to pay threshold of £50,000 are presented as a tornado diagram in Figure 37.

[redacted]



Key: AC, axi-cel; BSC, best supportive care; MCM, mixture cure model; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; SCT, stem cell transplant; WTP, willingness to pay.

As shown in the tornado diagram, the three most influential parameters on the model result were the mean cure fraction (pi) used in the mixture cure model for modelling axi-cel OS, the constant coefficient for modelling axi-cel PFS, and the constant coefficient used for modelling BSC OS.

Scenario analysis

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

- Time horizon: 10- and 20-year time horizons were explored
- Discounting: costs and outcomes were discounted at 1.5%
- Model type for axi-cel OS: alternative gamma mixture-cure model
- Model type for BSC OS:
  - Alternative single parametric curves (exponential, gamma, loglogistic, lognormal and Weibull)
  - Alternative Weibull, gamma and lognormal mixture-cure models
- Axi-cel PFS distribution: gamma parametric curve, as it provides the second best statistical fit

- BSC PFS:
  - 100% of time spent alive in the BSC arm is spent in the pre-progression state
  - 100% of time spent alive in the BSC arm is spent in the post-progression state
- SCHOLAR-1 dataset to be explored, with the choice of the following:
  - Unadjusted, full population, Gompertz parametric curve
  - Propensity score adjusted, full population, Gompertz parametric curve
  - Crude adjustment, excluding ECOG 2–4 and post-refractory SCT, Gompertz parametric curve
- Utility source: utilities of 0.76 for the pre-progression health state and 0.68 for the post-progression health state, as were used in the Pixantrone submission
- Assuming additional mortality of “not cured” patients (HR = 1.1) for axi-cel using mixture-cure model
- Utility for patients who have been in PFS for more than 2 years to be 90% of age-matched general population mortality

The results of the scenario analyses are presented below in Table 61.

Table 61: Scenario analysis results

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case		[redacted]	[redacted]	[redacted]	0%
Time horizon = 10 years	44 years	[redacted]	[redacted]	[redacted]	107%
Time horizon = 20 years		[redacted]	[redacted]	[redacted]	25%
Discount rates = 1.5%	3.5%	[redacted]	[redacted]	[redacted]	-22%
Mixture cure model used for BSC	PSM with single curves	[redacted]	[redacted]	[redacted]	7%
100% progression-free in BSC arm	Based on ZUMA-1 OS/PFS ratio	[redacted]	[redacted]	[redacted]	4%
100% progressed in BSC arm		[redacted]	[redacted]	[redacted]	-23%
Unadjusted, all	Unadjusted, excl. ECOG 2–4	[redacted]	[redacted]	[redacted]	0%
Unadjusted, excl. ECOG 2–4 and SCT		[redacted]	[redacted]	[redacted]	-10%
Propensity score adjusted		[redacted]	[redacted]	[redacted]	0%
Utility from literature (pixantrone)	ZUMA-1 safety population	[redacted]	[redacted]	[redacted]	-1%
AC PFS distribution: gamma	Gompertz	[redacted]	[redacted]	[redacted]	32%
BSC OS distribution: exponential	Gompertz	[redacted]	[redacted]	[redacted]	-21%
BSC OS distribution: gamma		[redacted]	[redacted]	[redacted]	-13%
BSC OS distribution: loglogistic		[redacted]	[redacted]	[redacted]	-20%
BSC OS distribution: lognormal		[redacted]	[redacted]	[redacted]	-18%
BSC OS distribution: Weibull		[redacted]	[redacted]	[redacted]	-19%
AC OS distribution (MCM): Gamma	Weibull	[redacted]	[redacted]	[redacted]	-3.5%
Multiplier for DLBCL/PMBCL/TFL patients in long-term remission (general population utility values): 0.9	1	[redacted]	[redacted]	[redacted]	9.1%
Multiplier for DLBCL/PMBCL/TFL patients in long-term remission (life tables): 1.1	1	[redacted]	[redacted]	[redacted]	1.7%

Key: AC, axi-cel; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; QALY, quality adjusted life year.

ICERs from the scenario analyses ranged between [redacted] and [redacted]. The results demonstrate that the most influential scenario on the model results was the reduced time horizon of 10 years, over which the costs and benefits of treatment are considered. The scenario resulted in an 107% increase in ICER compared to the base case. Additional to this, only two other scenarios resulted in an increased ICER of greater than 10%. These were the use of the gamma distribution to model axi-cel PFS, and the use of a 20-year time horizon.

The choice of time horizon is expected to have a significant impact on model results given the significant proportion of long-term survivors anticipated for patients treated with axi-cel and hence full benefits of treatment with axi-cel will not be captured over a shorter time horizon compared with a longer time horizon A shorter time horizon also penalises the axi-cel arm because the largest costs related to axi-cel (leukapheresis, conditioning chemotherapy, acquisition of axi-cel and infusion and monitoring) are all accrued during the first model cycle, and thus remain the same regardless of the time horizon.

Using a discount rate of 1.5% rather than 3.5% reduces the ICER by 22%. In treatments that can have a potential long-term benefit (in this case a significant proportion of patients treated with axi-cel is expected to have long-term remission), and have high upfront costs, it is reasonable to consider using a lower discount rate. We believe this scenario analysis is very relevant to this decision problem.

As expected from Figure 17, the use of the unadjusted SCHOLAR-1 full patient population and the corresponding propensity score analysis on the SCHOLAR-1 full patient population have a very small impact on the ICER; using the adjusted SCHOLAR-1 population with ECOG 2–4 and SCT subjects removed reduces the ICER by 10%.

Summary of sensitivity analyses results

The probabilistic ICER was [redacted] which is relatively congruent with the deterministic ICER of [redacted], suggesting that the model results are fairly robust to parameter uncertainty. The proportion of simulations considered cost-effective at a cost-effectiveness threshold of £50,000 was 0.43%.

The deterministic sensitivity analyses showed the large effects of changing the inputs for the survival analyses (e.g. “cure fraction” for mixture-cure model for axi-cel OS). This is also expected due to the uncertainties associated with extrapolation of axi-cel, which has a relatively short follow-up period and has an innovative mechanism of action making it very challenging for extrapolation.

ICERs from the scenario analyses ranged between [redacted] and [redacted], with similar numbers of the scenarios resulting in a reduced ICER compared with the base case as opposed to an increased ICER. This demonstrates that the selected model base case is plausible.

B.3.9. Subgroup analysis

No subgroup analyses have been implemented.

B.3.10. Validation

Validation of cost-effectiveness analysis

The cost-effectiveness model has been internally quality checked by an independent health economist who was not involved in the development the model. The errors and issues identified were addressed following the model quality check.

The key assumptions of the model have been validated by UK clinical experts. These include:

- Patients still alive towards the end of follow-up period for ZUMA-1 are likely to be “cured” and have the same mortality to the gender- and age-matched general population
- Existing treatment options (including pixantrone) used in UK clinical practice can be represented as a blended comparator in the model. These treatment options have similar efficacy
- Patients who have been in PFS for more than 2 years have similar health utility compared to the age-matched general population
- Evidence for DLBCL patients can be assumed to also apply to all aggressive B-cell NHL patients in the absence of more specific data

- Grade 3 or higher axi-cel-related and conditioning chemotherapy-related AEs occurring in ≥10% of subjects in ZUMA-1 are included in the model

As seen in Section B.3.3, within the ZUMA-1 and SCHOLAR-1 follow-up period, the model base case closely represents the observed OS and PFS.

Table 62: Validation of the de novo cost-effectiveness analysis

Validation performed by	Nature of validation	Date	Aspects covered
Dr Robert Marcus	Clinical validation	January 2018	Clinical inputs and assumptions used in the model
BresMed	Quality-control check	December 2017	Cost-effectiveness model

B.3.11. Interpretation and conclusions of economic evidence

In the model base case, axi-cel was associated with an ICER of [redacted]. This ICER consisted of incremental costs of [redacted] per patient with a [redacted] LY gain and [redacted] incremental QALYs. PSA results showed that the probability of axi-cel being more cost-effective compared to BSC is 0.43%, given a willingness to pay threshold of £50,000 per QALY. Clinical inputs for axi-cel OS and PFS and cost inputs relate to up-front costs of axi-cel appear to have the biggest impact on model outcomes based on OWSA. Scenario analyses showed that the base case is plausible, with similar numbers of scenarios producing higher or lower ICERs compared to the base case, and that model results are relatively robust to alternative data sources and assumptions.

The model results consider only the full populations of the ZUMA-1 and SCHOLAR-1 trials, i.e. subgroup analyses were not explored. Although subgroup analyses were not included as part of the model, largely because of the small patient population in ZUMA-1, following clinical opinion and validation, it is anticipated that the full population is generalisable to the patient population identified in the decision problem. Specifically, comments from the clinical ad-board were that, while the subpopulations are different in terms of front-line treatment, they are very much similar in terms of onward management.

A key limitation of the economic analysis is the lack of randomised control trial evidence comparing axi-cel against BSC (i.e. the ZUMA-1 trial is a single arm study). However, various adjustments have been explored to make the ZUMA-1 and SCHOLAR-1 populations comparable. For the base case, this has been done by removing the ECOG 2–4 population from SCHOLAR-1, as ZUMA-1 only includes ECOG 0–1 patients. A propensity score analysis was performed (as a scenario analysis) to try to balance the differing patient characteristics between ZUMA-1 and SCHOLAR-1. The comparison between the propensity score analysis and the corresponding unadjusted analysis shows that the propensity score has a minimal impact on the SCHOLAR-1 OS and model outcomes. Removing individuals who are ECOG 2–4 or who went on to receive ASCT result in worse OS for SCHOLAR-1 and hence reduce the ICER.

An additional limitation of the analysis was that PFS data are not available from SCHOLAR-1; however, extreme scenario analyses in which 100% of time alive in the BSC arm was assumed to be spent in either the progression-free or progressed health state were associated with relatively small changes to the ICER of +4% and -22%, respectively, which appear to show the model base case assumption is conservative.

Further adding to model uncertainty, there are no long-term OS clinical data for patients treated with axi-cel given that ZUMA-1 is the only available clinical study investigating axi-cel in this indication and that it has a relatively short follow-up period. Based on the mechanical of action of axi-cel, clinical rationale and expert opinion, a range of plausible extrapolations were explored (including more novel mixture-cure models) and their plausibility assessed. However, without observed longer-term OS data for axi-cel, the uncertainty of the extrapolation persists.

B.4. References

1. Kite/Gilead. Clinical Validation: Interview with Dr Robert Marcus. 23 January 2018 2018. Data on File.
2. Kite/Gilead. Clinical ad board. February 2018 2018. (Updated: February 2018) Data on File.
3. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol*. 2016; 174(1):43-56.
4. Nicholson IC, Lenton KA, Little DJ, et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. *Mol Immunol*. 1997; 34(16-17):1157-65.
5. Kite Pharma Inc. KTE-C19-101 A phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive nonhodgkin lymphoma (ZUMA-1). (Clinical Study Report: KTE-C19-101) 28 July 2017 2017. Data on File.
6. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017; 130(16):1800-8.
7. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *NEJM*. 2017.
8. Kite Pharma Inc. Summary of Product Characteristics. YESCARTA (axicabtagene ciloleucel). 25 July 2017 2017. Accessed: 01 December 2017.
9. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015; 33(6):540-9.
10. Finney HM, Lawson AD, Bebbington CR and Weir AN. Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. *J Immunol*. 1998; 161(6):2791-7.
11. Restifo NP, Dudley ME and Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. *Nat Rev Immunol*. 2012; 12(4):269-81.
12. Kite Pharma Inc. Orphan designation decision for KTE-C19 for the treatment of DLBCL, PMBCL and FL. 28 July 2017 2017. Data on file
13. European Medicines Agency. Confirmation of eligibility to PRIME scheme for KTE-C19 in the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) who have not responded to their prior therapy, or have had disease progression after autologous stem cell transplant (ASCT),. 26 May 2016 2016. Data on file.
14. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*. 2013; 381(9880):1817-26.
15. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. *J Clin Oncol*. 2017; 35(5):544-51.
16. Kansara R, Savage K, Villa D, et al. Outcome in Unselected Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) Following R-CHOP When Stem Cell Transplantation Is Not Feasible. *Blood*. 2014; 124(21):3069.

17. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. *Bone Marrow Transplant*. 2016; 51(1):51-7.
18. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015; 26 Suppl 5:v116-25.
19. National Cancer Institute. Adult non-Hodgkin lymphoma treatment (PDQ®) – Health Professional Version. 2017. (Updated: 27 October 2017) Available at: https://www.cancer.gov/types/lymphoma/hp/adult-nhl-treatment-pdq. Accessed: 30 November 2017.
20. Lymphoma association. Diffuse large B-cell lymphoma. 2016. (Updated: July 2017) Available at: https://www.lymphomas.org.uk/about-lymphoma/types/non-Hodgkin-lymphoma/diffuse-large-b-cell-lymphoma. Accessed: 30 November 2017.
21. Kite/Gilead. Decision Resource group study conducted for Gilead. February 2018 2018. Data on file.
22. Hutchinson CB and Wang E. Primary mediastinal (thymic) large B-cell lymphoma: a short review with brief discussion of mediastinal gray zone lymphoma. *Arch Pathol Lab Med*. 2011; 135(3):394-8.
23. Dabrowska-Iwanicka A and Walewski JA. Primary mediastinal large B-cell lymphoma. *Curr Hematol Malig Rep*. 2014; 9(3):273-83.
24. Savage KJ, Al-Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol*. 2006; 17(1):123-30.
25. Sehn LH, Antin JH, Shulman LN, et al. Primary diffuse large B-cell lymphoma of the mediastinum: outcome following high-dose chemotherapy and autologous hematopoietic cell transplantation. *Blood*. 1998; 91(2):717-23.
26. Casulo C, Nastoupil L, Fowler NH, et al. Unmet needs in the first-line treatment of follicular lymphoma. *Ann Oncol*. 2017; 28(9):2094-106.
27. Lymphoma association. Follicular lymphoma. 2016. (Updated: August 2017) Available at: https://www.lymphomas.org.uk/about-lymphoma/types/non-Hodgkin-lymphoma/follicular-lymphoma. Accessed: 24 January 2018.
28. Casulo C, Burack WR and Friedberg JW. Transformed follicular non-Hodgkin lymphoma. *Blood*. 2015; 125(1):40-7.
29. Lossos IS and Gascoyne RD. Transformation of follicular lymphoma. *Best Pract Res Clin Haematol*. 2011; 24(2):147-63.
30. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995; 333(23):1540-5.
31. Josting A, Reiser M, Rueffer U, et al. Treatment of primary progressive Hodgkin's and aggressive non-Hodgkin's lymphoma: is there a chance for cure? *J Clin Oncol*. 2000; 18(2):332-9.
32. Ardeshna KM, Kakouros N, Qian W, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol*. 2005; 130(3):363-72.
33. Hitz F, Connors JM, Gascoyne RD, et al. Outcome of patients with primary refractory diffuse large B cell lymphoma after R-CHOP treatment. *Ann Hematol*. 2015; 94(11):1839-43.

34. Telio D, Fernandes K, Ma C, et al. Salvage chemotherapy and autologous stem cell transplant in primary refractory diffuse large B-cell lymphoma: outcomes and prognostic factors. *Leuk Lymphoma*. 2012; 53(5):836-41.
35. Matasar MJ, Czuczman MS, Rodriguez MA, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. *Blood*. 2013; 122(4):499-506.
36. Moskowitz CH, Bertino JR, Glassman JR, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. *J Clin Oncol*. 1999; 17(12):3776-85.
37. Seshadri T, Stakiw J, Pintilie M, et al. Utility of subsequent conventional dose chemotherapy in relapsed/refractory transplant-eligible patients with diffuse large B-cell lymphoma failing platinum-based salvage chemotherapy. *Hematology*. 2008; 13(5):261-6.
38. Guglielmi C, Gomez F, Philip T, et al. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the Parma trial. *J Clin Oncol*. 1998; 16(10):3264-9.
39. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol*. 2012; 30(36):4462-9.
40. Nagle SJ, Woo K, Schuster SJ, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. *Am J Hematol*. 2013; 88(10):890-4.
41. Van Den Neste E, Schmitz N, Mounier N, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. *Bone Marrow Transplant*. 2017; 52(2):216-21.
42. Straus DJ, Hamlin PA, Matasar MJ, et al. Phase I/II trial of vorinostat with rituximab, cyclophosphamide, etoposide and prednisone as palliative treatment for elderly patients with relapsed or refractory diffuse large B-cell lymphoma not eligible for autologous stem cell transplantation. *Br J Haematol*. 2015; 168(5):663-70.
43. Yost KJ, Thompson CA, Eton DT, et al. The Functional Assessment of Cancer Therapy - General (FACT-G) is valid for monitoring quality of life in patients with non-Hodgkin lymphoma. *Leuk Lymphoma*. 2013; 54(2):290-7.
44. National Institute for Health and Care Excellence (NICE). NICE pathways: Treating diffuse large B-cell lymphoma. 2017. (Updated: 21 November 2017) Available at: https://pathways.nice.org.uk/pathways/non-hodgkins-lymphoma#path=view%3A/pathways/non-hodgkins-lymphoma/treating-diffuse-large-b-cell-lymphoma.xml&content=view-index. Accessed: 7 December 2017.
45. National Institute for Health and Care Excellence (NICE). Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. 2014. Available at: https://www.nice.org.uk/guidance/ta306. Accessed: 19 December 2017.
46. Flowers CR, Sinha R and Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. *CA Cancer J Clin*. 2010; 60(6):393-408.
47. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-

prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006; 7(5):379-91.
48. Maurer MJ, Ghesquieres H, Jais JP, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol*. 2014; 32(10):1066-73.
49. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology; Non-Hodkin's Lymphomas, Version 1.2014. 2014. (Updated: 2014) Available at: https://www.nccn.org/about/nhl.pdf. Accessed: 13 December 2017.
50. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol*. 2014; 32(31):3490-6.
51. Colosia A, Njue A, Trask PC, et al. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review. *Clin Lymphoma Myeloma Leuk*. 2014; 14(5):343-55 e6.
52. Horesh N and Horowitz NA. Does gender matter in non-hodgkin lymphoma? Differences in epidemiology, clinical behavior, and therapy. *Rambam Maimonides Med J*. 2014; 5(4):e0038.
53. Ngo L, Hee SW, Lim LC, et al. Prognostic factors in patients with diffuse large B cell lymphoma: Before and after the introduction of rituximab. *Leuk Lymphoma*. 2008; 49(3):462-9.
54. Sarkozy C, Mounier N, Delmer A and et al. Impact of BMI and gender on outcomes in DLBCL patients treated with R-CHOP: A pooled study from the LYSA. Lymphoma. 16 January 2014 2014.
55. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Mol Ther*. 2017; 25(1):285-95.
56. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. *J Clin Oncol*. 2017; 35(16):1803-13.
57. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. *Mol Ther*. 2017; 25(10):2245-53.
58. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007; 25(5):579-86.
59. Wang Z and Han W. Biomarkers of cytokine release syndrome and neurotoxicity related to CAR-T cell therapy. *Biomark Res*. 2018; 6:4.
60. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018; 15(1):47-62.
61. American Society of Clinical Oncology (ASCO). Clinical Cancer Advances. 2018. (Updated: 2018).
62. Narasimhan V. Novartis CTL019 – JULIET data on DLBCL Investor call. 2017. (Updated: 16 June 2017) Available at: https://www.novartis.com/sites/www.novartis.com/files/2017-06-ir-call-ctl019-dlbcl-juliet-presentation.pdf. Accessed: 7 December 2017.
63. Simon R, Blumenthal GM, Rothenberg ML, et al. The role of nonrandomized trials in the evaluation of oncology drugs. *Clin Pharmacol Ther*. 2015; 97(5):502-7.

64. Hamid O and Carvajal RD. Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. *Expert Opin Biol Ther*. 2013; 13(6):847-61.
65. Wolchok JD, Hodi FS, Weber JS, et al. Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma. *Ann N Y Acad Sci*. 2013; 1291:1-13.
66. Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. *Blood*. 2012; 119(12):2709-20.
67. Kymes SM, Pusic I, Lambert DL, et al. Economic Evaluation of a Plerixafor for Stem Cell Mobilization. *The American journal of managed care*. 2012; 18(1):33-41.
68. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess*. 2017; 21(7):1-204.
69. Woods B, Sideris E, Palmer S, et al. NICE DSU Technical Support Document 19: Partitioned survival analysis for decision modelling in health care: a critical review. 2017. Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed: 02 January 2018.
70. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. 2011. (Updated: March 2013) Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. Accessed: 19 December 2017.
71. Othus M, Bansal A, Koepl L, et al. Accounting for Cured Patients in Cost-Effectiveness Analysis. *Value Health*. 2017; 20(4):705-9.
72. Lambert PC, Thompson JR, Weston CL and Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics*. 2007; 8(3):576-94.
73. Bansal A, Lin V, Sullivan SD, et al. Estimating Long-Term Survival for Patients with Relapsed or Refractory Aggressive Non-Hodgkin Lymphoma Treated with Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy: A Comparison of Standard and Mixture Cure Models. *Biology of Blood and Marrow Transplantation*. 24(3):S310.
74. Faria R, Alava M, Manca A and Wailoo A. NICE DSU technical support document 17: the use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data. 2015. Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD17-DSU-Observational-data-FINAL.pdf.
75. National institute for Health and Care Excellence (NICE). Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. 2009. Available at: https://www.nice.org.uk/guidance/ta169. Accessed: 19 December 2017.
76. Office for National Statistics. National life tables: England and Wales. 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables. Accessed: 13 November 2017.

77. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. Accessed: 02 January 2018.
78. Eyre TA, Linton KM, Rohman P, et al. Results of a multicentre UK-wide retrospective study evaluating the efficacy of pixantrone in relapsed, refractory diffuse large B cell lymphoma. *Br J Haematol*. 2016; 173(6):896-904.
79. London Cancer Alliance. Non-Hodgkin's Lymphoma. TWG Agreed Regimens. Available at: http://www.londoncanceralliance.nhs.uk/information-for-healthcare-professionals/forms-and-guidelines/south-east-london-cancer-network/haematology/non-hodgkins-lymphoma/. Accessed: 10 November 2017.
80. Thames Valley Strategic Clinical Networks. Lymphoma group. R-VP. Available at: http://nssg.oxford-haematology.org.uk/lymphoma/pdf-protocols/L-40-r-vp.pdf. Accessed: 10 November 2017.
81. National Institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L valuation set. 2017. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf. Accessed: 02 January 2018.
82. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012; 15(5):708-15.
83. Knight C, Hind D, Brewer N and Abbott V. Rituximab (MabThera) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation. *Health Technol Assess*. 2004; 8(37):iii, ix-xi, 1-82.
84. Huntington SF, Svoboda J and Doshi JA. Cost-effectiveness analysis of routine surveillance imaging of patients with diffuse large B-cell lymphoma in first remission. *J Clin Oncol*. 2015; 33(13):1467-74.
85. Janssen B and Szende A. Population Norms for the EQ-5D. In: Szende A, Janssen B and Cabases J, (eds). *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht: Springer Netherlands, 2014, p.19-30.
86. Department of Health. NHS National Schedule of Reference Costs 2015 to 2016. 2016. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.
87. Department of Health. Drugs and pharmaceutical electronic market information (eMit) Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed: 14 November 2017.
88. NHS Digital. Hospital Episode Statistics. Hospital Admitted Patient Care Activity, 2015-16: Healthcare Resource Groups. 2016. Available at: http://content.digital.nhs.uk/article/2021/Website-Search?productid=23488&q=title%3a%22Hospital+Episode+Statistics%2c+Admitted+patient+care+-+England%22+or+title%3a%22Hospital+Admitted+Patient+Care+Activity%22&sort=Relevance&size=10&page=1&area=both#top. Accessed: 28 Auguest 2017.
89. Curtis L. Unit Costs of Health and Social Care 2016. Canterbury, Kent: Personal Social Services Research Unit. Available at: http://docplayer.net/7404866-Unrelated-donor-stem-cell-transplantation-in-the-uk.html. Accessed: 28 August 2017.
90. National Audit Office. End of Life Care Available at: https://www.nao.org.uk/wp-content/uploads/2008/11/07081043.pdf. Accessed: 28 August 2017.

91. UK Stem Cell Strategy Oversight Committee. Unrelated Donor Stem Cell Transplantation in the UK. Available at: http://docplayer.net/7404866-Unrelated-donor-stem-cell-transplantation-in-the-uk.html. Accessed: 28 August 2017.

B.5. Appendices

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

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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

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

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional evidence from ZUMA-1

Appendix M: Manufacturing process

Appendix N: Description of the mixture cure model

Appendix O: Description of the propensity score matching

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Single technology appraisal

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Dear Kite - a Gilead company

The Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York and the technical team at NICE have looked at the submission received on 15 February 2018 from Kite - a Gilead company. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Monday 26 March 2018.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Lorna Dunning, Technical Lead (lorna.dunning@nice.org.uk). Any procedural questions should be addressed to Stephanie Callaghan, Project Manager (Stephanie.callaghan@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals

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On behalf of:

Dr. Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. The search strategy used for MEDLINE and Embase excludes search terms for scope-relevant comparator treatments yet includes terms for treatments not included in the NICE scope. For example, vinorelbine, oxaliplatin and mitoxantrone are included in the search terms, but these are neither listed in the systematic literature review eligibility criteria (Table 5 in appendices document) nor in Table 1 of the main submission (the decision problem table). Conversely, the eligibility criteria include cisplatin + cytarabine + dexamethasone (DHAP) but the search does not contain search terms for cisplatin, DHAP, R-DHAP, carboplatin or ICE/R-ICE. When search statement 8 was re-constructed using PubMed on 21st February 2018 it identified 8573 records compared to 0 recorded in the company submission. In light of these omissions and discrepancies please comment on the likelihood of relevant comparator treatment studies being missed by the database searches.

A2. **Priority question:** The SCHOLAR-1 refractory subgroup is categorised as 'first refractory' and 'last refractory', in which the first refractory categorisation maximises cases in the analyses (page 93). Please clarify if the last refractory categorisation is based on the last time the patient was determined as refractory, and if this includes all 'First refractory' patients at the last line of treatment they were refractory. If so, please explain how the 'Last refractory' categorisation provides a reduced number of cases for analysis. Please provide greater clarity on the meaning of these categorisations.

A3. **Priority question** on patient groups who would be considered eligible for Axi-cel:
   a. Please amend the first bullet point listed on page 22 of the company submission; the current text and Figure 3 are unclear as to whether this relates to patients being refractory after second-line therapy - corresponding with the far left green-highlight in Figure 3, or if a green Axi-cel highlight should be added to the "Refractory after 1st line" box of Figure 3 (even though only 2% of the ZUMA-1 population occupied this stage in the pathway).
   b. Please clarify the proposed position of the second bullet point on page 22 describing relapsed patients who are ineligible for ASCT due to age and comorbidities. The ZUMA-1 eligibility criteria were designed to "restrict enrolment to subjects who would have been considered eligible for ASCT if

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they had had chemosensitive disease" (page 34 of the clinical study report). Please provide evidence for this specific population.

A4. **Priority question**: *ZUMA-1 updated analysis cohort n=108 (page 39)*. Please clarify if the n=108 comprises 101 patients from phase 2 plus 7 from phase 1, with no overlap of patients across phases, and if the full analysis population including all enrolled patients would therefore be n=119. Please provide a CONSORT flow diagram for the full intention-to-treat (ITT) population. Please include the number of patients assessed for eligibility, and those who were excluded, giving reasons for exclusion, such as declined to participate, intolerant to 1st line chemotherapy etc.

A5. **Priority question**: For the outcomes presented in Tables 15 and 16 of the main submission please provide results for the following populations/subgroups without any standardising:
   a. SCHOLAR-1 evaluable patients (n=508/497) vs ZUMA-1 n=108
   b. SCHOLAR-1 evaluable ECOG 0-1 patients vs ZUMA-1 n=108
   c. SCHOLAR-1 evaluable ECOG 0-1 patients vs ZUMA-1 n=108 split by refractory subgroups: primary refractory, refractory to second or later line, and relapse within 12 months of ASCT.

A6. Please clarify how the covariates were chosen in the propensity scoring analysis. For the propensity score dataset please provide a baseline characteristics table (same characteristics as detailed in Table 9 of the appendices document). Please include the sample sizes used in the propensity scores dataset for each study, including how many unique SHOLAR-1 patients were included.

A7. Table 4 and supplemental Figure 2 in the SCHOLAR-1 2017 paper by Crump et al report OS results by patient subgroup for the N=636 cohort. Please provide the ECOG subgroup results and associated Kaplan-Meier curves for the cohort relevant for comparison with ZUMA-1 (i.e. N=497 as described on page 21 of the submitted appendices document).

A8. For the [redacted] (page 74) please provide details as to how many had B-cell aplasia in the updated analysis (i.e. minimum 1 year follow up, median of 15.4 months) and how many had concomitant persistence of CAR-T cells in the blood in the updated analysis.

A9. Please provide the supplementary appendix for reference 7, Neepalu 2017.

Section B: Clarification on cost-effectiveness data

Previously published studies

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B1. **Priority question:** The search for published cost-effectiveness studies was conducted on 27th September 2017. More recently, the Institute for Clinical and Economic Review (ICER) published an evidence report on the comparative effectiveness and value for axicabtagene ciloleucel (https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Evidence_Report_021518.pdf).
Please provide a short summary and critique of the cost-effectiveness model, highlighting any important similarities and differences in approaches and results.

Effectiveness inputs

B2. **Priority question:** Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival (PFS), and overall survival (OS):

a. For the Full Analysis Set (defined as all subjects enrolled) in ZUMA-1 phase 1/ 2 from the time of enrolment.
b. For the modified ITT population in ZUMA-1 phase 1/2, by response status (complete response, partial response, stable disease).
c. For the modified ITT population in ZUMA-1 phase 1/2, separately for cohort 1 and cohort 2.
d. For the 10 patients in ZUMA-1 phase 1/2 who were retreated with axi-cel.

B3. **Priority question:** Please provide the following information relating to the mixture cure models (MCM):

a. The command and specification of the MCM in STATA (e.g. strsmix) and confirmation of whether the models incorporate the expected background mortality rate.
b. Justification for why the MCM models were not fitted for PFS.
c. Replicate the following tables (28, 29, 32, 33) and figures (20 to 22, 26 to 27) using the mixture-cure method for PFS (axi-cell and best supportive care [BSC]).
d. Comment on any differences in size of the cure fraction between PFS and OS and possible explanations.
e. Please provide a revised economic model which includes functionality to select mixture-cure models for the axi-cel and BSC PFS curves.

B4. **Priority question:** Although the costs of leukapheresis and conditioning therapy are included for those who did not undergo axi-cel infusion (i.e. difference between the Full Analysis Set and the modified ITT population), the analysis does not capture the survival and QALYs of those patients. As a result, the use of the modified ITT instead of ITT data from ZUMA-1 Phase 1/2 for PFS and OS may lead to potential bias in the cost-effectiveness estimates when comparing with BSC.

a. Please present an additional scenario which explores the potential impact of including the Full Analysis Set population (e.g. using the PFS and OS data from the Full Analysis Set or using a simple decision tree to weight the overall costs

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and QALYs in patients who were infused with axi-cell and those who received leukapheresis but were not subsequently infused with axi-cell).

b. Please summarise the approach and assumptions used.
c. Please provide a revised economic model which includes this scenario.

B5. Please specify the statistical model used for propensity score matching of SCHOLAR-1, which was used to generate the BSC OS curve in the model, and provide the rationale for model/variable selection.

Health related Quality of Life

B6. Please define the safety management cohort referred to in page 34 of the company submission in terms of inclusion criteria and provide baseline patient characteristics as per table 11 in the company submission (pages 55-57). Please clarify if EQ-5D-5L was collected in any other patients in ZUMA-1. If so, please replicate Table 8 (page 35 company submission) for the full set of patients who provided EQ-5D-5L data.

Resource use and costs

B7. Please provide a breakdown of the proportion of patients in ZUMA-1 who underwent a second round of conditioning chemotherapy due to delays in the manufacture of axi-cel. Please incorporate the resulting cost in the updated model.

B8. Please confirm whether the list price and average cost of a course of treatment (Table 2 – company submission) is a provisional or final price.

B9. **Priority question**: Please provide further details on the process of administration, tracking and shipping of apheresis products and the management of severe toxicity. In response to this question please refer to the recent article by *Perica* et al and summarise whether similar processes are likely to be required within the NHS, highlighting any additional resource/cost implications that have not been formally quantified (e.g. additional administration costs associated with ensuring the chain of custody of the cell product, whether ITU beds may need to be made available even if not used etc).

Reference: *Karlo Perica, Kevin J. Curran, Renier J. Brentjens, Sergio A. Giralt, Building a CAR Garage: Preparing for the Delivery of Commercial CAR T Products at Memorial Sloan Kettering Cancer Center, Biology of Blood and Marrow Transplantation (2018), https://doi.org/10.1016/j.bbmt.2018.02.018*).

Adverse events

B10. [redacted] in ZUMA-1 are reported to have experienced [redacted]. IVIG has been identified as an important element of cost in previous studies. Please provide the average duration of IVIG treatment for

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hypogammaglobulinemia in ZUMA-1 and incorporate this cost and disutility in an updated version of the economic model.

B11. Please provide a full breakdown of the number of patients in ZUMA-1 with Grade 1 and 2 cytokine release syndrome (CRS), and the proportion of those who received treatment for CRS with tocilizumab. Please incorporate this cost in the updated economic model.

B12. Not all adverse events (AEs) reported in ZUMA-1 are incorporated in the economic model. For example, only encephalopathy is included of all the neurological AEs, although grade 3 aphasia and headache were reported. Please provide further justification for the specific AEs included in the model.

B13. Leukapheresis-related AEs were not included in the model. Please update the model, to include disutility associated with incidence of leukapheresis-related AEs as reported in Table 48 of the clinical study report.

Section C: Textual clarifications and additional points

C1. Table 51, appendix O. Number of patients from each study do not match what has been reported in the company submission. Please correct if it is an error or provide detail on why the numbers do not match the ones reported in the company submission. If different subsets of the study population were used, please report patient characteristics for each study as per Table 11 in the company submission (pages 55-57).

C2. Figure 28 in the company submission (page 113) appears to depict the OS curve axi-cel, rather than the PFS one. Please submit the correct graph.

C3. Please provide the bibliographical reference to the list of chemotherapy regimens used in UK clinical practice, as compiled by the Oxford University Hospitals (OUH) NHS Foundation Trust (page 99 of the company submission).

C4. Please clarify the number of patients who received subsequent ASCT after treatment with axi-cel in the ZUMA-1 trial. [redacted] patients are reported on page 82 of the company submission but [redacted] of patients are reported on page 94 in Table 24.

Single technology appraisal

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Dear Nicola,

Thank you for the opportunity to respond to the clarification questions from the Evidence Review Group, Centre for Reviews and Dissemination and Centre for Health Economics – York and the technical team at NICE. We thank the team for their general comments on the submission and hope that our responses below provide clarity for our approach in the submission.

As requested, we have uploaded to NICE Docs two versions of this response letter: one with academic/commercial-in-confidence information clearly marked and one with this information removed, along with the completed checklist, the additional references for questions A9 and B10, and an updated cost-effectiveness model.

Should you have any questions regarding our responses below, please do not hesitate to get in touch.

Yours sincerely

[redacted]
On behalf of Kite a Gilead Company

Section A: Clarification on effectiveness data

A1. The search strategy used for MEDLINE and Embase excludes search terms for scope-relevant comparator treatments yet includes terms for treatments not included in the NICE scope. For example, vinorelbine, oxaliplatin and mitoxantrone are included in the search terms, but these are neither listed in the systematic literature review eligibility criteria (Table 5 in appendices document) nor in Table 1 of the main submission (the decision problem table). Conversely, the eligibility criteria include cisplatin + cytarabine + dexamethasone (DHAP) but the search does not contain search terms for cisplatin, DHAP, R-DHAP, carboplatin or ICE/R-ICE. When search statement 8 was re-constructed using PubMed on 21st February 2018 it identified 8573 records compared to 0 recorded in the company submission. In light of these omissions and discrepancies please comment on the likelihood of relevant comparator treatment studies being missed by the database searches.

The scope-relevant comparators i.e. DHAP, GDP, ICE, IVE, are combination therapies whose “individual” therapies terms are present in the searches. For example, DHAP is cisplatin + cytarabine + dexamethasone. Therefore, as dexamethasone was present in the searches, any study which assess this combination (or similar) should have been identified.

Furthermore, it is correct that oxaliplatin, vinorelbine, mitoxantrone were present in the searches but not in Table 5 of the appendices document and in Table 1 of the main submission. However, they were being searched at a very early stage before the final NICE scope was available. Although not of value, keeping these interventions in the searches will not increase the likelihood of relevant studies being missed.

Additionally, "oxaliplatin" term is a typographic error for Medline, so statement 8 in Table 3 for Pubmed searches can be modified to 8573. As oxaliplatin is not a relevant comparator (not present in Table 5), this does not have an effect on the relevant comparator treatment studies being missed by the database searches.

A2. **Priority question:** The SCHOLAR-1 refractory subgroup is categorised as 'first refractory' and 'last refractory', in which the first refractory categorisation maximises cases in the analyses (page 93). Please clarify if the last refractory categorisation is based on the last time the patient was determined as refractory, and if this includes all 'First refractory' patients at the last line of treatment they were refractory. If so, please explain how the 'Last refractory' categorisation provides a reduced number of cases for analysis. Please provide greater clarity on the meaning of these categorisations.

Patients may be refractory to therapy multiple times throughout the treatment course. Therefore, the refractory subgroup was classified in 2 ways: 1) based on the first time a subject was determined to be refractory (First Refractory Categorization) and 2) based on the last time in the treatment course the subject was determined to be refractory (Last Refractory Categorization). Patients can only be analysed for an outcome if a line of therapy after determination of refractory status is present in the database. This, coupled with the fact that almost all subjects in the SCHOLAR-1 database have a record of 1st and 2nd line therapy, but fewer have records of later line therapy, leads to a reduction in the number of subjects available for analysis when categorized according to the Last Refractory categorization. The presence of treatment records in the database defining inclusion into SCHOLAR-1 analyses is a critical component of the SCHOLAR-1 design. Subjects without records of therapy may have been lost to follow up or not sought further treatment. Such subject cases are not comparable to the ZUMA-1 population and hence were not included in analyses of Last Refractory Categorization.

As a result, analyses by last refractory categorization may not necessarily include all first refractory patients. For example, a patient refractory to 1st and 3rd line therapy with records of 1st, 2nd and 3rd line therapy will be classified as primary refractory with response to 2nd line therapy used in the analysis, but will not be included in the by Last Refractory categorization group as no 4th line therapy is present in the database.

A3. **Priority question** on patient groups who would be considered eligible for Axi-cel:

a. Please amend the first bullet point listed on page 22 of the company submission; the current text and Figure 3 are unclear as to whether this relates to patients being refractory after second-line therapy - corresponding with the far left green-highlight in Figure 3, or if a green Axi-cel highlight should be added to the "Refractory after 1st line" box of Figure 3 (even though only 2% of the ZUMA-1 population occupied this stage in the pathway).

As you have highlighted there should be a green axi-cel highlight in fig 3 for the primary refractory population.

b. Please clarify the proposed position of the second bullet point on page 22 describing relapsed patients who are ineligible for ASCT due to age and comorbidities. The ZUMA-1 eligibility criteria were designed to "restrict enrolment to subjects who would have been considered eligible for ASCT if they had had chemosensitive disease" (page 34 of the clinical study report). Please provide evidence for this specific population.

Our clinical advisory board indicated there could be a small group of patients who would not be eligible for ASCT but could be considered eligible for axi-cel therapy. It opens up the potential for long term remission/cure which is not available to these patients. The criteria for fitness for ASCT and axi-cel therapy are very similar and overlap considerably or almost completely. So, if not fit for ASCT it is unlikely that a patient would be fit enough for CAR-T therapy. The advisors did think it important to consider this group as eligible for axi-cel because of the lack of any other potentially curative options. However, when pushed the advisors found it challenging to come up with a clear list of identifying factors for such patients.

A4. **Priority question**: *ZUMA-1 updated analysis cohort n=108 (page 39)*. Please clarify if the n=108 comprises 101 patients from phase 2 plus 7 from phase 1, with no overlap of patients across phases, and if the full analysis population including all enrolled patients would therefore be n=119. Please provide a CONSORT flow diagram for the full intention-to-treat (ITT) population. Please include the number of patients assessed for eligibility, and those who were excluded, giving reasons for exclusion, such as declined to participate, intolerant to 1st line chemotherapy etc.

The n=108 does comprise 101 patients from phase 2 (P2) and 7 patients from phase 1 (P1), there is no overlap, and the full analysis population (P1+P2) is n=119.

Figure 1. Consort Diagram for Phase 1 (full analysis set)

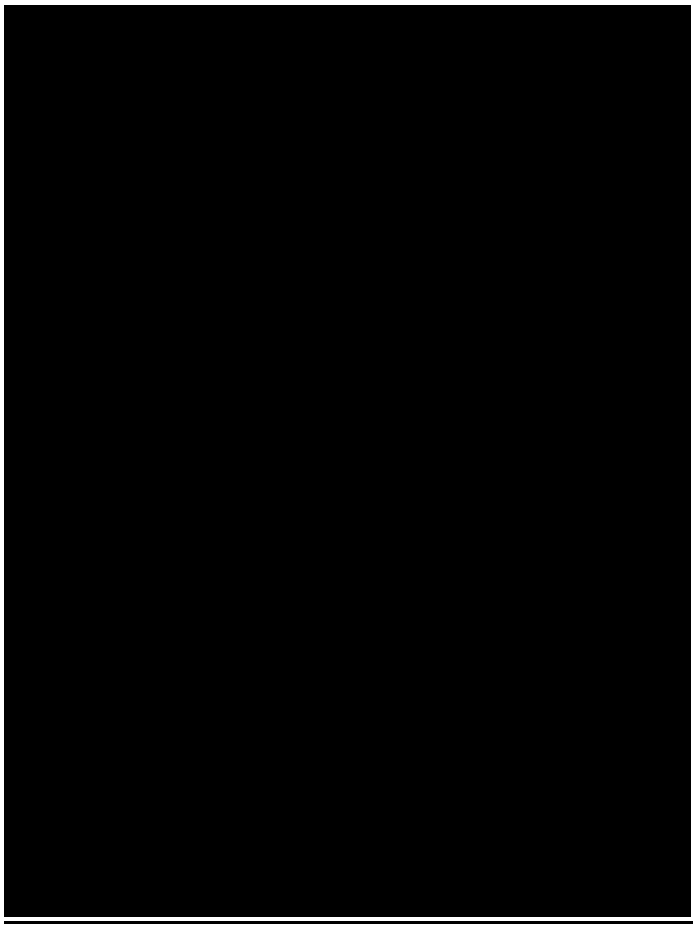
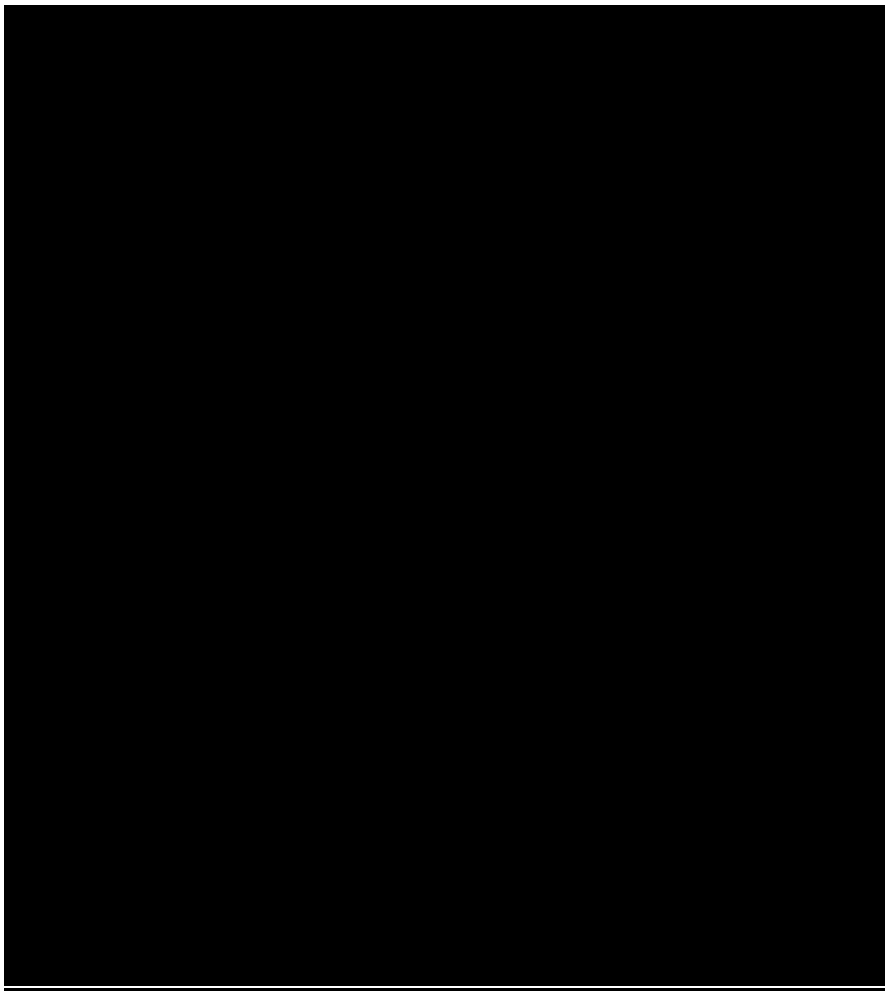


Figure 2.Consort diagram for Phase 2 (full analysis set)



[redacted]

A5. **Priority question**: For the outcomes presented in Tables 15 and 16 of the main submission please provide results for the following populations/subgroups without any standardising:

a. SCHOLAR-1 evaluable patients (n=508/497) vs ZUMA-1 n=108

Table 1. Response and Complete Response Rates: ZUMA-1 Safety Population and SCHOLAR-1 (Last Refractory Categorization)

	ZUMA-1 mITT (N=108)	**SCHOLAR-1 Response (N=508)**	**Difference (95% CI)[a]**	**Odds ratio (95% CI)**
ORR	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]

[a] 95% confidence interval calculated with Wilson's Score method.

Table 2. Overall Survival: ZUMA-1 Safety Population and SCHOLAR-1 (Last Refractory Categorization)

	ZUMA-1 mITT (N=108)	**SCHOLAR-1 Survival (N=497)**
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

NR – not reached

b. SCHOLAR-1 evaluable ECOG 0-1 patients vs ZUMA-1 n=108

Table 3. Response and Complete Response Rates: ZUMA-1 Safety Population and SCHOLAR-1 ECOG 0-1 (Last Refractory Categorization)

	ZUMA-1 mITT (N=108)	**SCHOLAR-1 Response (N=230)**	**Difference (95% CI)[a]**	**Odds ratio (95% CI)**
ORR	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]

[a] 95% confidence interval calculated with Wilson's Score method.

Table 4. Overall Survival: ZUMA-1 Safety Population and SCHOLAR-1 ECOG 0-1 (Last Refractory Categorization)

	ZUMA-1 mITT (N=108)	SCHOLAR-1 Survival (N=226)
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

NR – not reached

c. SCHOLAR-1 evaluable ECOG 0-1 patients vs ZUMA-1 n=108 split by refractory subgroups: primary refractory, refractory to second or later line, and relapse within 12 months of ASCT.

Table 5. Response and Complete Response Rates: ZUMA-1 Safety Population (Primary Refractory) and SCHOLAR-1 ECOG 0-1 (Primary Refractory) (Last Refractory Categorization)

	ZUMA-1 mITT (N=3)	SCHOLAR-1 Response (N=65)	Difference (95% CI)[a]	Odds ratio (95% CI)
ORR	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]

NE – not estimable

Table 6. Response and Complete Response Rates: ZUMA-1 Safety Population (Refractory to Second or Later Line) and SCHOLAR-1 ECOG 0-1 (Refractory to Second or Later Line) (Last Refractory Categorization)

	ZUMA-1 mITT (N=80)	SCHOLAR-1 Response (N=123)	Difference (95% CI)[a]	Odds ratio (95% CI)
ORR	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]

Table 7. Response and Complete Response Rates: ZUMA-1 Safety Population (Relapse within 12 Mos of ASCT) and SCHOLAR-1 ECOG 0-1 (Relapse within 12 Mos of ASCT) (Last Refractory Categorization)

	ZUMA-1 mITT (N=25)	SCHOLAR-1 Response (N=42)	Difference (95% CI)[a]	Odds ratio (95% CI)
ORR	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]

Table 8. Overall Survival: ZUMA-1 Safety Population (Primary Refractory) and SCHOLAR-1 ECOG 0-1 (Primary Refractory) (Last Refractory Categorization)

	ZUMA-1 mITT (N=3)	SCHOLAR-1 Survival (N=65)
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

Table 9. Overall Survival: ZUMA-1 Safety Population (Refractory to Second or Later Line) and SCHOLAR-1 ECOG 0-1 (Refractory to Second or Later Line) (Last Refractory Categorization)

	ZUMA-1 mITT (N=80)	SCHOLAR-1 Survival (N=121)
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

Table 10. Overall Survival: ZUMA-1 Safety Population (Relapse within 12 Mos of ASCT) and SCHOLAR-1 ECOG 0-1 (Relapse within 12 Mos of ASCT) (Last Refractory Categorization)

	ZUMA-1 mITT (N=25)	SCHOLAR-1 Survival (N=40)
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

A6. Please clarify how the covariates were chosen in the propensity scoring analysis. For the propensity score dataset please provide a baseline characteristics table (same characteristics as detailed in Table 9 of the appendices document). Please include the sample sizes used in the propensity scores dataset for each study, including how many unique SHOLAR-1 patients were included.

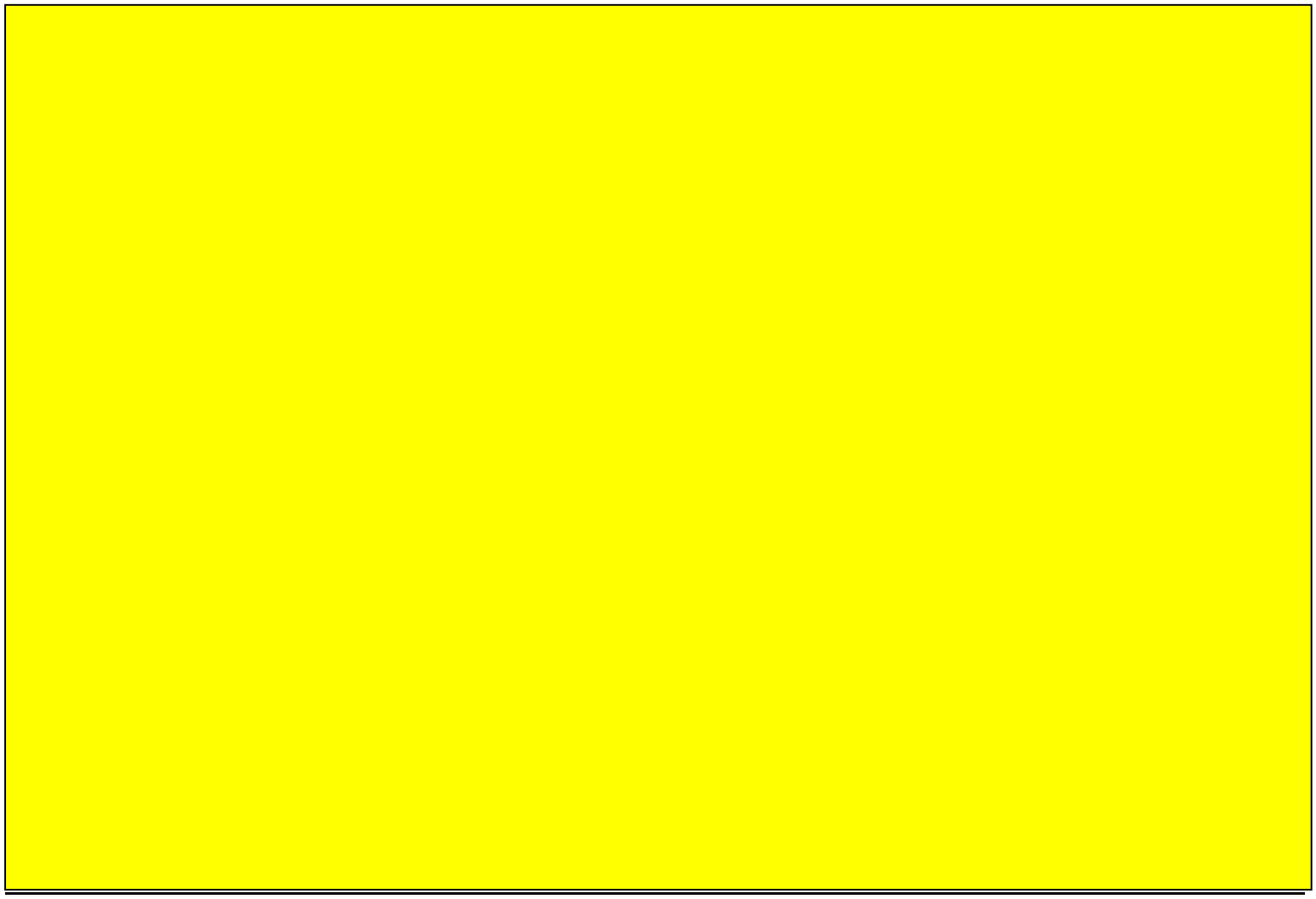
Covariates for the propensity score matching were selected using the following criteria: (i) inclusion in both datasets (which is of course necessary); (ii) perceived prognostic relevance; and (iii) the extent to which data were commonly missing for a given variable. Although it

would have been preferable to include covariates, such as ECOG or disease stage, in the propensity score analysis, the extent of the missing data in SCHOLAR-1 would have required discarding many outcomes. Therefore, it was thought that the approach used provided the most data points and a more robust analysis and you would not expect a difference in the distribution of baseline characteristics from those in Table 9. A clarification of the sample sizes is provided in the response to C1.

A7. Table 4 and supplemental Figure 2 in the SCHOLAR-1 2017 paper by Crump et al report OS results by patient subgroup for the N=636 cohort. Please provide the ECOG subgroup results and associated Kaplan-Meier curves for the cohort relevant for comparison with ZUMA-1 (i.e. N=497 as described on page 21 of the submitted appendices document).

The ECOG subgroup results are provided in Figure 3. Subjects are included in this analysis if ECOG was measured within 3 months of determination of refractory status (Last Refractory categorization). Given that not all subjects had a measurement of ECOG status within 3 months of determination of refractory status, the number of subjects included is [redacted] rather than n=497.

Figure 3. Overall survival by ECOG classification



A8. For the [redacted] evaluable patients at Month 6 who had B-cell aplasia (page 74) please provide details as to how many had B-cell aplasia in the updated analysis (i.e. minimum 1 year follow up, median of 15.4 months) and how many had concomitant persistence of CAR-T cells in the blood in the updated analysis.

At Month 6 (n = [redacted] subjects), [redacted] subjects [redacted] had detectable CAR-T cells and no detectable B cells, [redacted] subjects [redacted] had detectable CAR-T cells and detectable B cells, [redacted] subject [redacted] had no detectable CAR-T cells and detectable B cells, and [redacted] subjects [redacted] had no detectable CAR-T cells and no detectable B cells.

At Month 12 (n = [redacted] subjects), [redacted] subjects [redacted] had detectable CAR-T cells and no detectable B cells, [redacted] subjects [redacted] had detectable CAR-T cells and detectable B cells, and [redacted] subjects [redacted] had no detectable CAR-T cells and detectable B cells.

At Month 15 (n = [redacted] subjects), [redacted] subjects [redacted] had detectable CAR-T cells and no detectable B cells, [redacted] subjects [redacted] had detectable CAR-T cells and detectable B cells, and [redacted] subjects [redacted] had no detectable CAR-T cells and detectable B cells.

Overall, these data indicate a decline in the number of subjects with detectable CAR-T cells along with an increase in the number of subjects with detectable B cells over time.

A9. Please provide the supplementary appendix for reference 7, Neepalu 2017.

Submitted to NICE Docs.

Section B: Clarification on cost-effectiveness data

B1. **Priority question:** The search for published cost-effectiveness studies was conducted on 27th September 2017. More recently, the Institute for Clinical and Economic Review (ICER) published an evidence report on the comparative effectiveness and value for axicabtagene ciloleucel (https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Evidence_Report_021518.pdf).
Please provide a short summary and critique of the cost-effectiveness model, highlighting any important similarities and differences in approaches and results.

The ICER report aimed to evaluate the comparative clinical and cost effectiveness of CAR-T therapies with current standard of care for the treatment of B-cell acute lymphoblastic leukaemia and aggressive B-cell non-Hodgkin's lymphoma. To assess the cost-effectiveness of axi-cel versus best supportive care (BSC) in the treatment of relapsed/refractory aggressive B-cell lymphoma, ICER built a two-part model consisting of a short-term decision tree and long-term semi-Markov partitioned survival model. The key measures of benefit assessed were overall survival and health-related quality of life, with intermediate outcomes of response, event-free survival and remission.

The short-term phase of the model followed patients from leukapheresis and tracked patient response status, receipt of SCT and treatment-related costs. Following assessment of response, a partitioned survival approach was used to model long-term treatment outcomes by extrapolating OS and PFS over a period of 5 years, using the following health states:

- Alive and responding to treatment (PFS)
- Alive and not responding to treatment (OS-PPS)
- Dead (1-OS)

Note, the ICER model did not use separate OS and PFS based on response status, instead, the overall OS and PFS (combining responders and non-responders) were used. ICER did not have access to ZUMA-1 and SCHOAR-1 patient level data, instead, the published OS and PFS curves were digitised and pseudo patient level data constructed (using the Guyot algorithm) to fit the survival curves in the ICER model.

The 5-year time horizon was chosen under the assumption that patients who were alive and responding to treatment at that time were long-term survivors and thus had survival equal to that of the age- and gender-matched general population. For those patients who were alive and not responding to treatment, these did not transition to general population mortality and instead were assumed to die at 5 years.

A summary of the similarities and differences in the approaches used in the ICER report and the submitted NICE model is presented below.

Table 11: Comparison of the submitted NICE model and the ICER model

	ICER model	Submitted NICE model	Comments/critique on similarities and differences
Axi-cel survival data	Pseudo patient level data from the digitization of OS and PFS KMs. Phase 2 ZUMA-1 data was used.	Patient level OS and PFS KMs. Combined phase 1/2 ZUMA-1 data was used.	The pseudo patient level data used in the ICER model is a less accurate source of survival data to the patient level data used in the NICE submitted model. The use of combined Phase 1/2 ZUMA-1 data allows for a larger patient population to be utilised.
BSC survival data (SCHOLAR-1)	Pseudo patient level data from the digitization of the OS KM. The PFS curve was derived from available OS data for SCHOLAR-1 chemotherapies, by assuming the proportional relationship from a published PFS and OS curve for RDHAP in the same disease state.	Patient level OS KM. SCHOLAR-1 data was adjusted by removing patients with ECOG status of 2-4. PFS was derived from BSC OS by assuming the proportional relationship of ZUMA-1 PFS and OS.	The pseudo patient level data used in the ICER model is a less accurate source of survival data to the patient level data used in the NICE submitted model. The availability of SCHOLAR-1 patient level data allowed the data to be adjusted (i.e. by removing ECOG 2-4 patients), based on patient's baseline characteristics, to be more comparable to patients in the ZUMA-1 trial. Similar assumptions were used to create the PFS data – i.e. assuming the same proportionality relationship between OS and PFS from another trial.
Extrapolation methods	Parametric modelling was used for a 5-year time horizon, with a two-phase piece-wise approach to account for long-term survivors. After 5 years, OS equals general population survival and PFS remain constant for responders. After the 5-year time horizon, patients in the 'alive and not responding to treatment' state will be assumed dead.	Mixture-cure regression modelling for axi-cel OS; standard parametric modelling used for axi-cel PFS and BSC OS.	With the ZUMA-1 patient level data, it was possible for a mixture cure model to be fitted and used for the base case OS submitted NICE model. This is a statistical approach which is reported in the literature for its use in survival modelling where a plateau in the survival curve is observed (i.e. intervention resulting in long term survivors). The approach used in the ICER model similarly assumed a plateau in the OS and represented long-term survivors by directly applying general population mortality to responders after 5 years. As in both approaches, the 'good prognosis' patients have the survival probability equal to the general population. However, for the patients with poor prognosis, the ICER model uses a more arbitrary approach by assuming that all non-responding patients will be dead at 5 years.
Adverse events	Modelled AEs were any grade 3/4 that occurred in ≥ 5% of patients in any of the treatments and comparators.	Modelled AEs were any grade 3/4 that occurred in ≥ 10% of patients for the treatment only.	A difference between the AEs included in the submitted NICE model and the ICER model are the cut-offs used – the ICER model includes more AEs because of the lower cut-off (≥ 5% compared to ≥ 10%).

	ICER model	Submitted NICE model	Comments/critique on similarities and differences
	AE costs were assumed to be covered in the costs for hospitalisation and administration, except for CRS and B cell aplasia. For CRS, tocilizumab and ICU stay costs were applied. For B-cell aplasia, costs of IVIG treatment were applied.	AEs for BSC arm not included. AE costs were assumed to be covered in the costs for hospitalisation and administration, except for CRS - where tocilizumab and ICU stay costs were applied.	The assumptions differed around costs and disutilities associated with AEs for the comparator arm. It is conservatively assumed that no AE costs or disutilities are incurred in the BSC arm in the NICE model; while ICER presented costs and disutilities for AEs in the BSC arm. Similar methods for costing AEs were applied in both models. For the consideration of costs relating to B-cell aplasia in the NICE model, please see response to Question B10.
Utilities	After 5 years in the 'alive and responding to treatment' state, utilities are assumed equal to those of the age and gender matched general population	After 2 years in the progression-free state, utilities are assumed equal to those of the age and gender matched general population	In the NICE model, the use of a 2-year 'cut-off' as opposed to 5 years was chosen based on literature findings (Maurer et al, 2014), which found that DLBCL patients who were disease-free at 24 months had no significant difference in subsequent survival compared with that for the general population. When justifying the use of the 5-year cut off used in the ICER model, ICER referenced the York study. In contrast to the findings from Maurer which were specific to DLBCL, the York study was based on post-HSCT survival in ALL patients. Therefore the 2-year cut off, supported by Maurer, is the more relevant estimate because of the greater comparability to the patient population considered in this submission.
Axi-cel costs	Kite price + $100k 'mark-up' for hospital administration	Based on Kite price (no mark-up)	The axi-cel price used in the submitted NICE model considered the acquisition cost of axi-cel. The mark up of $100k used in the ICER model appears to be relatively arbitrary and is not based on a UK perspective.
Resource use costs	Monthly healthcare costs were assigned to patients for the remainder of their lifetime if they were alive and responding to treatment after five years.	Monthly healthcare costs were assigned to patients in the progression-free and progressed state for patients' lifetime. For progression-free patients, no cancer-related costs were applied after 2 years.	In the submitted NICE model, the use of a 2-year 'cut-off' for resource use in progression-free patients was based on the Maurer paper. It was assumed that patients who had not progressed after 2 years no longer required disease-related monitoring etc.
ZUMA-1 patients who did not receive axi-cel	The decision tree part of the model for axi-cel arm include patients who had leukapheresis but did not receive axi-	A modified intention to treat (mITT) population is used, including only patients in ZUMA-1 who receive axi-	It is challenging to compare ZUMA-1 and SCHOLAR-1 patients as they are from separate trials/observation studies. But the mITT population (rather than ITT population) in ZUMA-1 seems more

	ICER model	Submitted NICE model	Comments/critique on similarities and differences
infusion	cel infusion, and grouped them (based on reason for not receiving axi-cel) into death, due to AEs and due to manufacture failure, For patients who did not receive axi-cel due to AE, it was assumed these patients will not be able to tolerate other active therapies and transitioned to receive no further antileukemic/antilymphomic therapy (i.e., palliative care only) For patients who did not receive axi-cel due to manufacture failure, it was assumed these patients will receive active comparator treatment's average costs and outcomes	cel treatment (n=108, with combined Phase 1 & 2 data). The costs of leukapheresis and conditioning chemotherapy for patients who did not receive axi-cel were accounted for in the model by using cost multipliers. It was assumed only patients who receive axi-cel infusion will incur the drug cost.	comparable to SCHOLAR-1 patients because they are patients who actually receive the intended treatments which are also true for all SCHOLAR-1 patients used in the model. Further, the FDA and EMA approval and published ZUMA-1 trial manuscripts all use mITT as the bases for analysing ZUMA-1 data. Although different methods were used, the ICER model and NICE submitted model both used the mITT population for parametric curves for OS and PFS in the model (though one based on pseudo patient level data on Phase 2 patients, one based on patient level data on Phase 1&2 patients). Please see response to Question B4, where a scenario analysis is included in the NICE model using a similar approach in the ICER model to account for the patients who did not receive axi-cel (n=11).

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Effectiveness inputs

B2. **Priority question:** Please provide the Kaplan-Meier curves (with the number of patients at risk at each time point) for progression free survival (PFS), and overall survival (OS):

a. For the Full Analysis Set (defined as all subjects enrolled) in ZUMA-1 phase 1/ 2 from the time of enrolment.

The Kaplan_Meier plots for PFS and OS among all enrolled subjects, measured from the time of enrolment are in Figure 4 and Figure 5.

Figure 4. Progression-free Survival All Enrolled Subjects Phase 1 and Phase 2

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Figure 5. Overall Survival All Enrolled Subjects Phase 1 and Phase 2

b. For the modified ITT population in ZUMA-1 phase 1/2, by response status (complete response, partial response, stable disease).

The Kaplan_Meier plots for PFS and OS among the subjects in the mITT set in phase 1 and phase 2 are provided in Figure 6 and Figure 7.

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Figure 6. Progression-free Survival mITT Subjects Phase 1 and Phase 2

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Figure 7. Overall Survival mITT Subjects Phase 1 and Phase 2

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c. For the modified ITT population in ZUMA-1 phase 1/2, separately for cohort 1 and cohort 2.

The Kaplan_Meier plot for PFS among the subjects in the mITT set separately for cohort 1 and cohort 2 are provided in Figure 8 and Figure 9.

Figure 8. Progression-free Survival mITT Subjects by Cohort

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Figure 1.Overall Survival mITT Subjects by Cohort

d. For the 10 patients in ZUMA-1 phase 1/2 who were retreated with axi-cel.

Progression-free survival was not derived among subjects retreated with axi-cel, as the definition of progression-free survival applied to only the first axi-cel treatment. Overall survival among subjects retreated with axi-cel is provided in Figure 10.

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Figure 2. Overall Survival Among Retreated Subjects

B3. **Priority question:** Please provide the following information relating to the mixture cure models (MCM):

a. The command and specification of the MCM in STATA (e.g. strsmix) and confirmation of whether the models incorporate the expected background mortality rate.

The MCM in Stata was performed using the “ado” program “strsmix”. The actual relevant model commands are listed below:

```
stset  OS_YEAR , fail(OS_EVENT)   // identify the survival time and event variables
strsmix  if  Trt==1, dist(weibull) link(logistic) bhazard(baserate15)  // Weibull mixed cure model
strsmix if Trt==1, dist(lognormal) link(logistic) bhazard(baserate15)   // Lognormal mixed cure model
```

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strsmix if Trt==1, dist(gamma) link(logistic) bhazard(baserate15) // Gen Gamma mixed cure model

In the commands above:

- variable Trt holds the treatment with Trt==1 restricting the analysis to be run over axi-cel patients

- sub-command, “link(logistic)” indicates that a logit link is used for estimating the cure proportion. This link is of the same nature as occurs when applying a Generalised Linear Model, GLM, to binomial data and specifying a logit link. When specifying such in a GLM this amounts to a Logistic regression being performed. This explains why in the submission we have referred (page 103) to a Logistic regression being performed to establish the cure proportion. The mixed cure model actually estimates all parameters together using standard maximum likelihood techniques and does not actually run a separate logistic regression defined in the usual sense. We apologise if that has caused any confusion. The logit link was thought preferable to both the identity link (proportions call fall outside 0 - 1) and log(-log) link (not symmetric and seldom seen in mixed cure models unlike logit).

- sub-command, “bhazard(baserate15)“, indicates we have specified the patient level variable, “baserate15” for the baseline hazard, h_(t), at time of death or censoring. This variable was actually created in R and then exported to Stata (along with all other variables). By using R, we could extract USA mortality data for 2015 (standard “lifetable” variables split by age and sex) using the R package “MortalityLaws”. This package links directly to “The Human Mortality Database” (http://www.mortality.org/) allowing access to all such country level lifetables. For each patient, we added the time (decimals allowed) in years from study start to death/censoring to the age at study baseline. We then used standard database type matching commands to lookup the mortality rate for the patient’s sex and age at death/censoring combination from the USA 2015 mortality data and stored it in the variable “baserate15”. The majority of patients were from the USA and 2015 matched closest the ZUMA-1 trial dates. Hence “baserate15” informs the underlying coefficients of the cure model. However, for making OS predictions for the UK, the cure model coefficients are combined to UK general population expected survival estimates using standard cure model formula (as given in first equation listed in Section 2.2 of Lambert article - http://www.stata-journal.com/sjpdf.html?articlenum=st0131).

b. Justification for why the MCM models were not fitted for PFS.

In line with NICE TSD 14 guidance, PFS was extrapolated by fitting standard (single) parametric models to the data and assessing the appropriateness of the method by considering visual fit, statistical fit and clinical plausibility of the extrapolation. TSD 14

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guidance suggested that “Exponential, Weibull, Gompertz, Log-logistic, log normal and Generalised Gamma models should be considered and if these appear unsuitable due to poor fit or implausible extrapolation, the use of piecewise modelling and other novel survival modelling methods should be considered.” The Gompertz distribution was found to fit the KM data well and provided clinically plausible long-term estimates; this was therefore used in the model base case and no further modelling approaches (including MCM) were tested.

The interpretation of MCM and cure fraction are straightforward for OS - there is a clear clinical rationale underlying the method’s use for this end point. For PFS, however, the interpretation of the coefficient is less straightforward. There does not seem to be a consensus in the wider biostatistical literature as to whether MCM is an appropriate method to apply to PFS data. Neither is there a consensus concerning how the cure fraction for PFS should be interpreted. Please see response to Question B3(d) for more discussions.

c. Replicate the following tables (28, 29, 32, 33) and figures (20 to 22, 26 to 27) using the mixture-cure method for PFS (axi-cell and best supportive care [BSC]).

Please note that a MCM approach could not be used for BSC PFS because PFS data were not collected in the SCHOLAR-1 study. Presented below are the replicated tables and figures for the MCM of axi-cel PFS.

Table 12: Progression free survival for axi-cel: mixture-cure model coefficients

Distribution	Parameter	Mean
Weibull	Pi	-0.29
	Implied “cure fraction”	0.43
	Constant	1.70
	ln(gamma)	0.37
Gamma	Pi	-0.31
	Implied “cure fraction”	0.42
	Constant	-1.28
	ln(sigma)	-0.30
	Kappa	0.64
Lognormal	Pi	-0.39
	Implied “cure fraction”	0.40
	Constant	-1.46
	ln(sigma)	-0.11

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Table 13: Progression free survival for axi-cel: mixture cure model goodness of fit statistics

Model	AIC	BIC
Lognormal	107.95	116.00
Weibull	105.62	113.67
Gamma	106.22	116.95
Key: AIC Akaike information criterion; BIC, Bayesian information criterion.		

Combining the estimated cure fraction, the general population mortality (for "cured" patients) and the fitted parametric curves for "not cured", Figure 10 shows the overall estimated PFS for each mixture-cure model compared to the observed ZUMA-1 PFS KM.

Figure 11: Progression-free survival for axi-cel: KM with mixture cure model parametric curves

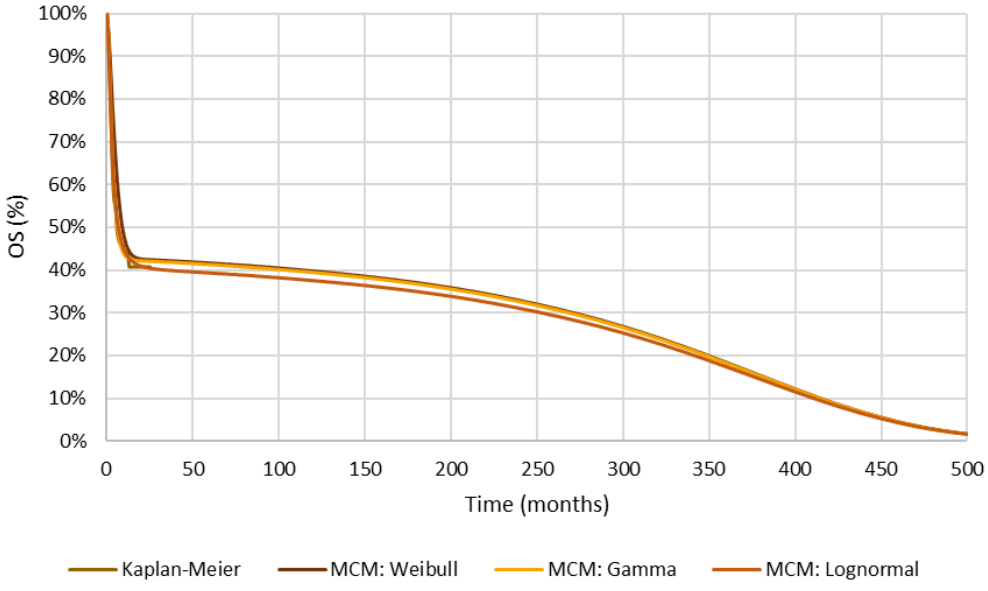

Figure 11 shows plots of modelled cumulative hazard over time and observed cumulative hazard over time.

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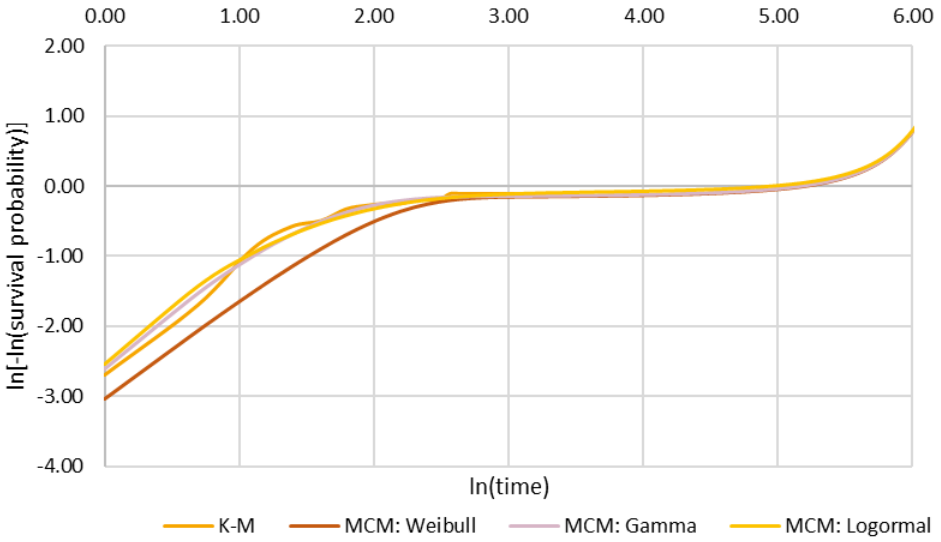
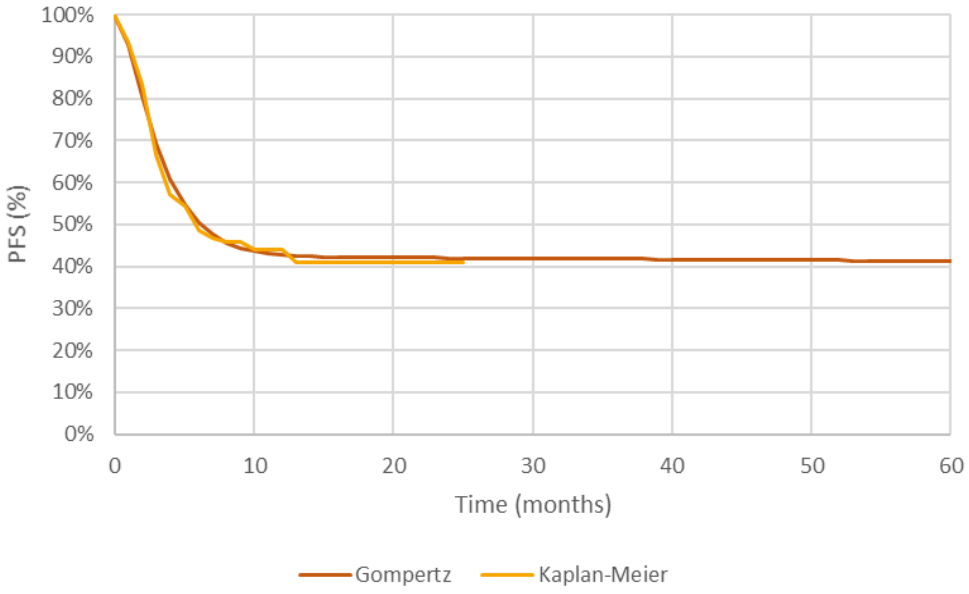
Figure 12: Progression-free survival for axi-cel: mixture-cure model log-cumulative hazard plot



Although the AIC and BIC statistics show that the Weibull MCM provides the best statistical fit, visual inspection suggests that the Weibull distribution actually fits the data poorly compared to the lognormal and gamma distributions, which were visually very similar. The gamma MCM is therefore presented below as this provided the second best statistical fit.

Figure 13: Progression-free survival for axi-cel: mixture-cure method



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d. Comment on any differences in size of the cure fraction between PFS and OS and possible explanations.

Obviously "cure" models are mathematical constructs that aim to identify two populations: (i) those with an excellent long-term prognosis (where there is a strong clinical rationale for believing such a group exists); and (ii) those whose prognosis is unaltered from the general disease trajectory. As discussed in B3, there is substantial precedent for using this method for the outcome of overall survival but very limited consensus concerning the validity of its use for progression free survival (as well as a lack of clarity as to how to interpret the coefficient). When interpreting the coefficients, it is important to remember that cure models actually possess two distinct routes that can be followed in raising or lowering a survival prediction: adjust the cure proportion only or adjust the relative survival proportion within the uncured only (or of course any combination of the two).

When comparing the difference in size of the cure fraction between PFS and OS there are two features that stand out – for Weibull and Gamma models, the proportion "cured" have fallen when moving from OS to PFS, whilst the reverse is true for the Lognormal model. The cure proportion for the "Log-Normal" in the OS analysis is clearly implausibly low at close to 1% - matched by survival prospects for the uncured that are implausibly lenient (their survival far too high). It is no surprise therefore that with more events (PFS guaranteed to have at least as many events as OS but likely more) this allows the Log-Normal model to adjust to a more reasonable position. This is supported by AIC comparisons – with OS the Log-Normal model is far inferior to Weibull (AIC difference of 3,3); for PFS although still inferior, the gap on AIC has narrowed to 2.3. The Log-Normal model, however, should still be considered inappropriate for PFS given these AIC results.

For Weibull and Gamma, the cure proportions have fallen, which is to be expected given the definition of the endpoints, as there will be a greater number of events for the PFS endpoint than is the case for the OS endpoint. If a model appears clinically plausible (which Weibull and Gamma do) in terms of the balance between the cure proportion and the predicted survival trajectories of the uncured, then with more events to deal with, one would expect the cure proportion to fall to help accommodate the necessarily lower "event survival" curve.

The problem of course returns to the issue of how to interpret and properly implement a PFS cure model that is to be used in a partitioned survival setting. For OS, there appears little controversy to implementing standard cure models which incorporate general population expected mortality rates when calculating all cure model coefficients. The expected mortality rates concern death which is the *exact same endpoint* used as the event in OS analysis. The definition of cure relates to the risk of *death* – meaning that those with improved prognosis face the same mortality rates as those faced by the general population at that patient's age within his/her sex (as noted in the response to B1 the recent ICER report stated that in the case of DLBCL this was the assumption best supported by the evidence available).

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Everything is in alignment and refers to the same phenomenon – death. Cure models incorporating background mortality (and their related siblings: relative survival models) have worked effectively in cancer OS predictions. The horizontal plateau in the longer-term OS curve for SCHOLAR-1 further supports the clinical rationale for using a cure model to estimate OS for those DLBCL patients who have a positive long-term prognosis.

There is less consensus concerning: (i) the validity of adopting the MCM approach to extrapolate PFS data; and (ii) the most legitimate way to implement the method if one chooses to use it. PFS estimates are a superset of OS (i.e. incorporate OS) and hence with regards to the OS element that is in PFS, we should adopt the same approach to its OS component. This is even more apparent on consideration of what the results are to be used in - partitioned survival HE modelling: the vertical distance between OS and PFS curves will not have the appropriate meaning if the OS components are not in alignment. For this reason, in the requested exploratory analysis we have used as "background mortality" in PFS cure modelling, the same USA background 2015 lifetable database holding general USA population mortality rates. The only difference being that if the PFS event occurred at a patient's age where they were 1 year younger than when they died then the background mortality rate entered would be slightly different – the year younger data applied. This is thought the best solution to the issues faced – mortality rates change little over a few years.

The above is not thought a perfect solution and for that reason we did not implement cure models for PFS in the company submission. Obviously, there is a mismatch by mixing background mortality rates with PFS patient endpoints. We therefore do not believe that the "cure proportions" from these PFS endpoints have a clear clinical meaning (in contrast to OS – the endpoint for which there is widespread previous use of the method). In conclusion, we believe the OS cure estimate predictions are still legitimate and the PFS cure results be treated with much caution because: (i) there is a clear clinical rationale for using the method for OS while there is not for PFS; (ii) the method is widely used for OS as an endpoint (when there is a reason to believe some patients will have an excellent long term prognosis) while this is not the case for PFS; and (iii) there is a lack of clarity concerning how best to implement the method for PFS and interpret the derived coefficients (unsurprising given the method was not developed with this endpoint in mind and has not been widely used for it).

e. Please provide a revised economic model which includes functionality to select mixture-cure models for the axi-cel and BSC PFS curves.

The model has been updated to include the option to use a MCM approach for axi-cel PFS as a scenario analysis (the functionality is added in Cell J32 in the "Key results" sheet). Using the revised NICE model, this resulted in similar results to the base-case analysis in which PFS was modelled using a Gompertz parametric curve (MCM results in an increased ICER of < £2,000). A comparison of the top-line model results when a gamma MCM is used for modelling axi-cel PFS and when Gompertz is used (base-case) is presented below.

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Table 14. Base-case model results (Gompertz parametric model used for axi-cel PFS)

	BSC	Axi-cel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

Table 15: Scenario model results (gamma MCM used for axi-cel PFS)

	BSC	Axi-cel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

B4. **Priority question:** Although the costs of leukapheresis and conditioning therapy are included for those who did not undergo axi-cel infusion (i.e. difference between the Full Analysis Set and the modified ITT population), the analysis does not capture the survival and QALYs of those patients. As a result, the use of the modified ITT instead of ITT data from ZUMA-1 Phase 1/2 for PFS and OS may lead to potential bias in the cost-effectiveness estimates when comparing with BSC.

a. Please present an additional scenario which explores the potential impact of including the Full Analysis Set population (e.g. using the PFS and OS data from the Full Analysis Set or using a simple decision tree to weight the overall costs and QALYs in patients who were infused with axi-cell and those who received leukapheresis but were not subsequently infused with axi-cell).

As explained in response to Question B1 Table 1, the mITT population is considered more suitable in this case for the comparison with SCHOLAR-1 data and therefore used as the base case in the NICE model. Nevertheless, a scenario analysis is incorporated into the updated model to consider the ITT population for ZUMA-1. Using the updated model, a comparison of the top-line model results between the mITT (base case) and ITT population is presented below. As expected, the total costs for axi-cel deceased in the ITT scenario because the 9.2% (11 out of 119) of ITT patients do not incur the drug cost for axi-cel; while the total QALYs also decreased because patients who did not receive axi-cel have worse survival and quality of life. Please see responses to Question b for the summary of methods and assumptions for this scenario analysis. Overall, there is a small increase in the ICER for the ITT scenario (£1,133 per QALY) compared to the mITT base case.

Table 16: Base-case model results (mITT for ZUMA-1)

	BSC	Axi-cel	Incremental

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Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

Table 17: Scenario model results (ITT for ZUMA-1)

	BSC	Axi-cel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]

b. Please summarise the approach and assumptions used.

A similar weighted average approach as used in the ICER model has been applied to incorporate the ITT ZUMA-1 population into the model. Based on patient level data from ZUMA-1, Table 8 below shows a breakdown of the 11 patients (10 patients from Phase 2 and 1 patient from Phase 1) who did not receive axi-cel in ZUMA-1.

Table 18: ITT patients in ZUMA-1 (combined Phase 1&2) including reasons for not receiving axi-cel

Patient categories	N	%	OS events	OS censored
mITT	108	90.8%		
Not receive axi-cel (death)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (due to AE)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (due to disease progression)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (due to non-measurable disease)	[redacted]	[redacted]	[redacted]	[redacted]
Total ITT population	119	100%		

As explained in response to Question B1 Table 1, the mITT population is considered more suitable in this case for the comparison with SCHOLAR-1 data and therefore used as the base case in the NICE model. Nevertheless, a scenario analysis is incorporated into the updated model to consider the ITT population for ZUMA-1. The following assumptions were made in the updated model for this ITT scenario analysis:

- For the [redacted] patients who did not receive axi-cel due to death or adverse events, a one-off QALY (0.19 QALY) is estimated by using their average OS (3.49 months) and post progression utility (0.65); and a one-off cost (£7,002) based on post-progression monitoring cost (£2,006 per month)

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- For the [redacted] patients who did not receive axi-cel due to disease progression or non-measurable disease, the discounted QALYs and costs from the BSC arm are used (directly linked to BSC results in the model). It is assumed these patients are similar to BSC patients starting from the beginning of the model

- The median time from leukapheresis to delivery of axi-cel to the treatment facility was 17 days (Neelapu 2018). The original mITT analysis used axi-cel infusion as the model start time. With the ITT analysis where the model start time for axi-cel starts at leukapheresis, a one-off QALY (0.034 QALY) is added to the mITT patient group by assuming a progression-free utility (0.72) over 17 days

- The ITT population overall costs and QALYs are then calculated as the weighted average of the three categories of patients (mITT, not receive axi-cel due to death and AE, not receive axi-cel due to other reasons)

- A separate sheet is created in the updated model "ITT scenario" to present the key inputs and calculations for the analysis. The key calculations are also presented in the table below.

Table 19: ITT scenario analysis results

Patient categories	N	%	One-off costs	One-off QALYs
mITT			[redacted]	[redacted]
mITT (adjusted for ITT scenario)	108	90.8%	[redacted]	[redacted]
Not receive axi-cel (death or due to adverse events)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (other reasons)	[redacted]	[redacted]	[redacted]	[redacted]
Total	119	100%	[redacted]	[redacted]

c. Please provide a revised economic model which includes this scenario.

The updated model includes the functionality to consider the ITT population for ZUMA-1 (Cell J27 in "Key results" sheet) and the results and methods/assumptions are summarised above.

B5. Please specify the statistical model used for propensity score matching of SCHOLAR-1, which was used to generate the BSC OS curve in the model, and provide the rationale for model/variable selection.

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Please find below the results of the binary logistic regression for membership of ZUMA-1 (vs SCHOLAR-1); N=634.

Table 20. Logistic regression results for membership of ZUMA-1 (vs SCHOLAR-1)

	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
AGE	.0299658	.0102856	2.91	0.004	.0098063	.0501253
Sex						
Male	.226487	.2403639	0.94	0.346	-.2446177	.6975916
Diagnosis						
PMBCL	2.254119	.5233903	4.31	0.000	1.228293	3.279945
TFL	1.846987	.3451129	5.35	0.000	1.170578	2.523396
Relapsed to ASCT						
Y	-.4568845	.2962858	-1.54	0.123	-1.037594	.123825
Refractory to ≥ 2 consecutive lines of therapy						
Y	-.2639637	.2415562	-1.09	0.274	-.7374051	.2094776
_cons	-3.372092	.6346675	-5.31	0.000	-4.616017	-2.128166

Health related Quality of Life

B6. Please define the safety management cohort referred to in page 34 of the company submission in terms of inclusion criteria and provide baseline patient characteristics as per table 11 in the company submission (pages 55-57). Please clarify if EQ-5D-5L was collected in any other patients in ZUMA-1. If so, please replicate Table 8 (page 35 company submission) for the full set of patients who provided EQ-5D-5L data.

The inclusion criteria for cohort 3 are the same as in cohorts 1 and 2 with the exception that relapsed DLBCL subjects may also be included. Demographics and baseline characteristics for cohort 3 are provided in Table 10 and Table 11. Despite relapsed subjects being eligible, all subjects enrolled were refractory.

EQ-5D was not collected in any other patients in ZUMA-1.

Table 21. Demographics (Cohort 3) Safety Analysis Set

Demographic variables	Phase 2 Cohort 3 (N34)
Age (years)	

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n	34
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Age Category n(%)	
<65 Years	[redacted]
>=65 Years	[redacted]
Sex n(%)	
Male	[redacted]
Female	[redacted]
Ethnicity n(%)	
Hispanic or Latino	[redacted]
Not Hispanic or Latino	[redacted]
Race n(%)	
Asian	[redacted]
Black or African American	[redacted]
White	[redacted]
Other	[redacted]
Country n(%)	
United States	[redacted]
Canada	[redacted]
Netherlands	[redacted]
Israel	[redacted]
Note: Percentages are based on number of subjects treated.	

Table 22. Baseline Characteristics (Cohort 3) Safety Analysis Set

Demographic variables	**Phase 2 Cohort 3 (N34)**
Height (cm)	
n	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]
Weight (kg)	
n	[redacted]
Mean (SD)	[redacted]
Median	[redacted]
Min, Max	[redacted]

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ECOG Performance Status n(%)	
0	[redacted]
1	[redacted]
Disease Type n(%)	
DLBCL	[redacted]
PMBCL	[redacted]
TFL	[redacted]
Disease Subtype n(%)	
DLBCL not otherwise specified	[redacted]
Primary mediastinal (thymic) large B cell lymphoma	[redacted]
Transformation of follicular lymphoma to DLBCL	[redacted]
Disease Stage n(%)	
I	[redacted]
II	[redacted]
III	[redacted]
IV	[redacted]
International Prognostics Index (IPI) n(%)	
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
Refractory Subgroup n(%)	
Primary refractory	[redacted]
Refractory to 2nd or greater line therapy	[redacted]
Relapse post ASCT	[redacted]
Prior Autologous Stem Cell Transplant (ASCT) n(%)	
Yes	[redacted]
No	[redacted]
Number of Prior Chemotherapy Regimen n(%)	
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
>5	[redacted]
Prior Anti-CD20 n(%)	
Yes	[redacted]
Prior Anthracycline n(%)	

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Yes	[redacted]
Prior Platinum n(%)	
Yes	[redacted]
No	[redacted]
Bone Marrow assessment at Baseline n(%)	
Negative	[redacted]
Positive	[redacted]
Note: Percentages are based on number of subjects treated.	

Resource use and costs

B7. Please provide a breakdown of the proportion of patients in ZUMA-1 who underwent a second round of conditioning chemotherapy due to delays in the manufacture of axi-cel. Please incorporate the resulting cost in the updated model.

No patients in ZUMA-1 received a second round of conditioning chemotherapy (i.e. who had > 3 doses of conditional chemo).

B8. Please confirm whether the list price and average cost of a course of treatment (Table 2 – company submission) is a provisional or final price.

This is the final proposed list price.

B9. **Priority question**: Please provide further details on the process of administration, tracking and shipping of apheresis products and the management of severe toxicity. In response to this question please refer to the recent article by *Perica* et al and summarise whether similar processes are likely to be required within the NHS, highlighting any additional resource/cost implications that have not been formally quantified (e.g. additional administration costs associated with ensuring the chain of custody of the cell product, whether ITU beds may need to be made available even if not used etc).

Reference: Karlo Perica, Kevin J. Curran, Renier J. Brentjens, Sergio A. Giralt, Building a CAR Garage: Preparing for the Delivery of Commercial CAR-T Products at Memorial Sloan Kettering Cancer Center, Biology of Blood and Marrow Transplantation (2018), https://doi.org/10.1016/j.bbmt.2018.02.018).

Perica et al. laid out the following series of 8 tasks for delivery of CAR-T therapy:
Task 1: Patient intake
Task 2: CAR-T cell consultation service
Task 3: CAR-T cell collection, ordering, shipping and receiving
Task 4: Bridging therapy
Task 5: CAR-T infusion

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Task 6: Post infusion care (day 0 to 30)
Task 7: Post-infusion care (day 30 onwards)
Task 8: Financing, regulatory and reporting requirements

In many cases the tasks and processes are similar, if not identical, to those that are required for stem cell transplant (SCT) e.g. patient intake and consultation:

Tasks 1 and 2: Patient intake and CAR-T consultation service
There is already a well-established process for considering the treatment of patients with lymphoma and for stem cell transplantation (SCT, auto and allogeneic) via the existing MDTs. This would be entirely appropriate for consideration of patients for CAR-T cell therapy and therefore there is no additional cost for implementation.

Task 3: CAR-T cell collection, ordering, shipping and receiving
The CAR-T delivery centres commissioned by NHSE and validated by Kite are likely to be large allogeneic-SCT centres experienced in apheresis, cell processing and tracking of cells for transplantation. In many ways these process for CAR-Ts are similar to the shipment, tracking and chain of custody that already exists for SCT. Of course, some time for training will be required for specifics related to processing and shipping for axi-cel.

Kite does not support “At risk collection” so this point does not apply to axi-cel.

Kite will utilise a straightforward web-based portal for ordering, scheduling apheresis and delivery. Kite staff will be available to assist as required, with one member of our office staff dedicated to coordinating logistics of the supply chain. The chain of custody/identity will begin at the patient’s apheresis centre via the portal with allocation of a unique Kite patient identification number. This, along with other identifiers such as patient name/local hospital number/NHS number/date of birth as per centre preference and permitted by local Caldicott guardians will ensure clear identification of the patient’s cells through the supply chain. An ISBT128 standard bar code together with these identifiers will be used on the apheresis bag, returned axi-cel cassette and product bag.

Task 4: Bridging therapy
Bridging therapy is used to hold progression of disease during CAR-T manufacture and delivery. However, ZUMA-1 did not allow bridging chemotherapy in the trial so no patients in the trial received it. In the real-world scenario careful patient selection should continue with evaluation of the pace of disease progression to ensure it is appropriate for the use of axi-cel therapy with appropriate allowance for the time of manufacturing and delivery. Only one patient in ZUMA-1 suffered rapid disease progression that prevented receipt of axi-cel using this approach. The rationale for exclusion of bridging chemotherapy in ZUMA-1 is that it made for a robust study with clean assessment of efficacy of the CAR-T cell therapy and no opportunity for confounding by the effect of bridging therapy. However, for many patients

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eligibility for CAR-T is considered because of poor response/refractoriness to chemotherapy and so bridging chemotherapy would be unlikely to be of great benefit.

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Task 5: CAR-T infusion

Many processes included in this section of the paper by Perica et al. are similar to other products used for treatment of lymphoma such as chemotherapy and rituximab. Processes that would be required for them too include e-prescribing protocols, use of infection prophylaxis according to local protocols and pharmacy involvement. The consent process is also likely to be similar to that for SCT with detailed provision of risks and benefits to allow informed consent.

Administration of axi-cel is via a single infusion as per the recommendation outlined below:

Preparing Patient for Axi-cel Infusion

Confirm availability of axi-cel prior to starting the lymphodepleting regimen.

Pre-treatment

• Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously on the fifth, fourth, and third day before infusion of axi-cel.

Premedication

• Administer paracetamol PO and diphenhydramine intravenously or PO approximately 1 hour before axi-cel infusion.

• Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of axi-cel.

Preparation of Axi-cel for Infusion

Coordinate the timing of axi-cel thaw and infusion. Confirm the infusion time in advance and adjust the start time of axi-cel thaw such that it will be available for infusion when the patient is ready.

• Confirm patient identity: Prior to axi-cel preparation, match the patient's identity with the patient identifiers on the axi-cel cassette.

• Do not remove the axi-cel product bag from the cassette if the information on the patient-specific label does not match the intended patient.

• Once patient identification is confirmed, remove the axi-cel L product bag from the cassette and check that the patient information on the cassette label matches the bag label.

• Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite number TBC).

• Place the infusion bag inside a second sterile bag per local guidelines.

• Thaw axi-cel at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend axi-cel in new media prior to infusion.

• Once thawed, axi-cel may be stored at room temperature (20°C to 25°C) for up to 3 hours.

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Administration

• For autologous use only.
• Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period.

Task 6: Post infusion care (day 0 to 30)

Cytokine release syndrome (CRS) and neurologic events (NE) are adverse events specifically associated with CAR-T therapy during this time period. Others such as neutropenia and infection are very familiar to the haematology staff managing their patients. The recommendations for identification and management of CRS and NE appear below (they are taken from the current US label and reflection in the UK SmPC is subject to change during the EMA review):

Management of cytokine release syndrome

Ensure at least 2 doses of tocilizumab are available prior to infusion of axi-cel. Monitor patients at least daily for 7 days at the validated hospital for signs of CRS. As an outpatient monitor patients for signs and symptoms of CRS for 4 weeks after infusion, and council them to seek immediate attention should signs or symptoms occur. Median onset time is 2 days (range 1-12 days); median duration 7 days (range 2-58 days). CRS is identified based on clinical presentation. Key manifestations are fever, hypotension, tachycardia, hypoxia and chills. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in table below with supportive care, tocilizumab alone or tociluzumab and steroids. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 23. Management of cytokine release syndrome.

CRS Grade	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention.	Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.

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Oxygen requirement less than 40% FiO2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity.	Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

Tociluzumab must be available for management of CRS.

Management of neurological sequelae

Monitor patients for signs and symptoms of neurologic toxicities at least daily for first 7 days at validated hospital and for 4 weeks after the infusion. Median onset time 4 days (range 1-43 days). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

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Table 24. Management of neurological sequelae

Grading Assessment	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.		
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.		
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.		

Additional notes:

A Risk Management Plan (RMP) is likely to be mandated by regulatory authorities, similar to the REMS required by FDA in the US. Kite Medical Scientific Liaisons (MSLs) will be available to help train staff in all specialties likely to be involved in the patient management on the identification and management of axi-cel related AEs such as CRS and NEs and will support validation of centres.

The condition of a patient necessitating ITU or HDU admission could vary between centres in the ZUMA-1 trials as based upon US practice. However, grade 3 or 4 CRS and NEs would generally require ITU admission because of the required monitoring or organs support

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required, in particular if ventilation is required. Centres delivering CAR-T therapy should have access to ITU should a patient need admission. However, based on trial experience a minority require ITU admission, retaining an empty bed available for each and every patient to be treated with CAR-T therapy is not required. The 12-month data cut from ZUMA-1 showed that 13 out of 108 patients (12%) had CRS ≥ Grade 3. The incidence of Grade 3 or higher CRS decreased as the ZUMA-1 clinical trial progressed, and the side effect profile of CAR-T therapy became better known and the robust, aggressive management algorithms were implemented. For example, the incidence of Grade 3 or higher CRS was 18% among the 62 subjects analysed at Interim Analysis-2 (IA2) and 5% among the subjects analysed after the IA2.

Task 7: Post-Infusion Care (Day 30 Onwards)

Follow up after day 30 will be according to usual standard of care with 3-4 monthly visits with discharge from clinic at 2 years with advice and support for patients with a complete response.

Task 8: Financing, regulatory and reporting requirements

Gilead is liaising with EBMT regarding a registry for long term follow up recording (BSBMT collect and submit data to EBMT's registry). EBMT already have a Cell Therapy Med-A form for collection of data related to CAR-T and other cell therapies. The centres that will be conducting CAR-T therapy already collect data via the BSBMT/EBMT registry for their SCT activities.

Adverse events

B10. 11 patients in ZUMA-1 are reported to have experienced Grade 1 or 2 hypogammaglobulinemia, or which 7 of these patients received intravenous immunoglobulins (IVIG) as treatment. IVIG has been identified as an important element of cost in previous studies. Please provide the average duration of IVIG treatment for hypogammaglobulinemia in ZUMA-1 and incorporate this cost and disutility in an updated version of the economic model.

The ZUMA-1 CSR reports [redacted] patients requiring treatment with IVIG. [redacted] of the [redacted] subjects were treated at the same unit (designation 003). The remaining [redacted] patients were treated in two separate units so it looks like IVIG use was largely a choice of a single unit. Use of IVIG was not consistent with DH guidelines and English practice as it was used in acute setting in many of these instances. The English recommendation and practice would be applied in this setting as in others like CLL and is "where severe infections with encapsulated bacteria are persistent despite prophylactic antibiotic therapy" i.e. use only with recurrent infections. Hypogammaglobulinaemia alone or in itself is not an indication of use of IVIG in

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England. In the case of CAR-T therapy specifically immunoglobulin levels and infection pattern monitoring would allow for stopping IVIG therapy when the risk of infection has passed, unlike in CLL when chronic IVIG is required and generally long term.

The standard of care in front line and salvage for DLBCL includes rituximab so most relapsed/refractory patients eligible for axi-cel will have received rituximab previously. A patient series of 211 patients treated for lymphoma with rituximab showed symptomatic hypogammaglobulinemia that prompted IVIG administration developed in 6.6% of patients, a rate not dissimilar to that observed in ZUMA-1. The largest group in this study were those with DLBCL (n=65). (*Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. Clin Lymphoma Myeloma Leuk 2013;13:106-111*).

The model has been updated to apply the cost of IVIG treatment and administration for the [redacted] patients.

The cost of intravenous administration cost of immunoglobulin (band 1) is £1,257 per infusion (NHS Reference Costs 2016/2017, XD34Z). For the IVIG treatment costs, these were derived from NICE TA359 (company submission) which stated a cost of £19 per 0.4g dose, which is equal to £4.75 per 0.1g. In line with the NICE report, a required dose of 0.5g/kg was assumed. Using the mean patient weight reported in the ZUMA-1 CSR (82.70kg), a cost per dose of £1,964 was calculated.

In the York report, the frequency of IVIG treatment was every 4 weeks; as the submitted NICE model considers a monthly cycle length, the treatment cost was adjusted to be monthly, using the following formula:

$$Cost\ per\ dose * \frac{365.25/12}{4*7}$$

Considering the proportion of patients requiring IVIG therapy and the cost of treatment administration and acquisition, the weighted average monthly cost of IVIG treatment is £203.52. The average duration of IVIG treatment for hypogammaglobulinemia in ZUMA-1 was not recorded, thus it was assumed to be 12 months.

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In line with the methods used in the York study, a disutility for hypogammaglobulinemia was not applied as it is not thought to result in a reduction of health-related quality of life.

This model update resulted in the base case ICER changed from [redacted] per QALY to [redacted] per QALY.

B11. Please provide a full breakdown of the number of patients in ZUMA-1 with Grade 1 and 2 cytokine release syndrome (CRS), and the proportion of those who received treatment for CRS with tocilizumab. Please incorporate this cost in the updated economic model.

A breakdown of the proportion of patients in ZUMA-1 experiencing grade 1 and 2 CRS is presented below. The ZUMA-1 CSR states that 17% of CRS patients (all grades) are treated with tocilizumab. The economic model has thus been updated so that 17% of ZUMA-1 patients incur the cost of CRS treatment, while the proportion of patients incurring the cost of CRS hospitalisation (ICU stay) remains the same at 13%; this is because ICU stay is only required in severe CRS cases, i.e. grade 3+, in line with the York study.

This model update resulted in the base case ICER changed from [redacted] per QALY to [redacted] per QALY.

Table 25: Proportion of patients in ZUMA-1 experiencing Grade 1-2 CRS

Cytokine release syndrome	Grade 1	Grade 2
Pyrexia	13%	52%
Hypotension	9%	23%
Hypoxia	1%	12%
Tachycardia	19%	1%
Chills	16%	4%
Sinus tachycardia	6%	2%
Headache	3%	2%
Reference: ZUMA-1 CSR, page 161, table 57.		

B12. Not all adverse events (AEs) reported in ZUMA-1 are incorporated in the economic model. For example, only encephalopathy is included of all the neurological AEs, although grade 3 aphasia and headache were reported. Please provide further justification for the specific AEs included in the model.

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In the economic model, only grade 3 or higher adverse events occurring in ≥10% of subjects in ZUMA-1 were included (with the exception of cytokine release syndrome which does not have the ≥10% cut-off). The model separately considers AEs related to conditioning chemotherapy and AEs relating to axi-cel treatment.

For the conditioning chemotherapy AEs, these were derived from the ZUMA-1 CSR, page 150 (table 50) which presents "Subject Incidence of Conditioning Chemotherapy-related AEs Occurring in ≥ 10% of Subjects in Phase 2 Cohort 1 and 2 Combined". Axi-cel-related AEs were derived from the ZUMA-1 CSR, page 151 (table 51) which presents "Subject Incidence of Grade 3 or Higher Axicabtagene Ciloleucel-related AEs Occurring in ≥ 10% of Subjects in Phase 2 Cohorts 1 and 2 Combined".

Therefore, other grade 3+ AEs following conditioning chemotherapy or axi-cel treatment were not included because they did not have an incidence of ≥ 10%.

B13. Leukapheresis-related AEs were not included in the model. Please update the model, to include disutility associated with incidence of leukapheresis-related AEs as reported in Table 48 of the clinical study report.

No leukapheresis-related AEs were included in the economic model because an AE incidence cut-off of ≥10% was implemented, as detailed in the response to B12. Therefore, because no grade 3+ leukapheresis related AEs had a subject incidence of ≥10%, these were not included in the model.

Section C: Textual clarifications and additional points

C1. Table 51, appendix O. Number of patients from each study do not match what has been reported in the company submission. Please correct if it is an error or provide detail on why the numbers do not match the ones reported in the company submission. If different subsets of the study population were used, please report patient characteristics for each study as per Table 11 in the company submission (pages 55-57).

The heading row in Table 51, appendix O should actually read n=523 (not n=521). The propensity score and assessment of baseline balance are based on N=634 patients (111 ZUMA and 523 SCHOLAR).

However, 521 is the number of subjects included in the Kaplan-Meier estimates and subsequent parametric extrapolations; two patients were excluded from this analysis because they had negative values for their overall survival time ('drop if OS_MON<0').

To clarify: the SCHOLAR-1 dataset provided contained 593 patients. 29 were excluded on the basis have having missing OS values (n=564). The propensity score model was estimated in the patients (n=523) who had no missing data across the explanatory variables

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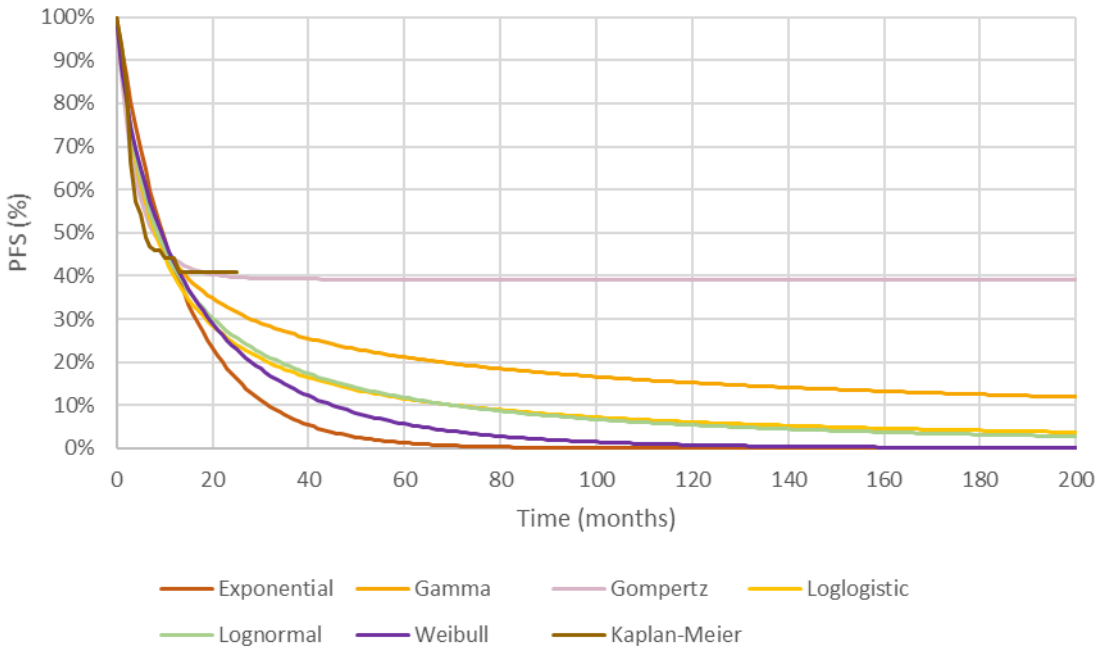
included in the statistical model above. However, the Kaplan-Meier estimates and subsequent extrapolations were based on n=521 subjects with non-negative OS data.

For ZUMA, the population used was the full analysis population including all enrolled patients (N = 111).

C2. Figure 28 in the company submission (page 113) appears to depict the OS curve axi-cel, rather than the PFS one. Please submit the correct graph.

Please see corrected graph below.



C3. Please provide the bibliographical reference to the list of chemotherapy regimens used in UK clinical practice, as compiled by the Oxford University Hospitals (OUH) NHS Foundation Trust (page 99 of the company submission).

There is no reference for this list other than these are the therapies used in this population in this centre. Both clinicians we spoke to in this centre were aligned on this list. The list was also validated by a Professor from Newcastle NHS hospital, who noted the clinicians at OUH as very sensible prescribers and considered the list reasonable whilst there were some geographical variations in prescribing among centres in the UK.

C4. Please clarify the number of patients who received subsequent ASCT after treatment with axi-cel in the ZUMA-1 trial. [redacted] patients are reported on page 82 of the company submission but [redacted] of patients are reported on page 94 in Table 24.

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It is correct that [redacted] patients had subsequent autologous stem cell transplant. The [redacted] of patients are reported on page 94 in Table 24 are patients who had allogenic stem cell transplant.

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Patient organisation submission

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma ID1115

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.

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	Bloodwise
3. Job title or position	Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Bloodwise's mission is to beat all blood cancers – stopping people from dying, improving the lives of everyone affected by blood cancer, and where possible preventing people getting blood cancer in the first place. We do this by funding world leading research, supporting all those affected by blood cancer, and campaigning for improvements in care and services. We are entirely funded by voluntary donations and have approximately 100 members of staff and 140 patient ambassadors plus many more volunteers and supporters.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We initially sent an email to our database of patient ambassadors asking them to contact us to share their experiences of diffuse large B-cell lymphoma (DLBCL), mediastinal B-cell lymphoma and follicular lymphoma and treatment with axicabtagene ciloleucel. We also consulted our medical advisory panel, an expert group of clinicians, to gain further insight into the condition and patients' experiences using this treatment from a clinical perspective. As CAR-T therapy is so new and the majority of the clinical trials so far have taken place outside the UK, it has been very difficult to track down patients to assist us with our submission. Our ambassadors contacted other members of the blood cancer community both within the UK and outside who they thought might be able to help but this did not lead anywhere. Fortunately, one of the clinicians we consulted was able to put us in touch with a colleague running a CAR-T academic trial for treatment of DLBCL in London. The clinician arranged for us to speak to one of

	the participants of the trial so we carried out an in depth interview with him covering all aspects of his treatment, the outcome and his views on his experiences. We also spoke separately to the aforementioned clinician. Our submission is based on these responses (although both the patient and clinician would like to remain anonymous). We have focussed on DLBCL in this submission as the evidence we obtained related to this condition.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	DLBCL is the most common type of high grade non-Hodgkin lymphoma. The most common symptoms are swollen lymph nodes usually in the neck, armpit or groin. If the swollen lymph nodes are deeper within the body, patients might experience chest or abdominal pain, bone pain, coughing or breathlessness. Patients might also suffer from B symptoms including high fevers, severe night sweats and unexplained weight loss. The patient we spoke to was initially diagnosed with follicular lymphoma following stomach pains which had continued for several months. His condition quickly metastasised into DLBCL with which he was diagnosed in April 2016 and he was very unwell. He underwent the conventional initial treatment for this condition, R-CHOP, a combination of chemotherapy drugs, cyclophosphamide, doxorubicin and vincristine, steroid, prednisolone and targeted therapy, rituximab, The treatment was successful after 6 sessions and he went into full remission in December 2016. However, the cancer returned in April 2017 when he was diagnosed due to a large lump on his tonsil which affected his breathing and was later found to be a large tumour. The cancer was also discovered just behind his heart. He was put on the R-DHAP regime also a combination of chemotherapy drugs, steroids and rituximab. This treatment failed and the next step was the strongest form of chemotherapy available to him, the ICE regime. Unfortunately he had a partial response only to this treatment and his condition deteriorated significantly as the cancer had spread throughout his body by this stage.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The patient who provided evidence for this submission described the harsh side effects he suffered as a result of multiple courses of chemotherapy. These included sickness, diarrhoea and mucositis, which caused painful ulcers in his mouth and combined with the sickness made it very difficult for him to eat. However, the key issue here is not the experience of chemotherapy versus the experience of treatment with CAR-T therapy as the CAR-T therapy treatment also includes an element of chemotherapy . It is a matter of survival. This patient was told following the ICE chemotherapy that the cancer was incurable and was offered the chance to participate in a CAR-T clinical trial for treating DLBCL which has not responded to salvage treatment as a bridge to allogeneic transplant essentially as a last resort.
8. Is there an unmet need for patients with this condition?	Yes. The unmet need here is for treatment that offers patients a better chance of achieving remission where traditional chemotherapy has failed. Our patient witness describes how the clinical trial and treatment gave him hope at a time when all his other options had failed. He describes that although the treatment is intensive, requiring several weeks' stay in hospital accommodation and a short course of intensive chemotherapy (therefore not removing the need for chemotherapy entirely) the therapy is over relatively quickly and if the patient responds well, as he did, improvements are seen very quickly which kept him motivated. The clinician we spoke to, who is leading on the trial, also highlighted that where patients with this condition do not respond to first line therapy, their options are exceptionally limited. Therefore, although the CAR-T therapy is not guaranteed to work, it offers these patients another chance so any response is positive and furthermore, when it does work, the results in trials to date have been "fantastic" with those patients that respond well achieving full remission and often going on to have transplants.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As stated above, the most significant advantage is that the treatment offers those patients who have failed to respond to one or more previous therapies another chance. Response rates in trials have been good and where a response is made, the results have been remarkable. In the case of the patient who fed into our submission, having relapsed and failed two lines of therapy, the cancer had spread throughout his body when he started the CAR-T trial. Following treatment, he had a completely clear PET scan and was able to proceed to transplant. The therapy is innovative and a real step-change in treatment of high grade non-Hodgkin lymphoma. As also outlined above, the patient feedback we obtained is that the treatment, although intensive, is over quickly and where a response is achieved, the improvements can be felt very quickly unlike with conventional chemotherapy.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The treatment is intensive and requires patients to be admitted or stay in ambulatory care close to the hospital for the duration of several weeks which can be difficult when patients and carers have other family responsibilities. A common side effect is the development of neutropenic sepsis following re-insertion of the engineered cells. Our patient witness suffered from this and was very unwell. However, he was advised from the start that it was likely that he would develop this condition so felt well-prepared and reassured by his proximity to the hospital as it meant he received the care he needed very quickly. He also advised that the inconvenience of this period was insignificant when compared with the possibility that he would respond well to the treatment.

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?	

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:

- CAR-T cell therapy is a step-change in the treatment of high grade non-Hodgkin lymphoma and patients should be given access to this innovative treatment.
- The treatment offers those who have run out of options a final chance at achieving remission and a bridge to transplant.
- Treatment is intensive but short in duration and improvements are seen very quickly which helps patients psychologically.
- Those patients who have responded to treatment in clinical trials have had exceptionally good results, with some achieving full remission as soon as the treatment has finished.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma ID1115

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

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 13 pages.

About you	
1. Your name	**Andrew McMillan**
2. Name of organisation	**Royal College of Pathologists and British Society of Haematology**

3. Job title or position	**Heamatology Consultant with a special Interest in Lymphoma. Past Chairman (2017-14) of the NCRI Lymphoma CSG High Grade NHL subgroup.**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**I am representing both a Royal College and a Professional Specialist Society. Both are primarily funded by member subscription.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	Treatment of Refractory Diffuse large B cell lymphoma (DLBCL) after the failure of 2 lines of therapy. Also included is DLBCL transformed form Follicular lymphoma and Primary Mediastinal B cell Lymphoma (PMBCL)

disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The aim of this treatment should be a Complete response, followed by a progression free survival and Overall Survival assessed at 2 years median follow up.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Continuing chemotherapy is largely ineffective though often attempted. Otherwise the treatment is palliation and best supportive care.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are BCSH Guidelines (I am a co-author) but they do not cover this therapy as it is too novel Br J Haematol. 2016 Jul;174(1):43-56. doi: 10.1111/bjh.14136. Epub 2016 May 16. Guidelines for the management of diffuse large B-cell lymphoma. Chaganti S[1], Illidge T[2], Barrington S[3], Mckay P[4], Linton K[5], Cwynarski K[6], McMillan A[7], Davies A[8], Stern S[9],

	Peggs K[10]; British Committee for Standards in Haematology.
• 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.)	The pathway of care is well defined for initial therapy (Rituximab and CHOP chemotherapy if performance status and co morbidity allows) The pathway of care for first failure is less well defined as there a number of equally effective salvage regimens (DHAP,ESHAP, IVE, ICE, GDP etc). If successful patients will proceed to autologous stem cell transplantation as consolidation if possible , usually with BEAM chemotherapy conditioning. Beyond second failure the pathway is poorly defined.
• What impact would the technology have on the current pathway of care?	For patients beyond second failure there would be a profound effect (STEPCHANGE) is the preliminary results are substantiated.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No The indication for this new agent is Relapsed diffuse large B cell Lymphoma (DLBCL) after failure of 2 lines of therapy (the 2 lesser indications can be regarded similarly). Transformed Follicular Lymphoma is effectively a similar entity to DLBCL and primary mediastinal NHL (PMBCL) is a related condition previously classified with DLBCL (by the WHO classification). The outcome of patients failing 2 lines of therapy, at present is very poor, probably of the order of less than 20% at 2 years (see the Scholar 1 reference: Crump et al Blood 2017 1800-08). Therefore the unmet need is very high as most of the patients suitable for this will currently receive ‘best supportive care’ or ‘palliation’ only. Some Patients with PMBCL may receive either Checkpoint inhibitors eg Nivolumab or Pembrolizumab or Immuno conjugates such as Brentuximab vedotion (or a combination) in clinical trials but these trial are too new to be able to comment on efficacy.

• How does healthcare resource use differ between the technology and current care?	Availability of this treatment in England, if approved, will be challenging for many reasons: 1. Current expertise and dedicated facilities are minimal. 2. Teams currently looking after these patients have no experience of this new Technology. 3. It is demanding on other departments in the hospital including Intensive care, Renal Medicine and Neurology/Neurosugery. 4. Cellular therapy expertise, in general, is largely limited to Allogeneic Bone Marrow Transplant Centres. 5. Cell collection facilities (Leucopheresis) are limited. 6. The financial costs involved are very high, but efficacy of the reported levels in otherwise untreatable patients may provoke a Public demand for charitable or similar funding to pay for treatment outside the UK.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The most likely setting is in Large Allogeneic Bone Marrow Transplant units across the country (I would estimate 6-12 centres in England.)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Substantial, this will need to be explored in the appraisal and is beyond the scope of my submission.
11. Do you expect the technology to provide clinically	Outcomes of recent clinical Trials of Axicabtagene ciloleucel and two similar agents (which are not included in this assessment but appear to have similar efficacy) were recently reported to the American Society of Haematology and simultaneously reported as an e publication in the New England Journal of

meaningful benefits compared with current care?	Medicine (Neelapu et al epub NEJM December 2017). I will not describe the results in detail as, no doubt, they will be reported in great detail elsewhere in the assessment. In summary, of 111 patients treated, there was a 40 % complete response rate and a 52% overall survival at 18 months. These results can be compared to the outcomes reported in the retrospective SCHOLAR-1 study (Crump et al Blood 2017 1800-08) where for patients with refractory DLBCL the 2 year survival was only 20%. There are 3 cautions: 1. There was considerable toxicity including some severe toxicity which will need to be carefully assessed. 2. Follow up for efficacy remains short so further scrutiny of this cohort will be essential. In particular there is speculation as to whether the CAR T cells transfused require to persist to maintain the remission. 3. In ALL therapy, there has been some failure as a result of the tumour cell loosing the target antigen and it will need to be know whether this occurs in Lymphoma. There are always difficulties in the interpretation of Phase 2, un randomised studies and a Phase 3 study should remain the gold standard and aspiration for the definition of a new Standard of care. However, with these caveats allowed for, the early CAR-T results in DLBCL (all 3 studies) were remarkable and potentially a step change in the management of these patients.
• Do you expect the technology to increase length of life more than current care?	YES
• Do you expect the technology to increase YEShealth-related quality of life more than current care?	YES, in particular a small number of patients currently receive allogeniec bone marrow transplant in this setting. Though early toxicity is considerable there are grounds for believing that the long term sequelae may be better e.g. related to retention of fertility.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients will require a good performance status and no significant co morbidities though this will require careful definition and assessment if /when the technology is rolled out.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	More difficult – see above
14. Will any rules (informal or	Yes, centres will need accreditation in cellular therapies and will need to demonstrate a high level of

formal) be used to start or stop treatment with the technology? Do these include any additional testing?	appropriate facilities and competence
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	YES
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	YES

• Is the technology a 'step-change' in the management of the condition?	YES
• Does the use of the technology address any particular unmet need of the patient population?	YES
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are mainly acute but high risk of severe or even fatal complications. Patients will need to be selected by experts with care.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No, not available except in a few clinical trial centres in set up.
• If not, how could the results be extrapolated to the UK setting?	The number of patients who may benefit is somewhat speculative at present. I am attempting a preliminary estimate based on our own MDT data and published data on outcome . This would suggest : I am making a preliminary assumption that few patients over 65 -70 years will have a Performance status

	that is sufficient for them to be considered as candidates for this demanding therapy. Our MDT serves a 1.1 million catchment and in 2017 we saw approximately 60 new cases of DLBCL. The median age is 70 years so only ½ of these will be assumed to be suitable. The overall cured fraction with frontline therapy can be conservatively assumed to be around 60% but younger patients will do better so I am assuming a failure rate of around 30% (100-70%) of these 30 patients under 70 years. Thus, 9/30 Patients would fail first line therapy. I would also assume that no more than 25% of these will be rescued by second line therapy and autologous stem cell transplant leaving 6.75 cases. A further proportion of cases are likely to progress quickly or have complications at the stage of second line therapy so I would assume that around 5-6 patients might need CAR T cell therapy in our 1.1 million catchment. This translates to around 250-300 cases per annum in England. This estimate will have very substantial margins of error but illustrates the scale of the problem for setting up a new service nationally. Case selection will be highly problematic and the precedent of the National MDT set up by Children's leukaemia doctors nationally may well be instructive.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free and Overall survival. The current poor outcome should allow the use of overall survival which would be the most informative.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Complete remission rate and progression free survival may not be reliable as durability will be a pivotal question.
• Are there any adverse effects that were not apparent in clinical trials	No, there a significant adverse events but they are generally well described in trial reports and there are 2 possible scoring systems for the clinical infusion reactions observed.

but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	The use of POLATUZUMAB VEDOTION and BENDAMUSTINE with Rituximab (abstract data at ASH 2017 and ASCO 2018) might need to be considered . Please note that I have a COI with respect to this data as I am a Co-author so would choose not to describe the results further.
21. How do data on real-world experience compare with the trial data?	It should be similar but careful adherence to patient selection and quality standards would be needed.
Equality	
22a. Are there any potential equality issues that should be taken into account when	Yes, age and comorbidity will tend to co segregate so it must be clear that older patients who have a satisfactory performance status can still be considered.

considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	Similar issue with current care and allogeneic bone marrow transplant
Key messages	
23. In up to 5 bullet points, please summarise the key messages of your submission. • High efficacy and step change • High current unmet need • Lack of existing facilities • Severe practical implementation difficulties • Challenging case selection if shortage of provision is as anticipated.	

Thank you for your time.

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

NHS England submission for NICE appraisal of axicabtagene ciloleucel for the treatment of patients with relapsed/refractory diffuse large B cell lymphoma, primary mediastinal B cell lymphoma and transformed follicular lymphoma

Likely EMA marketing authorisation (not yet finalised but Gilead consider FDA wording is expected)

1. Axicabtagene-ciloleucel (axi-cel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Current care pathway for relapsed/refractory diffuse large B cell lymphoma (DLBCL)

2. Chemo-immunotherapy remains the cornerstone of 1st line treatment for patients with DLBCL. If patients are to receive optimal therapy, they have to be medically fit to receive combination chemotherapy (cyclophosphamide, vincristine, doxorubicin and prednisolone) given in conjunction with rituximab. Such patients have a 70-80% chance of remaining free of disease progression.

3. Patients who relapse do so within the first 2 years after completing treatment and, if fit for optimal (but toxic) chemo-immunotherapy, have a low chance of remaining free of disease progression if just treated with conventional doses of chemotherapy. Patients who respond to 2nd line chemotherapy and who are sufficiently medically fit enough will usually be offered high dose chemotherapy and haemopoietic stem cell transplantation (SCT), usually autologous SCT. Such consolidation of a response to 2nd line chemotherapy with SCT is considered to be part of 2nd line chemotherapy. If not salvaged by 2nd line chemotherapy with or without SCT, life expectancy for most patients is short and usually measured in terms of single numbers of months. A minority of patients have further responses to chemotherapy and a small percentage is able to proceed to high dose chemotherapy and allogeneic haemopoietic SCT.

4. Salvage chemotherapy in DLBCL with new agents (eg B cell pathway inhibitors, checkpoint inhibitors, inotuzumab etc) have been disappointing and hence for relapsed/refractory DLBCL after 2 lines of chemotherapy, CAR T cell therapy is the only novel and truly efficacious treatment to potentially make a big difference to outcomes in DLBCL.

5. Small numbers of children and teenagers are also diagnosed with DLBCL and a few of these will have relapsed/refractory disease after 2nd line therapy. These patients would benefit from CAR T cell treatment even though their ages are very likely to be outside the marketing authorisation of axicabtagene ciloleucel.

Current care pathway for primary mediastinal B cell lymphoma (PMBCL)

6. There are about 60-80 patients diagnosed each year in England with PMBCL and approximately 80% will achieve freedom from disease progression with standard chemo-immunotherapy.

7. If patients relapse after 1st line treatment for PMBCL, successful salvage with standard 2nd line cytotoxic chemotherapy is rarely successful. Current clinical trials using checkpoint inhibitors and brentuximab offer theoretical promise in terms of potentially bridging patients to SCT but CAR T cell therapy currently offers the only novel and efficacious treatment for relapsed/refractory PMBCL.

8. Very small but important numbers of children and teenagers with relapsed/refractory PMBCL would have disease that is likely to benefit from CAR T cell therapy.

Current care pathway for transformed follicular lymphoma (TFL)

9. Follicular lymphoma has traditionally been considered to have about a 10% 10 year risk of transformation to an adverse histology, usually to DLBCL. In follicular lymphoma patients previously treated with doxorubicin-containing chemo-immunotherapy who then transform and have thus acquired adverse mutations and markers of resistance, the outlook is poor with a median survival in most series of about 1 year. As a consequence, high dose chemotherapy and SCT is incorporated into the treatment strategy of such patients if they are medically fit for high dose treatment and SCT.

10. Recent data suggests that the outlook for patients with TFL may be improving as a consequence of the incorporation of rituximab into treatment regimens and thus the need for such intensive (high dose chemotherapy and SCT) therapy is being questioned. CAR T cell treatment would be indicated in some patients with TFL (especially those with p53 deleted TFL) and in those that have been optimally pre-treated and who remain medically very fit.

<u>Potential patient numbers for whom axicabtagene ciloleucel would be indicated</u>

11. As yet the wording of the EMA marketing authorisation of axicabtagene ciloleucel is not known and hence the following estimates may change once this marketing authorisation has been established. The key issue is that in NHS England's view patients have to have either refractory or relapsed large B cell lymphoma **after** having received **2** lines of therapy.

Diffuse large B cell lymphoma (DLBCL)

12. The relevant issues in determining the potential number of patients eligible to receive axicabtagene ciloleucel are:
    - There are 5130 new patients diagnosed with DLBCL in the UK each year (data from the NICE IOG 2018 guideline which was derived from the

Haematological Malignancy Research Network [HMRN]). This means **4361** new patients with DLBCL in England each year

- It is important to note that the median age of patients with DLBCL at diagnosis is 70 years
- In the New England Journal of Medicine report of axicabtagene ciloleucel treatment in DLBCL (NEJM 2017; 377: 2531-2544), the median age of the 111 patients in the study was 58 years with an age range of 23-76 years and 24% were 65 years old or older. This bias towards selecting younger patients for CAR T cell therapies in this study reflects the need for patients to be very fit for a potentially highly toxic treatment and that older patients are excluded on account of increasingly significant comorbidities
- 20% of patients with DLBCL at diagnosis do not receive any active treatment. This figure comes from the HMRN for 2007 and is incorporated in a health economic model developed by the HMRN in conjunction with York University (Eur J Health Economics 2017; 18: 255-267). This 20% figure remains valid in view of the opposing trends that are evident: increasing diagnoses of DLBCL made since 2007, particularly so in the elderly (ie less likely to receive active treatment) and the ability of greater numbers of patients to undergo chemotherapy in 2018 that is better tolerated/supported than in 2007
- 5% of the total patients diagnosed will receive radiotherapy only
- 75% of the total patients diagnosed with DLBCL will receive chemotherapy, this equating to 3270 patients
- Not all of these 3270 patients will receive optimal 1st line chemotherapy but 2nd line chemotherapy is only likely to proceed in relapsed patients treated with optimal 1st line chemotherapy
- The HMRN/York economic model indicated that in 2007, **11.2%** of all DLBCL patients proceeded to have 2nd line chemotherapy, **3.2%** with subsequent SCT and **8%** without SCT. Most but not all of this **8%** in 2007 will have had aggressive 2nd line chemotherapy. Changes in practice since 2007 mean that more patients remain disease-free with 1st line chemotherapy and also that 2nd line salvage therapy is better tolerated and supported. Thus it is reasonable to assume similar percentages in 2018 to those in 2007 ie **3.2%** of all DLBCL patients still have 2nd line chemotherapy plus SCT (**142 patients** and mainly autologous SCT) and **8%** of all patients have 2nd line chemotherapy without SCT (**349 patients**)
- Of the 142 patients that have 2nd line chemotherapy and SCT (mainly autologous), approximately one quarter will remain disease-free. This therefore means that about 100 patients will relapse, often with very aggressive disease. Nevertheless, as these patients started 2nd line treatment as a fit group of patients, it is reasonable to assume that about **30-40** patients will subsequently be eligible for axicabtagene ciloleucel
- Of the 349 patients that have and nearly all fail 2nd line chemotherapy, a large proportion will be unfit for CAR T cell therapy either as a consequence of disease progression or because they lack the fitness required for CAR T cell treatment (see the selection criteria employed for the axicabtagene ciloleucel trial). It is important to note that DLBCL that has progressed after 2 lines of therapy is often rapidly growing and thus can cause a steep and rapid decline in a patient's performance status and therefore contra-indicate CAR T cell therapy. This therefore makes the

likely eligible number of fit patients with relapsed DLBCL who have not had SCT to be about a third of those that had such 2nd line chemotherapy – **110-120** patients

- In the axicabtagene ciloleucel study, 21% of patients had previously had SCT. Thus the proportional estimate of patients eligible for CAR T cell treatment post SCT in England (about 30-40 of such patients) is in broad accordance with the 110-120 patients estimated to have not had SCT
- In total, NHS England estimates that approximately **140-160** patients with relapsed/refractory DLBCL will be eligible for axicabtagene ciloleucel
- The numbers of children and teenagers with relapsed/refractory DLBCL will almost all be post SCT and the number estimated to be eligible for off label CAR T cell therapy is 5-10.

Transformed follicular lymphoma (TFL)

13. Estimating the number of patients with TFL is difficult as there is little data as to how many of such patients there are in England and as has been mentioned above, the number of such patients seems likely to be declining.

14. The mix of patients in the axicabtagene ciloleucel NEJM study was approximately one quarter comprised of TFL and PMBCL together (the split is one third PMBCL and two thirds TFL) and three quarters DLBCL. It is reasonable to assume about **40** patients with TFL being eligible for axicatagene ciloleucel as the ZUMA-1 trial results will encourage recruitment of TFL patients to consideration for CAR T cell treatment.

Primary mediastinal B cell lymphoma (PMBCL)

15. This type of lymphoma is rare (60-80 patients/year) and 80% are cured with 1st line treatment. Of the 12-16 patients who have relapsed/refractory disease, a few will have 2nd line chemotherapy and proceed to SCT. Most patients are difficult to salvage yet are fit at the time of 2nd relapse and thus about **10** patients can be expected to be eligible for axicabtagene ciloleucel

16. There will be 1-3 children/teenagers with PMBCL who would be eligible for off label CAR T cell therapy.

17. In total, NHS England estimates that there will be about **190-210 adult patients per year** eligible for treatment with axicabtagene ciloleucel within its expected licensed indication. There would be 6-12 children or teenagers who have diseases with similar biologies to adults and who would also benefit from CAR T cell treatment.

Further NHS England comments on axicabtagene ciloleucel for the NICE technology appraisal

The marketing authorisation

18. The key interpretation of the likely marketing authorisation when directed to clinical practice is whether ‘relapsed and refractory’ applies to the ‘2’ lines of therapy. NHS England’s interpretation is that patients whether relapsed after

or refractory to 1st line treatment must have failed standard 2nd line therapy ie if a SCT was planned in the current treatment pathway and patients respond sufficiently, then those patients should proceed to SCT as currently commissioned and not to CAR T cell therapy.

The comparator

19. Standard second line therapy would include regimes known as DHAP (cisplatin, cytarabine and dexamethasone ± rituximab), ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin ± rituximab), GDP (gemcitabine, cisplatin and dexamethasone ± rituximab), ICE (ifosfamide, cisplatin/carboplatin, etoposide ± rituximab) and IVE (ifosfamide, epirubicin, etoposide ± rituximab).Responding and fit patients would then proceed to SCT.

20. The comparator for axi-cel would therefore be what would be used in fit patients that have failed DHAP/ESHAP/GDP/ICE/IVE ± rituximab or responded to such 2nd line standard therapy and then relapsed after subsequent SCT. Such 3rd line therapies would be one of the second line regimens as described above or gemcitabine plus methyl prednisolone ± cisplatin, the combination of gemcitabine, cyclophosphamide, vincristine and prednisolone and (less so) the combination of rituximab, vinblastine and prednisolone. There is no 3rd line standard therapy as one is clearly not superior to the others. Other options would be clinical trials of novel therapies and symptomatic therapy. Since only patients of ECOG performance status (0 or 1) would be considered for CAR T cell therapy, such fit patients in the NHS would normally be offered further chemotherapy with the possible outcome of a stem cell transplant (10-15% or less of 3rd line treatment patients in the NHS). Pixantrone is not a comparator as it is rarely used in NHS clinical practice on account of its poor efficacy.

ZUMA-1 trial patients

21. ZUMA-1 recruited 3 groups of patients. The first was a group which consisted of patients refractory to 1st line therapy: those that had progressive disease to 1st line treatment or who had stable disease after 1st line treatment and progressed within 6 months of completing 1st line treatment (2 patients treated). The second group was patients refractory to 2nd or later lines of therapy: those that had progressive disease to 2nd line treatment or had stable disease and relapsed within 6 months of completing 2nd line therapy (78 patients treated). A third group was those patients that had autologous SCT and had relapsed within 12 months of receiving the SCT; a biopsy had to prove such a disease relapse and if the patients were treated with further chemotherapy, the patients must either have not responded or had relapsed following such chemotherapy (21 patients treated). NHS England believes that the 2nd and 3rd groups fall within the expected marketing authorisation for axi-cel but not the first group.

22. NHS England notes that all the patients in the ZUMA-1 trial were of ECOG performance status 0 or 1. The patient population was thus a fit one. This is important for safety reasons given the very considerable toxicity of CAR T cell therapy.

23. The case mix in the 111 patients enrolled consisted of 81 patients with DLBCL and 30 patients with either PMBCL or TFL. This is approximately the case mix that NHS England expects that would be treated with axi-cel in clinical practice.

24. It would be important for NICE and NHS England to see the ZUMA-1 trial screening log: the number of patients who were initially considered for the ZUMA-1 trial. This will offer a clearer picture of the degree of selection that was necessary in trial centres between the number of patients screened versus the number of patients actually selected for axi-cel treatment.

25. NHS England notes that 10% of patients entered into the study were leucapheresed but did not receive axi-cel: 4 of the 81 DLBCL patients and 6 of the 30 PMBCL/TFL patients. The main cause of this was progressive disease and its consequences in the time in between leucapheresis and arrival of the axi-cel for infusion

26. NHS England considers that the highly selected ZUMA-1 trial population is generalizable to the highly selected population of patients in the NHS which would be treated with axi-cel. The only difference in patient characteristics would be the number of previous lines of therapy. In future NHS practice this will be 2 lines of previous therapy for the great majority of patients and not the ZUMA-1 figures of 69% having had ≥ 3 lines of therapy and 40% having had ≥ 4 lines of treatment. Nevertheless, as 42% of ZUMA-1 patients were of ECOG performance status 0 and 58% of performance status 1, ZUMA-1 attracted very fit patients despite being heavily pre-treated. The population can thus be regarded as having outcomes which are generalizable to NHS practice.

ZUMA-1 trial outcomes

27. The current median duration of follow up in the axi-cel trial is 15.4 months. The efficacy results even for patients with relapsed/refractory DLBCL who have failed 2+ lines of therapy are immature.

28. NHS England notes that progression free survival (PFS) is plateau**ing** in ZUMA-1 but relapses have still occurred at 12 months. PFS rates at 6 months were 49%, at 12 months were 44% and at 15 months were 41%. NHS England notes that there are very few patients at risk after 14 months and so regards these PFS results as very encouraging but not mature.

29. Overall survival (OS) is also plateau**ing** but NHS England notes that deaths have occurred at 12-16 months and for this reason the 18 month OS figure of 52% is lower than the figure of 59% at 12 months which in turn is lower than 78% at 6 months. There are very few patients at risk after 16 months.

ZUMA-1 trial utilities

30. NHS England notes the utility data by response status and the small numbers in these analyses (0.74 for complete response, 0.79 for partial response, 0.64 for stable disease and 0.65 for progressive disease). It is counter intuitive for the partial response utility to be higher than that for a complete response.

Given that progressive disease after CAR T cell therapy is a disaster for patients, it is surprising that the progressive disease utility is not lower than 0.65. NHS England also notes that the results by health state also do not show much differential: 0.72 for remaining free of progression and 0.65 for progressed disease.

Axicabtagene ciloleucel toxicity

31. NHS England notes that treatment with axi-cel is associated with many side-effects, some of them being life threatening and particularly so in the first month of treatment. It observes that serious toxicity diminishes as experience with CAR T cell therapy increases but nevertheless recognises that it has to wrap all the appropriate 24 hour expertise around each patient in order to maximise safety and optimise outcomes for patients and the NHS. In the ZUMA-1 trial, 95% of patients experienced a grade ≥3 adverse event, [redacted] a grade ≥3 serious adverse event and [redacted] of patients died of a treatment-related cause.

32. The two most dangerous side-effects of axi-cel are of cytokine release syndrome (CRS) and neurotoxicity. Feedback to NHS England from the clinical trial centres in England who are currently involved in CAR T cell therapy consistently report how diverse the manifestations of toxicities can be and how alert patients and staff must be to apparently minor symptoms which can then escalate quickly if not heeded and acted upon.

33. 94% of patients recorded some degree of CRS but it is in 13% that grade 3 or worse CRS was seen. CRS occurs soon after treatment with axi-cel. Mild/moderate CRS requires considerable observation and supportive care but more severe CRS needs full intensive care plus the administration of tocilizumab and steroids. CRS toxicities resolved in all but [redacted] patients in which it was the cause of death in both. The need for training for all staff from the haematological ward to the intensive care unit is very great as the manifestations of CRS are so diverse and unexpected.

34. The other major side effect is neurotoxicity which can occur early or late. 64% of patients suffer neurological events, the majority of which are mild but 28% experience grade ≥3 toxicity (encephalopathy, confusion, aphasia, somnolence). The clinical manifestations are diverse with expert neurological input required to closely monitor progression of symptoms or signs. Grade ≥3 neurotoxicity takes a median of 17 days to resolve. Intensive care units must have the facility for 24 hour electroencephalography.

35. Other significant side-effects are infection in [redacted] of patients (bacterial, viral and fungal) and hypogammaglobulinaemia. In this population of adult patients, the long term need for intravenous immunoglobulin after CAR T cell therapy is likely to be modest.

Indirect comparison of ZUMA-1 with SCHOLAR-1

36. The indirect comparison of ZUMA-1 with SCHOLAR-1 has serious disadvantages given the heterogeneity of the 4 data sources that informed the outputs of SCHOLAR-1: a mixture of retrospective and prospective

databases, of audits and clinical trials, of ECOG performance status patients 0-4, of primary refractory patients and of previously received lines of therapy. Of note is that the SCHOLAR-1 trial OS curve flattening at about 7 years at about 13-14% of patients. This will be mainly related to the fact that [redacted] of SCHOLAR-1 patients received subsequent SCT. This [redacted] figure is higher than that recorded in NHS practice as part of 3rd line salvage chemotherapy (approximately 10-15% SCT rate). In addition, NHS England notes that Kite Pharma was directly involved in the funding of the study and in the writing of the SCHOLAR-1 publication. NHS England therefore has great reservations as to the comparability of ZUMA-1 and SCHOLAR-1.

Economic modelling

37. NHS England notes that in its economic model Gilead assumes that axi-cel overall survival has plateaued at 50% and then falls in line with the mortality decline for the general population. NHS England regards these 2 factors as being optimistic as the OS rate in ZUMA-1 may fall given the immaturity of follow up and the fact that these patients are heavily treated with chemotherapy which is known to add a survival disadvantage in the long term. In addition, a long term OS plateau at the latest percentage figure of patients remaining progression-free (42%) seen so far in the Zuma-1 trial might be a more realistic (but still optimistic) number to use rather than 50%.

38. NHS England observes that the long term OS rate in SCHOLAR-1 in the economic model is [redacted] .NHS England regards this figure as being high and presumably relates to the high number of SCTs assumed in the economic model. If there is a 10-15% rate of SCT in this group of patients in England as part of 3rd line chemotherapy (most of which will be allogeneic SCTs), there is likely to be about a 6-8% (or less) long term survival rate for patients embarking on 3rd line therapy.

39. No PFS data was reported in SCHOLAR-1. To overcome this, PFS was estimated for the comparator population in the economic model by assuming that the same ratio between PFS and OS at each time point in the axi-cel arm can be applied to the comparator arm. Since these two modalities of treatment are completely different, there must be significant uncertainty as to the validity of this assumption.

40. NHS England notes that the mean length of inpatient stay in the ZUMA-1 study was 17.6 days and that the company's model costs this according to NHS weighted inpatient haematological costs. What is unclear is how many intensive care unit days are incorporated and at what cost, especially considering that the type of intensive care unit has to be one which is capable of 24 hour EEG monitoring and interpretation. The considerable amount of expert neurology input does not appear to have been costed and nor has the multidisciplinary team costs given the need for respiratory, renal, hepatic and microbiological input.

41. Gilead assumes that the comparator chemotherapy is given as an inpatient and thus this attracts high costs as the costing comparison uses the weighted haematology inpatient costs. 3 of the 4 regimens used in the economic

analysis can be given as day cases and thus the costs of the comparator chemotherapy have been significantly inflated in the company's model.

42. The company appears to have applied a rate of [redacted] SCT to the comparator arm which appears to be a very significant overestimation of the likely SCT rate in such a population in England (10-15% SCT rate with a long term survival rate of 6-8%). As this [redacted] rate of SCT and the [redacted] long term rate of overall survival seem high, the economic model in this regard appears to have inflated both the survival and costs of the comparator population for axi-cel.

43. NHS England would wish to see confirmation that there is inclusion of leucapheresis costs for all the patients in whom Gilead manufactures axi-cell infusions, not just the patients who actually receive the axi-cell infusions.

44. NHS England plans to ensure that patients remain within a 1 hour travel time for the first 4 weeks after CAR T cell treatment. Some patients may be able to stay with relatives/friends but many will require either hostel or hotel accommodation. These costs of patients having to remain close to treating centres need to be included in the economic analysis.

45. NHS England recognises that assessing the hospital costs of introduction of CAR T cell therapy in this indication is difficult. A sensitivity analysis is recommended which uses the costs of procedures which bear some similarity to the infrastructure required for CAR T cell therapy. Clinical advice to NHS England therefore would suggest that using the inpatient and follow up costs of an allogeneic SCT for an unrelated donor (plus the separate and extra costs of ITU stay for axi-cel as ITU stay is not counted in the allogeneic SCT tariff) would offer a useful analysis to compare with the company and ERG's base case assumptions of the hospital costs of CAR T cell therapy.

46. The company estimates about 1000 patients being eligible for axi-cel but in its budget impact test submission reduces this number to 312 patients. NHS England regards this number as being too high partly because it is unclear from the company submission as to how 1st line refractory patients are being counted and partly because the company has underestimated the attrition to patient numbers which occurs when patients fail chemotherapy for an increasingly aggressive disease.

NHS England delivering CAR T cell therapy in practice

47. NHS England plans to initially have 4 CAR T cell therapy centres each treating at a rate of 25 patients per year **by the end of the 1st year of implementation**. It plans a 2nd wave of 4 CAR T cell treatment centres to be treating at a rate of 25 patients/year **by the end of the 2nd year of implementation**. This therefore means that NHS England will reach the currently expected capacity for CAR T cell therapy within 2 years of initial implementation such that 200 patients per year will be treated with relapsed/refractory large B cell lymphoma after 2 lines of systemic therapy. Given that it will take time for each CAR T centre to increase its capacity from an initial cautious rate and depending on the timing of any NICE

recommendation, 20-40 patients could be treated in 2018/19, about 100-140 patients treated in 2019/20, and approximately 200 patients/year thereafter.

48. All CAR T cell centres with be JACIE-accredited providers of allogeneic haemopoietic stem cell transplantation with on site level 3 intensive care units with documented, sustained and frequent experience in the management of multi-organ failure. CAR T cell centres will need immediate and 24/7 access to a wide range of support specialists in critical care, renal, respiratory, cardiovascular and neurological medicine. Such support must be co-located or on a directly contiguous site to both the ITU and CAR T cell treatment units. The ITU must have the availability of immediate and 24 hour electroencephalography monitoring as well as the expertise necessary for its interpretation.

49. Patients will often be inpatients for 3-7 days during their conditioning chemotherapy prior to CAR T cell infusion. They will be inpatients for a minimum of 7 days after CAR T cell infusion during which they will have twice daily assessments of cytokine release syndrome and 3 times daily testing for neurotoxicity. Patients will have to remain within a 1 hour travelling time of the CAR T cell centre for 4 weeks after infusion of axi-cel. CAR T cell centres will have to offer rapid admission pathways of care which offer immediate access to assessment by experienced and trained staff in managing the diverse complications of CAR T cell therapy. The provision of ambulatory care pathways in accordance with NICE Guideline (NG47) Haematological Cancers: Improving Outcomes (https://www.nice.org.uk/guidance/NG47/chapter/Recommendations#ambulatory-care) will enable centres administering CAR T cells to satisfy these objectives safely whilst accommodating patient experience.

50. CAR T cell centres will have cell therapy laboratory and pharmacy expertise in the handling, storage and thawing of advanced therapy medicinal products. In addition, centres will have considerable expertise in leucapheresis.

51. NHS England plans to institute a national large B cell lymphoma MDT for patients with relapsed/refractory disease who have failed 2 lines of therapy and in whom CAR T cell therapy is considered as a potential option. This national MDT will produce criteria for patient selection and prioritisation, take referrals from the CAR T cell centres, identify eligible patients for CAR T cell therapy, liaise closely with the 4-8 regional CAR T cell centres, direct which patients are to be treated with CAR T cell therapy and the associated timing, receive regular audits of outcomes from the regional CAR T cell centres and collate these audits into regular national assessments as to the efficacy and toxicity of CAR T cell therapy as well ensuring equity of access. Equity of geographical access from local MDTs will be assured through an equal allocation of centres per NHS England region and representation on the national MDT.

52. The 4-8 regional CAR T cell centres will have large B cell lymphoma CAR T cell MDTs which will be primarily concerned with taking referrals from specialist lymphoma MDTs in their respective regions, making individual

patient assessments prior to treatment, referring to the national lymphoma CAR T cell MDT, the initiation of therapy, the management of toxicity and the provision of regular audits of outcomes. There will be a regular mechanism through which treating centres can collectively discuss issues and experience such that there is as much sharing of expertise as possible.

Innovation

53. NHS England regards axicabtagene ciloleucel as highly innovative in terms of its mode of action: genetic engineering to T cells to recruit an immune response which results in a 'living' treatment against large cell lymphoma. But however clever or neat a technology may be, it is what a treatment does to meaningful outcomes for patients which results in NHS England concluding whether a new treatment is a game changer or not. CAR T cell therapy fulfils this definition of a potential game changer if it is confirmed that there are very or no few relapses in the period of 12-24 months after treatment and if there is no substantial long term toxicity.

Cancer Drugs Fund

54. NHS England regards axi-cel as a good candidate for the Cancer Drugs Fund as the PFS and OS results are still not mature. Relapses are still being observed at 12 months and few patients are at risk beyond 14 months. An extra 12 months of follow-up of ZUMA-1 patients would significantly reduce this uncertainty and thus make a potential NICE recommendation for routine commissioning decision one that ensures value for money for a very expensive technology.

NHS England commissioning treatment criteria

55. NHS England would wish to set treatment criteria for axi-cel therapy which reflects the known marketing authorisation, the relevant treatment pathways in England, the evidence base submitted to NICE and considerations to be made by the NICE technology appraisal committee. In view of the toxicity of the CAR T cell treatment and the evidence base solely being in fit patients being treated with axi-cel, NHS England considers it vital for patient safety that only patients of good performance status are treated with axi-cel (ie patients must have an ECOG performance status of only 0 or 1). These provisional criteria are set out below.

Axicabtagene ciloleucel as treatment for relapsed/refractory large B cell lymphoma after 2 or more lines of systemic therapy

1. I confirm that this application is made by and that treatment with axicabtagene ciloleucel will be initiated by a consultant haematologist specifically trained and accredited in the use of systemic anti-cancer therapy with day to day expertise in the use of allogeneic bone marrow transplantation **and** who is a member of the Trust's large B cell lymphoma CAR T cell multidisciplinary team

2. I confirm the patient has a confirmed histological diagnosis of diffuse large B cell lymphoma or primary mediastinal B cell lymphoma or transformed follicular lymphoma to large cell lymphoma (tick boxes as to which)
3. I confirm that the patient has received at least 2 prior lines of treatment and in relation to transformed follicular lymphoma, these 2 lines of treatment must refer to treatment of the large B cell component of the disease
4. I confirm that the patient has had a standard 2nd line treatment regimen such as DHAP±R, GDP±R, ICE±R or IVE±R (tick boxes to which)
5. I confirm that the patient has failed to respond to 2nd line treatment or has a biopsy-proven relapse within 12 months of receiving autologous stem cell transplantation
6. I confirm that the patient is of ECOG performance status 0 or 1
7. I confirm that the patient does not have any significant comorbidity which contraindicates CAR T cell therapy with axicabtagene ciloleucel
8. I confirm that the patient has had no previous therapy with any genetically modified autologous T cell immunotherapy
9. I confirm that approval for the use of axicabtagene ciloleucel has been formally given by the national adult large B cell lymphoma CAR T cell multidisciplinary team meeting
10. I confirm that following national approval for use of axicabtagene ciloleucel there has been local CAR T cell multidisciplinary team agreement that this patient has the necessary fitness for treatment and fulfils all treatment criteria listed here
11. I confirm that axicabtagene ciloleucel will be otherwise used as set out in its Summary of Product Characteristics

Prof Peter Clark
NHS England Chemotherapy Clinical Reference Group chair and clinical lead for the Cancer Drugs Fund

June 2018

NICE National Institute for Health and Care Excellence

Clinical expert statement

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Thank you for agreeing to give us 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.

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

Information on completing this expert statement

- 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 13 pages.

About you	
1. Your name	**John Anthony Radford**
2. Name of organisation	**The University of Manchester and the Christie NHS Foundation Trust**

3. Job title or position	**Professor of Medical Oncology**
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 this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't 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

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to induce remission and improve quality of life and survival in patients with diffuse large B cell lymphoma, mediastinal B cell lymphoma and follicular lymphoma recurrent after previous treatment and whose prognosis is considered poor.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement in progression free survival/overall survival compared with standard therapy
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Without any doubt. The prognosis of patients with non-Hodgkin lymphomas of the types specified recurrent after previous treatment is very poor. Considerable international effort has been put into identifying new, effective treatments and CAR-T therapy has demonstrated clear efficacy in these specifies subtypes of lymphoma. It is of note that patients are increasingly aware of the potential of CAR-T therapy and are requesting referral to large centres in an attempt to access this treatment. Others consider trying to raise sufficient funds to travel to the US where CAR-T cell therapy is available.

What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Relapsed refractory lymphomas are currently treated with salvage chemotherapy and if remission is achieved this is followed by high dose chemotherapy and autologous/allogeneic transplantation.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes. BSH guidelines are the most well-known and utilised in the UK
• 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.)	Well defined up to point of first salvage/ASCT. Beyond this there are differences in opinion and variations in practice (see paragraph 23a below) which in my view are not in the best interests of patients with lymphoma, research or progress.
• What impact would the technology have on the current pathway of care?	It could help to rationalise and optimise care/outcomes for patients with relapse/refractory lymphoma (se paragraph 11 below)
11. Will the technology be used (or is it already used) in the same way as current care	No. This treatment should only be used by appropriately constructed and trained teams located in a few specialist centres. I recommend establishing relapsed/refractory lymphoma networks with hospitals within each of these referring rel/ref patients to their designated centre for consideration of CAR-T therapy or alternative clinical trials where the former is deemed inappropriate or the patient declines.

in NHS clinical practice?	Indications for consideration of CAR-T therapy should be designed at a national level and patient outcomes and experience measured and compared across networks. Links with the relevant pharmaceutical companies are crucial so that manufacturing pathways for the therapeutic product can be optimised In setting up a bespoke framework of care for CAR-T therapy there will be benefits for all patients with rel/ref lymphoma. Even if CAR-T cell therapy is inappropriate other specialist options including clinical trials can be considered with a view to achieving best outcomes and gaining research knowledge in this group of patients where
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary centres for evaluation of rel/ref patients for inclusion on CAR-T programme or entry into a suitable clinical trial, apharesis, delivery of the therapeutic product, management of acute toxicity and early post-treatment care. Local hospitals in the relapsed/refractory lymphoma networks described in paragraph 11 above will play an important role in monitoring and supporting CAR-T patients once the period of high risk has passed.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This should be focused on a few centres so experience can be gained quickly and best practice developed. This type of therapy requires specialist teams of physicians, nurses, intensivists, laboratory technicians, data managers/analysts and pharmacists. Educational programmes will need to be developed and SOPs written. There will need to be an appropriate number of in-patient beds available and ready access to ITU facilities.
12. Do you expect the technology to provide clinically meaningful benefits compared	Yes – potentially a “game changer”

with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The selected sub-types of lymphoma are currently appropriate – it may be that future data may emerge of CAR-T benefits in other sub-types with equally poor outcomes.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current	More difficult and highly specialised. Requires properly resourced and trained teams in a few large centres.

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.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Guidelines for referral to a CAR-T centre and a treatment eligibility check list at the centre will be required. These however should be written/applied flexibly so patients who might benefit but fall outside specified inclusion criteria can still be treated. All outcomes should be measured and audited.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year	I'm not fully conversant with QUALY calculations and so prefer not to answer this question.

(QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes
• Is the technology a 'step-change' in the management of the condition?	Undoubtedly
• Does the use of the technology address any particular unmet need of the patient population?	Yes – the relapsed refractory population where it is generally agreed current treatment options are unsatisfactory
18. How do any side effects or adverse effects of the technology affect the management of the condition	Side effects may require intensive care and might be fatal. With increasing experience in the management of CAR-T cell therapy, focus of the technology on a few appropriately resourced centres and increasingly experienced teams the impact of these side effects will be minimised

and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	CAR-T cell therapy not generally available in the UK at present so this comparison not applicable
• If not, how could the results be extrapolated to the UK setting?	By identifying centres which can become expert in the use of CAR-T therapy and measuring outcomes.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Achievement of remission in a rel/ref population is highly relevant, duration of remission, toxicity (and grade), overall survival – all measured in clinical trials. Patient experience – not measured but this can be remedied if CAR-T cell therapy supported as part of relapsed/refractory lymphoma network (paragraph 11 above)
• 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	No

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Very similar in my view
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	Possibly. It is the unfortunately the case that some hospitals in some locations may be reluctant to refer patients to a large centre for consideration of clinical trials – because of financial pressures, not wishing to "lose" their patients and little clinician interest in innovative therapies.
23b. Consider whether these issues are different from issues with current care and why.	Very similar. This is why I strongly recommend the establishment of relapsed/refractory lymphoma networks

Topic-specific questions	
24a. All aggressive subgroup of B-cell NHL are included in the population eligible for Axicabtagene ciloleucel treatment. Would the approach to management be similar in patients with DLBCL, PMBCL and TFL? 24b. Is it likely the effect of treatment would be equal in these subgroup populations?	Yes The approach to management with CAR-T therapy will be the same for all lymphoma subgroups Similar but not necessarily identical.
25. Is the comparator pixatrone [excluded from the company submission] used in clinical practice in the NHS?	Pixantrone although approved for use in the relapsed refractory setting has not found much favour with UK physicians because of its unsatisfactory efficacy. Moreover using another line of chemotherapy in patients who have failed previous chemotherapy is illogical and entry into a CAR-T programme or clinical trial of a novel agent is far more rational.
26a. Do salvage regimes [included in the company	All can be considered to have similar efficacy – there are no clinical trials to my knowledge showing the superiority of one salvage therapy over another. Other commonly used salvage regimens include R-IVE, R-

submission as a blended comparator] GEM, GEMP-P RGCVP and RVP have equal efficacy? 26b. Are these regimes distributed equally to patients with R/R DLBCL, PMBCL and TFL in clinical practice in the NHS?	GDP, R-ICE and R-DHAP Their use is determined by local practice, different types of toxicity and number of required days of hospital stay.
27a. Treatment with CAR T therapy is likely to necessitate prolonged stays in hospital. Who is likely to manage these patients during their time in hospital? 27b. Would patients receiving CAR-T cell therapy require additional monitoring to what is currently provided to	With increasing familiarity with CAR-T cell therapy it is likely that some patients will be managed as outpatients. To begin with however all patients will be admitted for a period of observation and for those who develop severe toxicity admission may be required for a long period. Yes. SOPs would define what the monitoring should comprise.

inpatients?	
28a. The company list the two most common side effects of CAR-T therapy as cytokine release syndrome (CRS) and neurotoxicity. Are these events commonly seen in patients in current clinical practice?	These are the 2 commonest toxicities seen with CAR-T cell therapy. Although CRS can be seen with other immunologically based therapies (tumour targeted antibodies and interleukin-2 for example), the CRS seen with CAR-T therapy is generally more severe. The neurotoxicity is unusual with other types of therapy but quite common with CAR-T approaches.
28b. What additional treatment or care (if any) would be given to patients suffering from these adverse events compared to what is provided currently to patients in high dependent units?	There is an absolute need for a CAR-T cell therapy team comprising physicians (middle grade and senior), nurses, intensivists and technicians, a sufficient supply of in-patients beds and ready access to an on site ITU
28c.Would current clinical staff require additional training and support to manage patients who experience these adverse	Yes – this is essential

events?	
29. Would all low grade CRS events require treatment with tocilizumab?	No. The indications for tocilizumab will need to be carefully and clearly defined.
30. Would B-cell aplasia be an expected consequence of CART therapy? Would low grade reactions require additional treatment?	Yes – for up to one year has been reported. However the consequences of this are generally not severe (probably due to persisting plasma cells that do not express CD19) and can usually be successfully managed using antibiotics and immunoglobulin infusions until B cell populations recover.
31. What proportion of patients (R/R after 2nd line or who previously failed an ASCT) treated with salvage chemotherapy would become eligible for an ASCT?	Only a small minority of patients who are rel/ref after 2nd line chemotherapy become eligible for ASCT after a subsequent line of treatment (chemotherapy or a novel agent in clinical trial) and overall this group has an abysmal prognosis. Patients who relapse after ASCT also have a dire prognosis – if they respond to further salvage they are likely to be offered allogeneic transplantation if fit enough but this is only likely to be applicable to a small number of patients.
Key messages	

32. In up to 5 bullet points, please summarise the key messages of your statement.

- High level of unmet need in the specified subtypes of lymphoma
- CAR-T cell therapy is a potential game changer in the specified indications
- Significant but predictable and manageable toxicity
- CAR-T therapy should only be undertaken in specialised centres as part of a relapsed/refractory lymphoma network
- Referral guidelines and pathways of care will need to be carefully defined

Thank you for your time.

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

NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma ID1115

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

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

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- Your response should not be longer than 10 pages.

About you	
1. Your name	**Claire Foreman**
2. Name of organisation	**NHS England**

3. Job title or position	**National Programme of Care Senior Manager – Blood and Infection, Specialised Commissioning, NHS England**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England** NHS England leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**

Current treatment of the condition in the NHS	
6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE has published several technology appraisals relating to the treatment of lymphomas of various types. In addition there is a NICE Guideline relating to the diagnosis and treatment of Non-Hodgkin's lymphoma (NHL). NHS England has published a service specification in relation to the provision of chemotherapy in cancers and haematopoiec stem cell transplants which follow BSBMT guidelines. Relevant policies and specifications can be viewed here https://www.england.nhs.uk/commissioning/spec-services/npc-crg/
7. 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.)	The current pathways of care for the treatment of diffuse large B cell NHL, primary mediastinal NHL and transformed follicular NHL are well defined and thus there is little variation in them. Diffuse large B cell lymphoma (DLBCL) is by far the dominant type of NHL relevant to this CAR-T cell indication. National algorithms for the treatment of these types of NHL are in preparation. The new pathways of care which would incorporate axicabtagene ciloleucel are as yet not defined as the final wording of the marketing authorisation will be important in determining the place of axicabtagene ciloleucel in these treatment pathways, in particular the relevance to patients potentially eligible for high dose chemotherapy and stem cell transplantation.
8. What impact would the technology have on the current pathway of care?	This technology will have a significant impact on the current pathways of care for these NHLs, and on other specialities, whose major engagement in the treatment pathway will now be required or will need to increase as a result of the delivery requirements and side effect profile of the new technology. Although the allogeneic stem cell transplant pathway will provide an important foundation for the provision of expertise for the new technology, axicabtagene ciloleucel is significantly different in a number of ways. Unlike the current pathway, the new technology • Will require substantial workforce and infrastructure changes – there will be new training and accreditation requirements to meet in terms of all the steps required to bring the new technology to the bedside and the need to change access arrangements to ITU support (through changes in

	planning, 'booking' ITU beds and the need for expanded access to ITU facilities despite existing constraints and seasonal variation in demand). • Is a 'personalised medicine' and involves new arrangements for the preparation, procurement, storage, manufacture and administration of the technology for safety and quality assurance • Adds an additional line of therapy into the treatment pathway • May lead to a change in the lines of treatment for these conditions and the order in which they should be considered by clinicians for the treatment of their patients (for example, will HSCT be replaced by successful treatment using axicabtagene ciloleucel?) • Will require the addition of other treatments and expertise to support its use, such as tocilizumab for complications and the need for rapid access to neurological input to care after treatment. • Is expected to require 15 year safety monitoring as part of regulatory requirements. There is a wide range of side effects of the technology, with cytokine release syndrome (CRS), neurological complications and infections being the most serious. CRS and acute neurological deterioration are rare conditions in existing care pathways, and as such experience in treating them is currently limited. Conversely, these complications are expected as parts of the pathway for the new technology, although incidence and severity is not predicable at an individual patient level before treatment. Published data indicates about 30% of patients will experience severe grades of these side effects requiring ITU admission and support for a median of 8 days. The demand and impact on ITU of the CRS and neurological, renal and respiratory side effects of this technology is in our view subject to some uncertainty, particularly early in any implementation by the NHS. The impact is likely to be best mitigated in the immediate term by thorough and cautious capacity and treatment planning. This will avoid the risk of multiple CAR T cell treated patients needing ITU support at the same time. NHS England notes that in the US in centres with the most experience of CAR-T cell treatments, one patient per provider per month was treated at implementation, with treatment rates having been increased slowly to one per week per provider over a period of over 1 year. The impact on the provision of safe and effective CAR-T cell treatment is also very high for commissioners both financially and because of the need to ensure capacity for the CAR-T cell service without any adverse effect on current services. The consequences for the manufacturer of the technology are also significant in

	view of the logistics and timeliness in the provision of axicabtagene ciloleucel. As the technology is significantly different to current care, it will require a new service specification against which dedicated providers will be designated and established. The specifications for axicabtagene ciloleucel and another CAR-T product are currently in development and will be available by the time the NICE Technology Appraisal Committee meets in May 2018. Given the great service issues that need to be addressed in the provision of safe and effective treatment with axicabtagene ciloleucel as well as the need for many healthcare professionals to learn new and necessary procedures and skills, NHS England plans a phased implementation of CAR-T cell technology, both in the number of treating centres and in initial and subsequent capacity to treat. NHS England believes that the manufacturer will also seek phased implementation. In addition, NHS England notes the US experience which has stipulated that patients remain within a maximum of 2 hours travel distance from the treating centre for the first month after receiving CAR T cell therapy. NHS England would plan to adopt similar safety stipulations and is aware of the consequence of this for patients and their families, as well as the need for this to be factored into heath economic analysis of the technology (unless the manufacturer of axicabtagene ciloleucel pays for this). It is NHS England's clear view that a phased implementation and ongoing evaluation of the capacity needs in the NHS to successfully and safely deliver the treatment will be required from the point of view of patients, clinicians, hospital services and NHS England as the commissioner. As has been stated above, NHS England would expect to see the number of commissioned providers increase over time which will mean that more convenient geographical access for patients will be achieved over time. As this new technology requires substantial service change and has significant safety concerns both in the cell product production, transport and delivery but also the consequences of treatment as outlined above NHS England's view is that it is essential that the 90 day implementation rule is not be applied to this product. As this product is likely to trigger the new Budget Impact Test, this would provide a clear mechanism for NHS England to enter into commercial discussions with the company about affordability and the phased implementation of the new treatment should it receive a positive appraisal recommendation. The NHS is actively planning for the establishment of capacity in CAR-T treatments, mindful that NICE is

	appraising 2 products in immediate succession with at least one closely related indication. It is important that the NHS establishes the collective clinical capacity for both products particularly where they share common resource requirements such as critical care, and that the timescales for introduction are managed across the related NICE appraisals in a co-ordinated way.
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	Currently, this technology is available in a small number of sites through research trials only. The patient group is in those with haematological cancers, although the research pipeline is such that the indications for use are expected to expand over time across into other cancers (eg myeloma) and into non-malignant disorders. Such developments may in turn lead to additional or different challenges.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is not currently available within the NHS except as part of ongoing trials. It is anticipated that the technology will be used as a potentially curative intervention for relapsed/refractory diffuse large B cell NHL, primary mediastinal B cell NHL and transformed follicular NHL. Given the novelty, promise and toxicity of the treatment, it is expected that axicabtagene ciloleucel will make fundamental differences to the treatment pathways for these types of NHL as compared to the current pathway. Until the wording of the marketing authorisation of axicabtagene ciloleucel is known, its exact place in and the impact on the CAR-T cell therapy (eg stem cell transplantation in appropriate patients) will need to be clarified. If the technology receives a positive NICE guidance, it is likely to be used in accordance with its licence in those patients who are eligible for treatment and who want to undertake the treatment (unless NICE recommends optimised use of the technology).
• How does healthcare resource use differ	Please also refer to question 8

between the technology and current care?	The main difference in healthcare resource usage is: • specialist pharmacy resource as part of product procurement and quality assurance • significantly increased requirement for intensive care (ITU) beds • increased access to acute neurological expertise and support and also specific supportive drugs such as tocilizumab to treat potential side effects of treatment such as cytokine release syndrome and tumour lysis syndrome. Although the licence is awaited to confirm all the particulars, it is expected that patients will need to be admitted for the administration of the treatment and for a period thereafter and that ambulatory care is possible as long as the patient remains well and within a maximum of 2 hours travelling time of the provider for 4 weeks. The great majority of patients require admission for complications that are currently and regularly seen in patients undergoing allogeneic stem cell transplantation. It is the CRS that requires specialist observation and care with access to ITU support in 30% of cases. As this is a one-off treatment requiring new and considerable infrastructure / supportive care compared to chemotherapy which is a well-established treatment given over a number of cycles, determining the actual cost of treatment will require detailed health economic work, especially the likely high cost of the new technology itself and the infrastructure and support costs. Given that the likely indication for axicabtagene ciloleucel in DLBCL will easily exceed 100 new patients each year, it is expected that the cost of implementing this technology will be very considerable and likely to trigger the Budget Impact Test. The payment mechanism will therefore need ascertaining before NICE appraisal and also reviewing after a positive NICE recommendation. An alternative payment mechanism which is outside of current process may need to be developed and NHS England anticipates this may require input from the Treasury.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	CAR-T cell technology for NHL requires tertiary cancer centres who already provide a high throughput of allogeneic stem cell transplants and have ready access to specialist pharmacy services, on-site ITU and on-site neurophysiology / imaging as well as rapid access to acute neurological services. The service will need to be JACIE accredited and meet the requirements of the pharmaceutical company with respect to handling the product in accordance with the medicines regulations. It is unclear as yet to the exact requirements of the supplier with regard to quality assurance and contracting with provider sites, as there is

	a complex process and supply chain associated with the therapy. NHS England is drafting a new service specification to outline the requirements which will be specific to each CAR-T therapy and this will be available by the time NICE appraises axicabtagene ciloleucel.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	As above and question 8. The manufacturer will require and need to fund ongoing staff training to meet the safety requirements associated with the technology. We understand this can take up to six months as part of the manufacturer's agreements with NHS trusts. This may include training for pharmacy staff if pharmacy are required to handle and store the final product before administration to the patient. Specialist equipment may also be required. Since the final product will be delivered frozen in vapour phase nitrogen, special equipment will be required for storage while the patient undergoes conditioning. Potentially new dedicated ITU beds will be required over time. Other specialist capacity may also require investment such as neurophysiology monitoring (EEG) and emergency neurological care. Investment in the long term safety monitoring, data recording and data analysis will be required. Capacity to deliver this treatment is a key concern and in the early phases of implementation, NHS England would advise that patients will need to be prioritised for treatment with CAR-T cell treatment in order that access can be provided without compromising patient safety.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	CAR-T is a one-off treatment. Selection criteria for starting treatment will depend on the details of the marketing authorisation (MA) received for axicabtagene ciloleucel and any conditions put upon access by NICE Guidance and NHS England. Clinically, it is advised that a National MDT structure will need to be put in place to ensure appropriate and prioritised patient selection for axicabtagene ciloleucel and any other CAR-T cell treatments for NHL. NHS England will put this in place. Patients will need to undergo a chemotherapy conditioning regimen prior to treatment with CAR-T cell therapy and this does pose additional complexities with timing of treatment and access to the final product which is shipped in from US and Europe.

	The supplier will, as part of their risk management plan, need to ensure contracts are in place with provider sites. Test runs are performed before live product is used to ensure the supply chain works effectively. Scheduling of patient treatment with CAR-T cell therapy will initially be necessary (eg 1 new treatment per month) so as to allow expertise in logistics and patient care to be assimilated. More patients per month will be treated in time.
11. What is the outcome of any evaluations or audits of the use of the technology?	No audits have been undertaken. Trial data is available based on 8 months of follow up. There is therefore only very short and immature follow up. Whilst acute toxicity is known, long term side effects are not known. In addition, the incidence of later relapses is also an uncertainty.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	Over time, the aim is for this technology to improve equality issues by increase access to cure in a way which is geographically appropriate. Due to the novelty of the treatment, the expertise required and the logistics involved, all key stakeholders have indicated the need for a phased implementation if approved. This is likely to mean that geographical access at the start will be worse than current access to chemotherapy / HSCT. Clinical prioritisation of patients will be required. The eligible population is relatively small (<500) but while treatment configuration will require adequate geographical spread this is expected to take some time to achieve while capacity improves and more providers can be supported to offer the treatment.
12b. Consider whether these issues are different from issues with current care and why.	n/a These issues are different to the current pathway due to the novelty of the treatment, the complexity / toxicity profile, the interdependence on other services, capacity in the supply chain and the experience of the system in delivering the treatment.

Thank you for your time.

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Evidence Review Group's Report

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD Name of TAR Centre
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None

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Rider on responsibility for report

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

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Contributions of authors

Mark Corbett and Hollie Melton wrote the clinical effectiveness sections of the report. Ana Duarte wrote the cost effectiveness sections and conducted the ERG economic analyses. Simon Walker provided methodological and technical support for the cost-effectiveness sections and model validation. Kath Wright wrote the sections on the search strategies. Alison Eastwood provided advice, commented on drafts of the report and took overall responsibility for the clinical effectiveness sections. Stephen Palmer provided advice, commented on drafts of the report and took overall responsibility for the cost effectiveness sections.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined

Copyright statement

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List of abbreviations

AE	Adverse event
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
BSH	British Society for Haematology
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptor
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRS	Cytokine release syndrome
CS	Company submission
CSR	Clinical study report
DHAP	Cisplatin, cytarabine and dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DoR	Duration of response
ECOG	European Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EQ-5D	EuroQol 5-dimension quality of life questionnaire
ERG	Evidence Review Group

ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FL	Follicular lymphoma
GDP	Gemcitabine, dexamethasone and cisplatin
GEM	Gemcitabine and methylprednisolone
GEM-P	Gemcitabine, methylprednisolone and cisplatin
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
ICE	Ifosfamide, carboplatin, etoposide
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Unit
IPD	Individual patient data
IPI	International prognostic index
ITT	Intention-to-treat
ITU	Intensive treatment unit
IV	Intravenous
IVE	Ifosfamide, epirubicin and etoposide
IVIG	Intravenous immunoglobulins
IWG	International Working Group
KM	Kaplan-Meier
MA	Marketing authorisation
MCM	Mixture cure models
mg	milligram
MIMS	Monthly Index of Medical Specialties
mITT	Modified intention-to-treat
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service

NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PartSA	Partitioned survival analysis
PFC	Points for clarification
PFS	Progression free survival
PMBCL	Primary mediastinal B-cell lymphoma
PR	Partial response
PRIME P	riority medicines
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
R/R	Relapse/refractory
RCT	Randomised controlled trial
REMS	Risk Evaluation Mitigation Strategy
RGCVP	Rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone
RMP	Risk Management Plan
RVP	Rituximab, vinblastine and prednisolone
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology and End Results
SLR	Systematic literature review

SmPC	Summary of product characteristics
TA	Technology Appraisal
TFL	Transformed follicular lymphoma
UK	United Kingdom
USA	United States of America
VBA	Visual Basic for Applications
WHO ICTRP	World Health Organisation International clinical trials registry platform

1 Summary

Diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL) are aggressive subtypes of Non-Hodgkin's lymphoma (NHL) that originate in B-cells and express CD-19 antigen on the cell surface. DLBCL is the most frequent subtype, and accounts for 30% of new NHL diagnoses affecting patients of median age 61 years. DLBCL has a male predominance. PMBCL is reported as clinically and pathologically distinct, it more commonly affects females and accounts for 5% of new NHL diagnoses, with a median age of 35 years. TFL represents 1% of NHL cases and originates as follicular lymphoma which represents 20% of NHL patients. 3% of FL patients are estimated to transform into TFL.

Prognosis is dependent upon histology, disease stage and factors such as age, comorbidities, lactate dehydrogenase levels and tumour genetics. Clinical practice guidelines recommend using the International Prognostic Index (IPI) for prognosis. IPI considers risks in line with variables reported by the company, risk factors include age >60 years and ECOG performance status 2-4. IPI also considers serum LDH > normal, stage III-IV and >1 extranodal sites. Over 30% of DLBCL patients are expected to relapse.

1.1 Critique of the decision problem in the company's submission

The population considered in the CS differs slightly from the draft EMA SmPC. Both consider DLBCL, PMBCL and TFL but the CS specifies the disease "is refractory, or has relapsed after two or more lines of systemic therapy." The draft EMA SmPC specifies R/R patients who are ineligible for autologous stem cell transplant (ASCT). The scope of the submitted evidence includes ASCT eligible patients. Despite pathologically distinct diagnoses, their treatment is similar in clinical practice. The company estimates an eligible population of 972 in 2018, although this may reflect a population eligible for testing rather than treating. The submitted evidence is from a single-arm trial (ZUMA-1) with a comparison study composed of 4 pooled patient level data sets (SCHOLAR-1). The ZUMA-1 population matches that defined in the decision problem, but is restricted to participants with an ECOG performance status score of between 0-1 (from fully active to restricted physically strenuous activity). The SCHOLAR-1 population covers all ECOG scores (0-4). Only 57% of patients had up-to-date ECOG data; of those 80% were ECOG 0-1 and 20% were ECOG 2-4 (from ambulatory but unable to work to completely disabled).

The intervention was as specified in the final scope: axicabtagene ciloleucel (YESCARTA), herein referred to as axi-cel, as it was in the CS. Axi-cel is currently awaiting EMA marketing authorisation. The intended target dose of axi-cel is 2×10^6 anti-CD19 CAR T-cells/kg body weight (range: 1×10^6 – 2.4×10^6 cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T-cells (p14). Axi-cel is delivered as a single infusion in a single treatment. White blood cells are collected from patients by leukapheresis and shipped to the manufacturer to engineer T-cells with CAR. Pre-treatment

conditioning chemotherapy is delivered 5, 4, and 3 days prior to infusion. Delivery of axi-cel is anticipated to require specialist centres, with patients requiring prolonged observation and access to intensive care in the event of side effects (particularly cytokine release syndrome). For ASCT ineligible patients, the large overlap between ASCT and axi-cel fitness criteria is an important consideration. In their clarification, the company state their clinical advisors found it challenging to come up with a clear list of identifying factors for these patients and suggest it is unlikely a patient unfit for ASCT would be fit for axi-cel. Also, given the evidence and current NHS practice CAR-T is a highly uncertain first line salvage therapy in UK practice since other effective interventions with long-term evidence are available (including ASCT).

The following comparators were included in the final scope, with or without rituximab: DHAP, GDP, ICE, IVE; pixantrone and best supportive care (including radiotherapy). The CS excluded pixantrone on the basis of BSH guidelines and clinical consultation indicating little use in clinical practice. A blended comparator was used, due to heterogeneity between ZUMA-1 and SCHOLAR-1. The scope describes the blended comparator as including DHAP, GDP and ICE (with or without rituximab; the precise scope of comparators within SCHOLAR-1 is unclear). These are typically delivered in outpatient settings in local hospitals. Use of a blended comparator does not allow for comparison of axi-cel against any individual treatment and the CS assumes equality in effectiveness across all comparators. Given the heterogeneity of populations and availability of data, this can be considered a suitably pragmatic approach for the comparison.

The outcomes in the NICE scope are considered in the CS: overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life. The primary outcome in ZUMA-1 is ORR, defined as CR or PR per International Working Group response criteria determined by study investigators. PFS and HRQoL were measured in ZUMA-1 but were not endpoints in SCHOLAR-1.

1.2 Summary of clinical effectiveness evidence submitted by the company

The efficacy and safety analyses were based largely on ZUMA-1 which is an ongoing phase I/II multicentre, open-label, prospective single-armed study evaluating axi-cel. The trial recruited 108 patients with histologically confirmed DLBCL, PMBCL, or TFL and an ECOG performance status of 0 or 1.

The ORR (the study's primary outcome) was 82%; at a median follow up of 15.4 months 42% remained in response, including 40% with CR. The median duration of response was 11.1 months (95% CI 3.9 to could not be estimated). The CS reported PFS rates of 49% (95% CI, 39 to 58) at 6 months, 44% (95% CI, 34 to 53) at 12 months, and 41% (95% CI, 31 to 50) at 15 months. The OS rates were 78% (95% CI, 69 to 85) at 6 months, 59% (95% CI, 49 to 68) at 12 months, and 52% (95%

CI, 41 to 62) at 18 months. Ten patients were re-treated with axi-cel, in line with the trial protocol, though the anticipated market authorisation is not expected to allow retreatment with axi-cel.

The company used patient-level data from the SCHOLAR-1 study as the basis for forming a dataset of patients who received relevant comparator treatments. SCHOLAR-1 is a retrospective study of 636 patients (mostly from the U.S.) with refractory disease (mostly DLBCL) which pooled data from four datasets. Throughout the submission the SCHOLAR-1 analyses were based on the "last refractory categorisation" cohort of patients, which had a sample size of 593, though fewer patients were evaluable for response (n=508) and survival (n=497). The outcomes reported in SCHOLAR-1 which were available for comparison with ZUMA-1 were ORR and OS.

The covariates reported in the methods section of the SCHOLAR-1 paper were: IPI risk category, ECOG performance status, disease stage, line of therapy before refractory status, and refractory subgroup. When comparing baseline data across ZUMA-1 and SCHOLAR-1 differences were evident across all these covariates and missing data (in SCHOLAR-1) were an issue for all the covariates except refractory subgroup.

In an attempt to address the problem of baseline imbalances across the ZUMA-1 and SCHOLAR-1 studies the CS presented results from a "standardised" analysis. The methods used in this approach describe stratification of two covariates - ECOG performance status and last refractory subgroup - with weighting of outcomes across the strata. Results were also presented for standardisation based on refractory subgroup and subsequent ASCT. Standardisation by refractory subgroup and ECOG status produced a hazard ratio for survival of [redacted] showing a statistically significantly lower risk of death for patients treated with axi-cel; standardisation by refractory subgroup and subsequent ASCT produced a hazard ratio for survival of [redacted]

All patients had an adverse event (AE) and 95% of patients had a grade ≥3 AE (Table 19 of CS). [redacted] had a serious adverse event (SAE) and 43% had a grade ≥3 SAE. [redacted]

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Most of the company's systematic review methods were appropriate for the assessment. However, the almost complete lack of a narrative explaining how the company went from including 22 studies in the systematic review to then effectively excluding them and instead using the ZUMA-1 and SCHOLAR-1 patient-level datasets is a limitation of this aspect of the submission. SCHOLAR-1 was not identified as an included study in the systematic review, nor was it mentioned as a potentially useful excluded study.

The patients studied in ZUMA-1 appear to be representative of the various lymphoma population sub-groups for which there is a high unmet need for new treatments: nearly all patients had had at least two prior lines of therapy, with 40% of patients having had four or more prior lines of therapy (chemotherapy or ASCT). Appropriate outcomes were assessed in ZUMA-1, but the immaturity of the data available to date means there is uncertainty regarding the robustness of the OS and PFS results for follow up time-points beyond 12 months. Also, the ERG notes that 10% of patients who received a dose of axi-cel were re-treated (due to disease progression) but a re-treatment option is not likely to be reflective of future clinical practice, based on axi-cel's anticipated marketing authorisation.

The company tested whether significant heterogeneity was present across the four component studies which make up SCHOLAR-1, concluding that it was not and that the data were therefore suitable for pooling. However, the test used is known to be poor at detecting true heterogeneity, especially when the number of included studies is low. The ERG notes that the smallest study (MAYO) appears to be somewhat of an outlier when comparing the 2-year survival results (10% versus 17%, 22% and 23%) and median survival results (5.0 months versus 6.5, 6.6 and 6.6 months). The ERG considers that this raises questions about the clinical meaning of the pooled SCHOLAR-1 results.

In the absence of relevant RCT evidence, the ERG concurs with the CS statement that the availability of patient-level data to account for differences between patient characteristics and key prognostic factors is considered to be more rigorous and allows a more appropriate comparison (than using summary results from single-arm datasets). The main bias issue to address when comparing and analysing results from single-arm datasets is the adequate adjustment for important covariates. Given that five covariates were identified in the SCHOLAR-1 study, and that SCHOLAR-1 highlighted the prognostic importance of ECOG status, disease stage and IPI, the ERG considers that the CS standardised analyses do not adequately adjust for key baseline imbalances. Moreover, although they took account of the use of subsequent ASCT, they did not take account of patients who were re-treated with axi-cel.

The company also adopted a propensity score matching approach to adjusting baseline data, although results were not reported in the CS section on clinical effectiveness. The CS listed the covariates used in the propensity score matching as age, sex, disease stage, diagnosis and relapsed post-ASCT status. The CS also stated that these covariates had statistically significant differences (between ZUMA-1 and SCHOLAR-1) which became non-significant following "re-weighting". Only two of these covariates match the five covariates identified in the SCHOLAR-1 methods. In light of the response to a point of clarification about how covariates were selected, the ERG considers that the company's approach to the propensity score matching appears to have been concerned with maximising sample size and reducing statistically significant baseline differences across the two studies, rather than adjusting for clinically important imbalances (which may not necessarily be statistically significantly

different) in covariates known to be important in affecting outcomes. Consequently there is considerable uncertainty about the comparative effectiveness estimates.

The CS stated that "there remains a large amount of heterogeneity between the study populations which may have biased the results against ZUMA-1" (p82) citing differences in number of prior lines of therapy and in the proportion of patients receiving subsequent ASCT. However, the ERG thinks this is not a particularly even-handed representation since concern about this bias was not balanced by factors which may have biased the results against SCHOLAR-1, such as differences in ECOG status, re-treatment with axi-cel in 10% of ZUMA-1 patients (which would not happen in clinical practice) and uncertainty relating to the substantial levels of missing covariate data.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic submission included a systematic review of published evidence on the cost-effectiveness of axi-cel and a separate model. The review did not identify any previously published studies of axi-cel. The ERG identified one recently published US study which evaluated the clinical and cost-effectiveness of axi-cel versus chemotherapy for adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who were ineligible for autologous stem cell transplant (ASCT). The study reported an ICER of $136,078 per QALY gained for axi-cel versus chemotherapy.

Inevitably differences between the US health care system and the NHS makes it difficult to generalise the results. As a result, the ERG considers the company's model to provide the most relevant evidence for the decision problem. Nevertheless, the US study provides an important basis for comparing key structural assumptions and parameter uncertainties.

The population considered in the company's model is consistent with the anticipated license for axi-cel for the treatment of adult patients with DLBCL, PMBC and TFL, that is refractory, or has relapsed after two or more lines of systemic therapy. The most relevant comparator identified by the company was best supportive care (BSC) comprising salvage therapy with multi-agent chemotherapy. BSC was modelled using a blended comparator composed of several gemcitabine and/or platinum-based chemotherapy regimens. The regimens included in the blended comparator were:

- Gemcitabine and methylprednisolone (GEM)
- Gemcitabine, methylprednisolone and cisplatin (GEM-P)
- Rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone (RGCVP)
- Rituximab, vinblastine and prednisolone (RVP)

The company's model was based on a three health state (pre-progression, post-progression and death) partitioned survival model. The model also included an important additional structural assumption, specifically that those patients' who remain in the 'Pre-progression' health state for at least two years (in either treatment group), will subsequently revert to the same HRQoL and costs as the general population and will not incur any further costs related to their previous condition. This is equivalent to a separate structural 'cure' assumption applied in the model that prevents transitions from the 'Pre-progression' to the 'Post-progression' state after two years.

A lifetime horizon was assumed (44 years) and a 3.5% discount rate was applied for costs and health benefits, in line with NICE guidance. A separate scenario analysis using a lower discount rate on costs and benefits (1.5% per annum) was also presented. The company stated that this scenario would be relevant if the NICE committee considers that axi-cel meets the criteria for the use of a lower discount rate based on the NICE methods guide.

The OS and PFS extrapolations for axi-cel were based on the latest ZUMA-1 combined Phase 1 and 2 data cut (n=108, August 2017). This data is based on the mITT population (i.e. patients who received axi-cel). As a result, model entry for patients receiving axi-cel occurs from the time point of infusion of axi-cel, rather than from the time point of the initial leukapheresis procedure. Following a request in the point for clarification, the company adapted the model to explore an additional scenario which explores the potential impact of including the Full Analysis Set population (ITT).

Based on visual inspection of the axi-cel KM curves for PFS and OS, the company identified a plateau occurring from around 6 months in the PFS data and after around 10-12 months for OS. The plateauing of PFS and OS was considered by the company to indicate a proportion of patients experiencing long-term remission and survival. In order to appropriately capture the plateau in the OS data, the company investigated the use of more complex survival models (mixture cure models) as well as standard parametric models.

The company fitted a number of standard single parametric and mixture-cure models to the OS data of the mITT population in ZUMA-1. The base-case survival model selected was a mixture-cure model where the survival of 'not-cured' patients is modelled with a single parametric Weibull curve and the mortality of the 'cured' patients is considered equal of the age and gender matched general population mortality rate.

A historical control was used to establish relative effectiveness of axi-cel compared to BSC. OS data for the BSC treatment group was sourced from SCHOLAR-1. The company explored a range of alternative approaches to attempt to adjust for differences in population characteristics between ZUMA- 1 and SCHOLAR-1. The four adjustments proposed for the SCHOLAR-1 were:

1. Base-case analysis: Removal from SCHOLAR-1 of patients with known ECOG 2-4 at baseline;

2. Scenario 1: Unadjusted, all patients in SCHOLAR-1 included;

3. Scenario 2: Propensity score matching used to adjust survival data for all patients in SCHOLAR-1

4. Scenario 3: Removal from SCHOLAR-1 of patients with ECOG 2-4 at baseline and those who had received post-refractory SCT

Similar to the approach taken by the company to extrapolate the OS of axi-cel, a number of standard single parametric and mixture-cure models were fitted to the OS outcomes of the subset of patients in SCHOLAR-1. Mixture-cure models were not included in the base-case analysis for BSC because the Gompertz single parametric curve was considered to have a good statistical and visual fit. In the absence of PFS data collected on SCHOLAR-1, the company relied on an assumption that the relationship between PFS and OS for BSC would be similar to the relationship reported between OS and PFS for axi-cel.

The company's model only incorporates adverse events for the axi-cel treatment due to the lack of data reported in SCHOLAR-1. The company considered this approach to be conservative towards axi-cel. All adverse events included in the model were Grade 3 or higher, occurring in 10% or more of subjects in ZUMA-1.

Base-case estimates for the 'Pre-progression and 'Post-progression' health states were derived from EQ-5D data collected within the safety management cohort from ZUMA-1 (n=34), and no differences in health state utilities were assumed by treatment group. A crosswalk algorithm was applied to convert estimates from EQ-5D-5L to EQ-5D-3L values. After 2-years, patients in the 'Pre-progression' state were assumed to switch to the utility of the general population (age- and gender-matched). Utility decrements associated with adverse events were applied as a one-off decrement in the first cycle of the model.

Resource use and costs included: drug acquisition and administration costs, monitoring costs, costs related to the health states and adverse events, training costs and the cost of subsequent treatments (e.g. SCT). The cost of allogeneic SCT included two elements: (i) the initial cost of transplant (cost of the procedure and associated hospitalisation) and (ii) the cost of long-term care post-transplant. The model also included resource and cost estimates for the pre- progression and progression health states based on a previous NICE TA. The same health state costs were assumed for each treatment and hence differences between treatments were determined by differences in the proportion of patients

residing in each state over time. The company's base-case analysis assumed that patients remaining in 'Pre-progression' for two years would be in long-term remission, and no longer incur the costs of medical resource use after this period.

In the company base-case analysis (lifetime horizon, 3.5% discount rate) axi-cel was reported to be more costly (mean incremental cost difference of [redacted]) but also more effective (mean incremental difference of [redacted] LYG and [redacted] QALYs) compared with BSC. The resulting deterministic ICER for axi-cel vs BSC was [redacted] per QALY gained. The mean probabilistic ICER was [redacted] per QALY.

The one-way deterministic sensitivity analyses showed that the base-case cost-effectiveness results were most sensitive to the survival assumptions including the cure fraction (pi) used in the mixture cure model for axi-cel OS and the constant of the standard parametric curves (Gompertz) fitted to axi-cel for PFS and OS for BSC.

ICERs from the scenario analyses ranged between [redacted] (scenario where BSC patients were assumed to progress upon model entrance) and [redacted] per QALY (time horizon of 10 years). The key drivers of cost-effectiveness across the scenarios were: (i) time horizon; (ii) the discount rate; (iii) PFS for BSC and axi-cel and (iv) OS for BSC. Applying a 1.5% discount rate reduced the deterministic base-case ICER to [redacted].

In response to the points for clarification, the company revised their base-case assumptions to include additional costs associated with the treatment of CRS and B-cell aplasia. The combined costing revisions increased the mean total costs of axi-cel by [redacted] and the ICER of axi-cel vs BSC to [redacted] per QALY gained (3.5% discount rate).

As part of their response, the company also provide an additional scenario which explored the impact of using the ITT data from ZUMA-1. The resulting ICER for the ITT scenario was marginally increased to [redacted] per QALY compared to the revised mITT base case [redacted] per QALY). The company stated in their response that they considered the mITT population to provide a more appropriate approach for the base-case analysis.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The main concerns identified by the ERG include:

1. *The uncontrolled comparison and the subset of SCHOLAR-1 study used for BSC*

The comparison between axi-cel and BSC was based on an uncontrolled comparison between the mITT population of ZUMA-1 and a subset of the SCHOLAR-1 study population which excluded patients with baseline ECOG 2-4 (company base-case analysis). The ERG believed that restricting the

patient population in SCHOLAR-1 to patients with known ECOG 0-1 status (n=[redacted]) may provide a more appropriate basis for comparison with the ZUMA-1 population.

2. *The use of the mITT population for axi-cel*

The OS and PFS data for axi-cel were informed using the latest ZUMA-1 combined Phase 1 and 2 data cut (n=108, August 2017). The data was based on the mITT population (i.e. patients who received axi-cel). As a result, model entry for patients receiving axi-cel occurs from the point of infusion of axi-cel, rather than from the point of the initial leukapheresis procedure. The ERG considers that the period of time between the decision to use axi-cel and subsequent axi-cel infusion (i.e. the time between the initial leukapheresis procedure and receipt of axi-cel infusion) is likely to be significantly longer than the decision to use salvage chemotherapy and the start of chemotherapy.

3. *Uncertainties concerning the company's base-case OS extrapolation for axi-cel*

The ERG considered that the difference in the cure fractions across the alternative mixture cure models suggest that the OS data for ZUMA-1 is not sufficiently mature to be able to estimate a robust cure fraction for OS. This leads to significant uncertainties surrounding the company's base-case OS extrapolation approach.

The base-case mixture-cure model was considered overly optimistic by the ERG as a basis for the lifetime extrapolation of OS for axi-cel. The two modelling approaches presented in the company's submission, the mixture-cure and single parametric over the entire time horizon, were viewed by the ERG as the most optimistic and pessimistic assumptions for the OS estimates for axi-cel, respectively.

4. *The inclusion of additional structural assumptions related to cure*

The ERG did not consider that the assumption made that patients who remain in the 'Pre-progression' health state for at least two years in either treatment group, will subsequently revert to the same HRQoL and medical resource use cost of the general population was robustly supported by evidence. The assumption of cure at two years was based on one US study (n=767). However, the ERG identified several other studies that suggest that significant excess mortality remains up until at least five years post-diagnosis.

5. *Uncertainties surrounding the HRQoL and costs of adverse events associated with axi-cel (specifically for B-cell aplasia and CRS)*

The ERG identified a number of uncertainties concerning the HRQoL and costs of adverse events. The most important uncertainties related to the assumptions for CRS and B-cell aplasia, whose occurrence is specifically associated with CAR T-cell technologies.

6. *Uncertainty surrounding post-treatment SCT*

There are two important areas of uncertainty regarding post-treatment SCT: uncertainty surrounding the actual number of patients in ZUMA-1 who received a SCT; and uncertainty to whether patients received autologous or allogeneic SCT post-treatment. While the company assumes that only allogeneic SCT was performed in both treatment groups, evidence suggests that BSC patients only underwent ASCT, which is less costly than allogeneic SCT. Costs of SCT are an important element of cost for BSC due to higher rates of transplant for this treatment, and this is likely to have a significant impact on estimates of cost-effectiveness.

7. *Uncertainty surrounding broader infrastructure and training requirements*

Given the complexity of the intervention and the lack of a clear service specification for the provision and administration of axi-cel, the ERG considers that important uncertainties remain concerning whether the additional resource/cost implications for the NHS have been fully quantified. The ERG noted specific uncertainties concerning whether ICU beds may need to be made available (even if not used) to ensure that patients receiving axi-cel can be guaranteed access to appropriate services (and without detriment to other patients). The ERG also considers that the cost of training included in the model appears unlikely to reflect the level of training required by the risk management plan likely to be mandated by the regulatory authorities.

8. *Uncertainty surrounding whether the criteria are met relating to the application of end-of-life considerations and the appropriate discount rate*

A key issue regarding the cost-effectiveness results is whether the NICE appraisal committee consider that the existing criteria for end-of-life considerations and 1.5% discounting (applied to costs and health outcomes) are met.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. The company provided extensive additional evidence and analyses in response to the ERG's points for clarification.

1.6.2 Weaknesses and areas of uncertainty

The ERG considers that all estimates of comparative effectiveness in the CS are uncertain due to inadequate adjustment for confounding. Considerable uncertainty exists regarding long-term adverse effects.

The ERG also considers that the axi-cel OS extrapolation is affected by significant uncertainties that have not been fully explored in the company submission. However, the cure assumption as implied by the base-case mixture-cure model is considered overly optimistic by the ERG as a basis for the lifetime extrapolation of OS for axi-cel, given that:

i. Survival data in ZUMA-1 is too immature to robustly estimate the size of the cure fraction;

ii. Median follow-up is shorter than the two years that the company considers to be the time point at which cure can be observed;

iii. Cure at two years is in itself highly uncertain, as excess mortality risk appears likely to persist for at least 5 years.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

A series of alternative assumptions were explored by the ERG. The main scenarios addressed uncertainties related to: (i) the uncontrolled comparison and the subset of SCHOLAR-1 study used for BSC; and (ii) the company's axi-cel OS extrapolation and (iii) the additional structural assumptions related to timing of cure. These alternatives assumptions were combined in a scenario whereby BSC OS was extrapolated from the subgroup of patients in SCHOLAR-1 with ECOG 0-1, axi-cel OS was extrapolated with a single parametric curve constrained by the UK general population mortality to ensure consistent cure fractions for PFS and OS, and pre-progressed patients alive at the point of OS and PFS convergence were assumed to have the same HRQoL and costs as general population from that time point onwards. The combined impact of the alternative assumptions proposed by the ERG increased the ICER to [redacted] per additional QALY (mITT population, 3.5% discounting).

Further exploratory analyses assessed the impact of using an ITT population, altering the model on range of alternative cost assumptions. The ERG's combined assumptions on survival extrapolation and timing of cure based on the ITT population increased the ICER to [redacted] per additional QALY.

The cost assumptions were varied on the company's revised base-case and focused on costs of CRS management, SCT, BSC treatment and administration, and training costs. Overall, the costs scenario analyses had a marginal impact on the estimates of cost-effectiveness with the ICERs of axi-cel vs BSC varying between [redacted] (for a blended comparator composed equally of non-rituximab containing regimens) and [redacted] per additional QALY (for discounted long-term SCT costs and BSC SCT assumed autologous).

The alternative assumptions on OS extrapolation and timing of cure were combined within the ERG alternative base-case. A number of further amendments were also proposed including:

1. The cost of ICU (£1,363) is assumed to represent a per-diem estimate and is applied to the average ICU hospitalisation period (4 days);

2. The follow-up costs assumed for patients receiving SCT are discounted;

3. The proportion of BSC patients who received SCT are assumed to have all undergone ASCT.

At a 3.5% discount rate, the ICER based on the alternative ERG base-case varied between [redacted] and [redacted] per QALY (mITT vs ITT approach). At a 1.5% discount rate, the ICER varied between [redacted] and [redacted] per QALY (mITT vs ITT approach).

The ERG's additional analyses highlight that cost-effectiveness results appear to be highly sensitive to alternative assumptions on survival, particularly to the axi-cel OS extrapolation approach and source of BSC OS data. Important sources of uncertainty in the submission are not fully addressed by the ERG's additional analyses due to data limitations. While the ERG's approach to OS extrapolation and cure assumptions provides a plausible alternative to the optimistic and conservative approaches considered by the company, results remain highly uncertain. Another important area of uncertainty relates to wider issues regarding how CAR T-cell therapies will be provided in the UK context and the resulting implications in terms of potential additional resource use/costs to the NHS, which cannot be fully quantified within the scope of this review.

The CS presents evidence to support axi-cel as an end-of-life therapy. The ERG considers that there is some uncertainty on whether the first criterion for end-of-life considerations, i.e. treatment indicated for patients with a life expectancy of less than 24 months, is met. The mean OS suggested by the company's original model for BSC is greater than two years, while the median OS from SCOLAR-1 is approximately 6 months. Regarding the second criterion by which treatments should offer a survival extension of at least three months, the ERG notes that while the predicted survival gains for axi-cel are subject to significant uncertainties, there is sufficient evidence to indicate that this is met. Furthermore, axi-cel appears to represent a step-change in the management of R/R adult patients with DLBCL, PMBCL or TFL who are ineligible for ASCT.

Finally, the ERG did not consider that the criteria for applying a 1.5% discount rate were met. The ERG considers that the evidence submitted is not sufficiently mature to robustly demonstrate that cure occurs, and the duration of health benefits is driven by a highly uncertain extrapolation of survival estimates. Furthermore, the sustainability of the health benefit over at least 30 years appears unlikely given that the age of the population who is likely to receive this treatment in this specific indication. The ERG also concludes that the NICE Appraisal Committee will also have to consider if the NHS investment required to implement this technology is of a magnitude that is constitutes an irrecoverable cost.

2 Critique of company's decision problem, description of the technology and clinical care pathway

2.1.1 Population

The CS provides an overview of the decision problem (p8) and defines the target population, in line with the final scope, as:

"adult patients with large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, that is refractory, or has relapsed after two or more lines of systemic therapy."

This does not exactly match the draft EMA SmPC, which is indicated for R/R adult patients with DLBCL, PMBCL or TFL who are ineligible for autologous stem cell transplant (ASCT). The given scope of the company submission and submitted evidence includes the ASCT eligible.

Although the diagnoses are pathologically distinct, as the CS indicates, they are treated similarly in clinical practice. The ERG clinical advisor confirmed the similarity in treatment while TFL has a poorer prognosis.

The company estimates 972 patients will be eligible for axi-cel in 2018. This is difficult to estimate with accuracy and it is unclear how the company calculated this, so should be interpreted with appropriate caution. The clinical advisor to the ERG expected that many patients may be eligible for testing, but few of those eligible will actually receive it. The company estimate is more likely to reflect a population eligible for testing, rather than treating.

Evidence submitted is from the single arm trial: ZUMA-1. The ZUMA-1 population matches that defined in the decision problem, but is restricted to participants with performance status ECOG 0-1 (from fully active to restricted physically strenuous activity). Of ZUMA-1 patients, 24% are over 65 years old. Evidence for the comparison comes from the SCHOLAR-1 study, composed of 4 studies with patient level data. The SCHOLAR-1 population is broadly comparable in age to ZUMA-1 but includes all ECOG scores. Fourteen percent of SCHOLAR-1 patients were over 65 years old and a majority of patients that were assessed for performance status had ECOG 0-1. Only 57% of patients were assessed, of those 80% were ECOG 0-1 and 20% were ECOG 2-4 (from ambulatory but unable to work to completely disabled) (Appendix Table 9, p22). These data were taken from Table 9 of the Appendix rather than the main submission as these represent the patients that were entered into analyses.

2.1.2 Intervention

The intervention was as specified in the final scope: axicabtagene ciloleucel (YESCARTA), herein referred to as axi-cel as it was in the CS. Currently awaiting EMA marketing authorisation, CHMP approval is expected April 2018. In 2015 it was granted Orphan Medicine Designation by EMA for patients with DLBCL, PMBCL and TFL. In 2016 EMA granted PRIME status for adult patients with refractory DLBCL or progression post-ASCT, and in 2017 received FDA approval.

The intended target dose of axi-cel is 2×10^6 anti-CD19 CAR T-cells/kg body weight (range: 1×10^6 – 2.4×10^6 cells/kg), with a maximum of 2×10^8 anti-CD19 CAR T-cells (p14). Prior to manufacture, patients undergo leukapheresis to collect white blood cells, these are shipped to the manufacturer to engineer T cells with CAR. Pre-treatment conditioning chemotherapy is delivered on days 5, 4, and 3 prior to infusion. Axi-cel is delivered as a single infusion in a single treatment. Delivery of axi-cel is anticipated to require specialist centres, with patients requiring prolonged observation and access to emergency care in the event of side effects. Further details of the intervention and delivery process are discussed in section 2.2.

The company propose that axi-cel is an end of life and curative intervention, as the eligible population would otherwise have the option of palliative care or entry into a clinical trial. However, the evidence submitted does not have appropriately long term follow-up to support a claim of being curative. Further discussion regarding evidence supporting axi-cel as an end-of-life therapy can be found in section 6. Figure 3 in the CS proposes where axi-cel would be placed in the clinical pathway, not replacing a therapy but offering a further line. The place in the treatment pathway is further discussed in 2.3.

2.1.3 Comparators

The final scope included the following comparators; with or without rituximab: DHAP, GDP, ICE, IVE; pixantrone and best supportive care (including radiotherapy). The CS excluded pixantrone on the basis of clinical consultation indicating little use in clinical practice, and the BSH guideline not recommending pixantrone as an intervention.[1] Clinical advisor to the ERG agreed, not considering it a comparator, while the ESMO guidelines suggest preference for enrolling heavily treated R/R DLBCL patients in clinical trials for novel drugs. Despite these views, pixantrone is nevertheless a NICE approved treatment.

Heterogeneity between ZUMA-1 and SCHOLAR-1 is reported in the CS as reason for using a blended comparator. The scope describes the blended comparator as including DHAP, GDP and ICE (with or without rituximab; it is unclear the precise scope of comparators within SCHOLAR-1) which are typically delivered in outpatient settings in local hospitals. Use of a blended comparator does not allow for comparison of axi-cel against any individual treatment and the CS assumes equality in effectiveness across all comparators. Given the heterogeneity of populations and availability of data,

this can be considered a suitable pragmatic approach for the comparison. Stem cell transplant is not listed as a comparator in the final scope but a proportion of both ZUMA-1 ([redacted]) and SCHOLAR-1 ([redacted]) patients went on to receive stem cell transplant.

2.1.4 Outcomes

The outcomes in the NICE scope are considered in the CS; overall survival, progression-free survival, response rate, adverse effects of treatment and health-related quality of life.

The primary outcome in the submitted evidence is ORR defined as CR or PR per International Working Group response criteria determined by study investigators. Secondary outcomes were ORR by central review, DoR and OS. PFS and HRQoL were measured in ZUMA-1 but were not endpoints of SCHOLAR-1. HRQoL was measured in a selected subset of ZUMA-1 patients. The selection of this group was unclear although the company provided demographics/characteristics for these patients in their clarification (indicating they were younger than average in the submitted evidence).

2.2 Description of the technology being appraised

The company describe axi-cel as the first of a novel class of CAR T cell therapies engineering autologous human T-cells to express a novel surface receptor fragment antibody that identifies and locks onto CD19 cells.

The CS reports the completely personalised immunotherapy as highly innovative and delivered as a single infusion, single treatment. The process of axi-cel requires collection of patient's white blood cells by leukapheresis, their delivery to the manufacturing centre, manufacture, return to the clinical centre and conditioning chemotherapy before administration to the patient by central venous IV (p11). Details of the cell manufacture process are found in appendix M of the CS. The company state the complete process takes 21-24 days, which has considerable implication for eligible patients due to the pace of disease progression and their estimated life expectancy of 3-6 months. Disease progression is rapid, as the ERG clinical advisor highlighted, therefore time taken to manufacture and deliver the product has potential for serious patient deterioration.

Pre-treatment conditioning chemotherapy of cyclophosphamide 500mg/m^2 IV and fludarabine 30mg/m^2 IV are delivered on the 5th, 4th and 3rd day prior to axi-cel. The CS reports this to be delivered in an outpatient setting, however, the clinical advisor to the ERG suggested that although this is possible it would be more likely to be delivered at the centre administering axi-cel (that also has proximity to intensive care for delivery of axi-cel). In their clarification the company state that retaining an ITU bed for every patient treated with CAR-T is not necessary, however, access to an ITU bed is. The NHS England stakeholder submission indicates that in practice axi-cel would require

inpatient admission and booking ITU beds, further detail on the impact on care pathways and infrastructure are given below in Infrastructure and implementation and section 2.3.

Delivery and handling of the intervention will require specific care, Appendix M refers to use of a validated cryoshipper. This was among issues raised by NHS England in their stakeholder submission (discussed further in Infrastructure and implementation, below).

Infrastructure and implementation

The NHS currently lacks the infrastructure for CAR-T technology although the ASCT pathway provides a foundation for implementation according to the NHS England stakeholder submission. The NHSE submission also highlighted substantial workforce and infrastructure changes required, however, details of infrastructure issues are beyond the scope of this report. Considerations include training and accreditation of staff to handle and administer the technology, as well as increased ITU access without detriment to current provision and constraints. New arrangements for preparation, procurement, storage and manufacture of axi-cel were also noted as issues to address, in the NHS England stakeholder submission.

Key concerns with implementation are also clinical capacity, resource requirement and planning (for which the USA experience would be informative). NHSE comments indicated that phased implementation could be used, for example treating one patient per month to allow safe and adequate resource in the case of adverse events.

2.3 Description of health condition and position of the technology in the treatment pathway

Health condition

The company's description of the health condition was appropriate and relevant to the decision problem. DLBCL, PMBCL and TFL are aggressive subtypes of NHL that originate in B-cells and express CD-19 antigen on the cell surface (p17). DLBCL is the most frequent subtype, the CS reports that it accounts for 30% of new NHL diagnoses and affects patients of median age 61 years. DLBCL has a male predominance. PMBCL is reported as clinically and pathologically distinct, accounting for 5% of new NHL diagnoses with median age of 35 years and more commonly affects females. TFL represents 1% of NHL cases and originates as follicular lymphoma which represents 20% of NHL patients. 3% of FL patients are estimated to transform into TFL.

Prognosis

As the CS states, prognosis is dependent upon histology, stage and factors such as age, comorbidities, lactate dehydrogenase levels and tumour genetics. Both BSH and ESMO clinical practice guidelines recommend using the International Prognostic Index (IPI) for prognosis. IPI considers risks in line with variables reported by the company, risk factors include age >60 years and ECOG performance

status 2-4. IPI also considers risk factors as serum LDH > normal, stage III-IV and >1 extranodal sites. Over 30% of DLBCL patients are expected to relapse.[2]

Table 3 in the CS gives a summary of outcomes for R/R aggressive B-cell NHL patients treated with current standard of care. When interpreting the figures presented, of note are the small sample sizes which can cause unstable estimates. Much of the presented evidence in the table relies on ORR. PFS and OS are preferred outcomes in multiply relapsed patients, as ORR is a measure of anti-tumour activity which does not have direct relationship with increased OS.[3] This is reflective of results reported by the trials, rather than the company's submission.

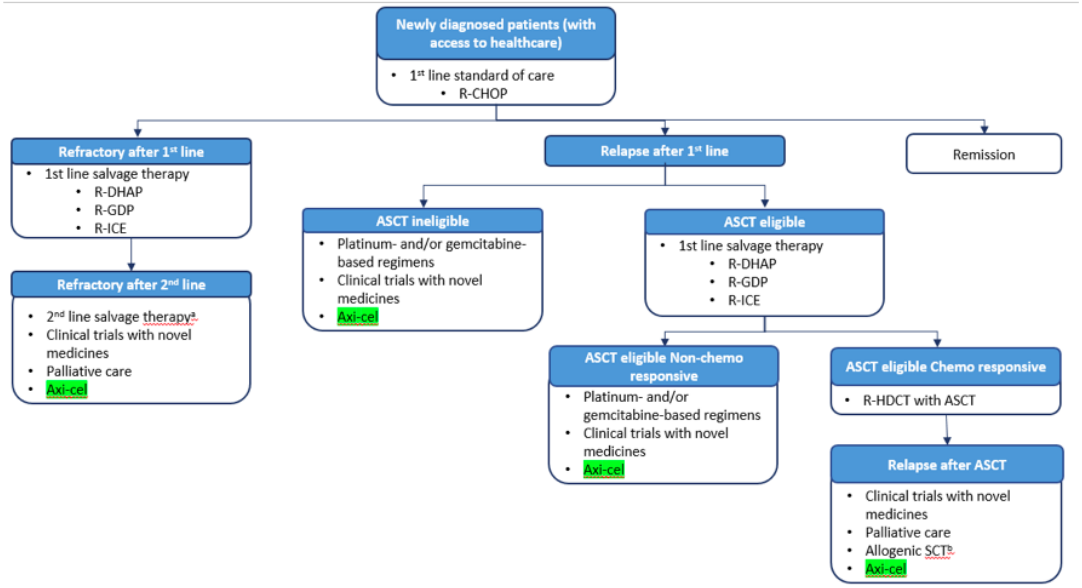
Limited quality of life evidence is available, as the CS reports. Findings from an ASCT ineligible R/R DLBCL, PMBCL and TFL R/R group, over 60 years of age, showing poor quality of life are presented. A quality of life burden is expected to be seen in younger patients also, due to the progression of the illness and previous treatments.

Clinical pathway

The company's description of the current clinical pathway was generally appropriate. Axi-cel is posed to offer an additional line of therapy to the current clinical pathway.

Clinical guidelines relevant to the population specified within the decision problem are extremely limited as stated in the CS. NICE recommended salvage therapies are R-GDP or ASCT in chemosensitive eligible patients. ESMO guidelines specifically refer to R/R DLBCL patients, indicating that patients 65-70 years without major organ dysfunction and good performance score are also recommended to follow treatment as per NICE guidelines.[2] Heavily treated patients are suitable for pixantrone (a NICE approved intervention). However, doubts about its efficacy were expressed by clinicians and the ESMO guidelines state "these patients should be preferably enrolled in clinical trials testing the activity of other novel drugs".[2] The clinical advisor to the ERG agreed that options are limited for ASCT ineligible patients, with little change seen in the last decade and clinical trials a common option. For patients R/R to second or later line therapies, palliative care and clinical trials are the remaining options.

Figure 1 Clinical pathway of care for patients with R/R aggressive NHL and proposed placements of axi-cel



Key: ASCT, autologous stem cell transplantation; BEAM, BCNU, etoposide, cytarabine and melphalan; HDCT, high-dose chemotherapy; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, cisplatin, cytarabine, dexamethasone; R-GDP, rituximab, gemcitabine, dexamethasone and cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; SoC, standard of care.
Notes: a, For second-line salvage therapy, patients may be treated with an option that they did not use for first-line salvage, i.e. one of R-DHAP, R-GDP or R-ICE; b, a small proportion of patients who relapse after ASCT may be eligible to receive allogenic SCT, and would be considered for conditioning therapy, followed by allogenic SCT if they are able to achieve a response.
Source: BSH guidelines for DLBCL treatment[3], NICE clinical pathway for DLBCL[44]; EMSO guidelines for treating R/R DLBCL[18]

Page 22 and Figure 3 in the CS (shown above in Figure 1) illustrate where axi-cel is intended to be positioned in the treatment pathway, the company clarified that axi-cel should feature in the top left box of Figure 3 also. Four groups of patients are considered eligible (p22):

- Patients who were refractory after first-line therapy (primary refractory)
- Patients who relapsed after first-line therapy, but were ineligible for ASCT following second-line therapy for reasons of age and comorbidities (a very small number of patients)
- Patients who relapsed after first-line therapy, and would be eligible for ASCT at second-line but who do not respond to salvage therapy
- Patients who relapsed after first-line therapy, were eligible and treated with chemotherapy and ASCT and subsequently relapse (a small number of these patients who are young may progress to allogeneic SCT)

Reasons for ASCT ineligibility are also listed as below:

- Age >70 years or ≥65 with comorbidities
- Inadequate response to salvage therapy or early relapse (within 12 months) after first ASCT.
- Relapse after second or later line of therapy
- Failure to mobilise stem cells for ASCT
- Presence of significant comorbidities or unresolved toxicities

The company distinguish between autologous and allogeneic stem cell transplant by using the terms ASCT and SCT respectively, as they have in Figure 3 of the CS. They suggest that SCT would be rarer.

Of the suggested positions in the clinical pathway, the latter two seem reasonable, although no patients received allogeneic stem cell transplant despite one of the proposed positions in the clinical pathway being after this line of treatment. These points also fit well with the final scope. However, given the evidence and current NHS practice, the first two of the proposed positions seem uncertain. CAR-T is an unlikely first line salvage therapy in UK practice while other effective interventions with long-term evidence are available (including ASCT).There are just 2 primary refractory patients in the submitted evidence (Table 8, p35), leaving high uncertainty regarding the ability to generalise from the submitted evidence into UK practice. For ASCT ineligible patients, the large overlap between ASCT and axi-cel fitness criteria is an important consideration. The ERG clinical advisor expressed concern that therefore few patients may receive axi-cel at this point in the pathway. In their clarification, the company state their clinical advisors found it challenging to come up with a clear list of identifying factors for these patients and suggest it is unlikely a patient unfit for ASCT would be fit for axi-cel.

In suitable patients, care needs to be taken to make sure therapies used do not impact future CAR-T treatment (eg min-BEAM; p24 CS), however, dose limiting is a possible concern as it may mean using less effective earlier therapy to ensure eligibility. According to ESMO guidelines, treatments should be stratified for age, IPI and feasibility of dose-intensified regimens – creating concern for treatment which is moderated for the possibility of future relapse and intervention, as it may lead to increased likelihood of future relapse.[2]

The NHS England stakeholder submission also set out the impact the technology will have on the care pathway and the requirement for staff training, availability of specialists for adverse events, ITU arrangements and interventions associated. Side effects of CAR-T (such as cytokine release syndrome) are rare in the current pathway and require specific expertise; it was noted in the CS that increased experience in dealing with these led to reduced incidence of severe CRS and neurotoxicity in the later course of the trial (p71). Increased involvement from relevant expertise and managing adverse events was an implementation issue raised by both NHSE and the ERG's clinical advisor.

The side effect profile of CAR-T therefore requires a period of extended access to intervention. Figure 2 of the CS proposes hospital monitoring for ~15 days post-infusion. Stakeholder comments refer to the USA experience, requiring patients to stay within 2 hours of the hospital for a month post-infusion. This has consequence for both patient and family, as well as the discussed resource implications.

Unmet need populations

The CS includes a section regarding the limitations of treatment and the unmet need populations identified. Patients with unmet needs listed on p27 of the CS appropriately line up with the stated position of axi-cel in the clinical pathway (p22). The EMA draft SmPC gives the therapeutic indication as ASCT ineligible, although the submitted evidence includes ASCT eligible patients.

As outlined by the company, R/R DLBCL, PMBCL and TFL patient outcomes are poor, which the submitted evidence reflects (see 3.1.4). For patients with R/R disease ASCT is one of the remaining curative options, though ineligibility and relapse within a year indicate that a majority are left uncured. The company report poorer survival for patients ineligible for ASCT and primary refractory patients, however, patients ineligible for ASCT are likely to be ineligible for axi-cel, and primary refractory patients are poorly represented in the submitted evidence.

2.4 Critique of company's equality considerations

Equality considerations made in the CS are not clear and fail to address high priority issues such as equality of delivery. The CS considers two issues, gender and age.

The CS reports a greater proportion of males are diagnosed with DLBCL, who then experience poorer outcomes. However, the ERG notes that, contrastingly, more females are diagnosed with PMBCL representing 5% of NHL diagnoses each year (p18). The CS reports gender differences favouring women with current SoC (p27), but the CAR-T mechanism does not suggest a gender-specific action. Nonetheless, gender does not form the foundation of the company's submitted analysis.

The CS reports elderly patients are ineligible for ASCT and also less likely to be able to receive high intensity chemotherapy (p27). Therefore, the CS indicate the benefit of CAR-T being less burdensome conditioning chemotherapy. However, the ERG suggest this does not account for the burden of receiving CAR-T, which has similar fitness criteria to ASCT.

3 Clinical Effectiveness

This section contains a critique of the methods of the review of clinical effectiveness data, followed by a description and critique of the studies included in the review, including a summary of their quality and results and the results of any analyses of studies.

3.1 Critique of the company's systematic review methods

The company conducted a systematic review to identify studies to determine the efficacy, safety and tolerability of the available therapies for treating relapsed/refractory DLBCL.

3.1.1 Searches

The databases used for the effectiveness review are reported as being MEDLINE and Embase (using the embase.com interface), MEDLINE in Process (using PubMED interface) to identify in-process citations and e-pubs, and the Cochrane Library. The date the searches were conducted is provided. No searches of trial registers (e.g ClinicalTrials.gov or the WHO ICTRP) were carried out. Studies published in languages other than English were excluded.

The information about the literature searching is provided in Appendix section D.1. The search strategies used are reproduced in this section of the submission. The numbers of records retrieved matches the number given in the PRISMA diagram provided on page 14. Additional searches of conference websites were conducted to identify potentially relevant posters and abstracts.

The strategy used consists of terms for 1) diffuse large B cell lymphoma 2) drug interventions and 3) study type (RCT or other study type). Records of letters, editorials, notes, reviews are removed from the search results as are records of case reports or animal studies.

The ERG queried a typographical error in the search statement for "oxaliplatin" at line 8 of the MEDLINE search strategy (as presented in Table 3) that retrieved 0 records. The company acknowledged that this should be modified to 8573 and confirmed that as oxaliplatin is not a relevant comparator (not listed in Table 5) the omission did not result in any relevant comparator treatment studies being missed by the database searches.

The ERG also queried the absence of search terms for the drug protocols DHAP, GDP, ICE and IVE. The company's response was that relevant individual terms such as "dexamethasone" were included in the searches, so any study which assessed a combination that included these drugs should have been identified. This assumption was subsequently confirmed by an additional search carried out by the ERG.

3.1.2 Eligibility criteria

Review eligibility criteria were presented in Table 5 of the CS in Appendix section D1. The population criterion matched the NICE scope, namely adults with relapsed or refractory DLBCL, PMBCL and TFL. The list of eligible comparators in Appendix D1 Table 5 differed from the comparators listed in the NICE scope, many chemotherapy treatments were listed as eligible which were outside of the NICE scope. As described above in the search section, the company explained that this was due to the review eligibility criteria being defined at an early stage, before the final NICE scope was available. Although this led to the unnecessary screening and data extraction of many studies, it should not have adversely affected the identification of scope-relevant studies.

Eligible review outcomes included all the outcomes listed in the NICE scope: OS, PFS, response rate, adverse effects of treatment, health-related quality of life in addition to two further outcomes - stable disease and progressive disease. The final entry listed in the Outcomes section of Table 5 was 'any other relevant outcome of interest'; there was no exclusion based on outcomes. Although this criterion had the potential to make the review prone to selective outcome reporting, it should not be problematic provided a clear focus was made on the outcomes listed in the NICE scope.

Study design criteria included RCTs, non-RCTs and single-arm trials, observational studies were excluded. Two reviewers independently screened titles and abstracts and full-texts for eligibility with disagreements resolved by a third reviewer. These methods were appropriate for minimising the possibility of reviewer errors and biases affecting the final list of studies included in the review.

3.1.3 Included and excluded studies

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was presented as Figure 1 in the CS Appendix, Section D1. A total of 6,106 unique records were identified for screening, of which 1190 underwent full-text assessment. The CS reported that 43 unique studies from 106 publications met the review eligibility criteria: 12 RCTs and 31 non-RCTs. After data extraction six RCTs and 15 non-RCTs were excluded because the treatment regimens used were "not relevant to the final scope of the submission" (p13 of CS Appendices). Twenty-two unique studies from 63 publications were therefore found to be eligible for inclusion in the submission: six RCTs and 16 non-RCTs. Tables 16 and 17 in the CS show that most of these non-RCT studies were single-arm studies, with a few being comparative studies with non-applicable comparator group data.

The CS reported that data were extracted into Microsoft Excel by one researcher and checked by a second researcher. Characteristics and results of the eligible studies were presented in Tables 13-21 in Appendix Section D4 of the CS. These tables highlighted that results data were somewhat limited for

many studies. The most frequently reported outcomes were ORR, CR and overall survival rate, though few studies reported results data for all three outcomes.

Despite the identification of the 22 eligible studies the CS stated (p30) that since it was extremely difficult to make any valid comparisons between these studies and the ZUMA-1 axi-cel study, only studies for which patient-level data were available would be used. The reasons stated for this approach were the "large amounts of heterogeneity between the comparator studies identified and the limited evidence available in a comparable population to the ZUMA-1 trial". The CS then stated that "it was considered more appropriate to use studies for which patient-level data were available to inform a historical comparator study; SCHOLAR-1". It is not clear how this decision was made in the context of the systematic review results since the SCHOLAR-1 study was not included in the systematic review. Moreover, SCHOLAR-1 pooled data from four studies – only two of which (two RCTs) were identified in the company's systematic review. The two retrospective database studies (referred to as MDACC and IA/MC) which were also used in SCHOLAR-1 were not included in the systematic review, presumably excluded because they were retrospective observational studies (a stated exclusion criterion in Table 5 of the CS Appendices). No studies of axi-cel were identified as being eligible for inclusion in the systematic review according to Tables 6 and 7 of the CS appendices. It should be noted that SCHOLAR-1 was part-funded by Kite Pharma, the manufacturers of axi-cel; the published paper stated that three of the study's authors are employed by Kite Pharma and have equity ownership.

3.1.4 Quality assessment of ZUMA-1 and SCHOLAR-1

The CS presented separate quality assessments of the ZUMA-1 study and the SCHOLAR-1 study in Tables 11 and 12 in the CS Appendix section D. The Downs and Black checklist was used in which 26 questions were answered Yes, No, Unclear or Not applicable.[4] This approach to quality assessment has limitations. Firstly, no information is provided to support or justify how decisions were made to answer the questions; such information adds transparency to this important stage in any systematic review. Secondly, several questions (e.g. questions 1-4 in Table 11 the CS Appendix) are based on quality of *reporting* rather than on the quality of study methods or conduct. Thirdly, no insight or interpretation was provided in the CS regarding how to arrive at an overall judgement on quality/bias; the CS simply stated on p39 that 'ZUMA-1 was considered to be a good quality study' (p39), without describing how this judgement was arrived at. No overall judgement was provided for the SCHOLAR-1 study. Finally, no insight or description was provided regarding the relative importance of the implications of negative answers; for example, for SCHOLAR-1 (Table 11 of CS Appendices) were the implications of a 'No' to the question on whether the interventions were clearly described more, less, or as important as a 'No' to the question on attempted blinding of outcome assessors? Additional to these concerns, no details were provided about how many researchers were involved in

the quality assessment process, so the possibility of errors or bias affecting the assessments cannot be ruled out. Also, arguably the key 'study quality' concern for the purposes of this type of assessment relates to the methods and conduct of the individual patient data comparison of the ZUMA-1 and SCHOLAR-1 patient cohorts which is discussed in section 3.2.4.

3.1.5 Evidence synthesis

No synthesis or meta-analysis was undertaken. The CS did not state why data from the three axi-cel studies cited in the submission were not pooled. However, it seems likely that this was because two of those three studies (a proof-of-concept study and a dose-finding study) were from phases too early in the development of axi-cel to justify pooling with data from the pivotal study on which the CS analyses were based.

No network meta-analysis was undertaken. As described earlier, no suitable RCT evidence was available so the company compared treatments using individual patient data from single-arm studies (or single arms of comparative trials).

3.1.6 Summary critique of the company's systematic review

The company's systematic review searches and eligibility criteria were much broader than the criteria defined in the NICE scope. An explanation for this was provided by the company, and the identification of studies outside of the NICE scope in itself is not problematic for the purposes of this TA. Most of the review methods described in the submission are robust. However, the almost complete lack of a narrative regarding how the company went from including 22 studies in the review to then effectively excluding them and instead using the SCHOLAR-1 IPD dataset is a limitation of this aspect of the submission. SCHOLAR-1 was not identified as an included study in the systematic review, nor was it mentioned as a potentially useful excluded study. It seems highly likely that SCHOLAR-1 was undertaken for the purpose of providing data for comparison with the ZUMA-1 study. The ERG acknowledges the many potential advantages of utilising patient-level data to compare single-arm datasets. Nevertheless, the description in the CS of how this approach was developed over time, and in particular how it related to the systematic review, was very limited and could have been much clearer.

3.2 Description and critique of the submitted clinical evidence

3.2.1 Axi-cel studies

Patient numbers

The CS efficacy and safety analyses were based largely on one study: ZUMA-1 is an ongoing phase I/II multicentre, open-label, prospective single-armed study that is evaluating axi-cel in 108 patients with refractory aggressive NHL.[5-7] Also included in the CS were two smaller axi-cel studies: a proof-of-concept study (n=22)[8] and a dose-finding study (n=7).[9, 10]

The ERG asked the company to clarify details regarding patient numbers included in ZUMA-1. The company confirmed that the sample size of 108 comprises 101 patients from phase II plus 7 from phase I, with no overlap of patients across phases; these numbers relate to the modified intention-to-treat (mITT) population – i.e. patients who received an axi-cel infusion. The full analysis population, which includes all enrolled patients, was comprised of 119 patients; in a point of clarification response the company also provided the ERG with reasons why patients were unable to receive axi-cel. Basic details of the different analysis datasets are presented in Table 7 of the CS (p34) which presents three cohorts: the 'updated analysis' set (phases I and II combined, n=108, median follow up 15.4 months); the primary analysis set (phase II only, n=101, median follow up 8.7 months) and the safety management cohort (n=34). Understandably the focus of the CS was on the updated analysis dataset, as it included more patients and provided a longer duration of follow up.

All the CS tables of ZUMA-1 baseline characteristics (Tables 8 and 11 in the CS and Table 9 in the CS appendices) reported data for the 101 patients in the 'primary analysis' phase II cohort, rather than for the updated analysis cohort of 108 patients. Some basic baseline data for the 7 phase I patients were briefly described on p49 of the CS. Notwithstanding the omission of some key baseline data for the phase I patients, the ERG's clinical advisor was of the opinion that the ZUMA-1 population should be broadly generalizable to patients seen in NHS settings who have an ECOG status of 0-1.

Although the CS presented trial results for the updated analysis cohort (n=108) in isolation in section B.2.6, when it came to comparisons with SCHOLAR-1 the CS presented results relating to the phase II cohort (n=101), with updated data. The data used in the model relate to the updated n=108 cohort. It is not clear why the CS switched between sample sizes across different parts of the submission. This issue also arose when examining the company's propensity scoring matching exercise, where a sample size of 111 was used (despite the fact that only 108 patients received axi-cel, see section 3.2.4).

Methods

A summary of the ZUMA-1 study methods is presented in Table 1 (adapted from Table 6 of the CS).

Table 1 Summary of the ZUMA-1 trial methods

Trial number	NCT02348216
Location	The study was conducted at 24 centres (23 in the US and 1 centre in Israel).
Trial design	ZUMA-1 is an ongoing Phase 1/2 multicentre, open-label study that is evaluating the safety and efficacy of axi-cel in patients with refractory aggressive NHL.
Eligibility criteria for participants	**Inclusion criteria:** • Histologically confirmed DLBCL, PMBCL, or TFL • Chemotherapy-refractory disease, defined as one or more of the following:

	– No response to first-line therapy (primary refractory disease); patients who are intolerant to first-line therapy chemotherapy were excluded – No response to second or later lines of therapy • Refractory after ASCT, defined as occurrence of disease progression or relapse ≤ 12 months after ASCT (must have biopsy proven recurrence in relapsed patients) or, if salvage therapy was given after ASCT, the patient must have had no response to or relapsed after the last line of therapy • Prior therapy including anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen • Measurable disease according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (hereafter referred to as IWG 2007 criteria) • No evidence of CNS lymphoma, age 18 or older, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate haematologic, renal, hepatic, pulmonary and cardiac function **Exclusion criteria:** • History of allogeneic SCT, autologous stem cell transplant within 6 weeks of informed consent • Prior CD19 targeted therapy with the exception of patients who received axi-cel in this study and are eligible for retreatment • Prior CAR therapy or other genetically modified T-cell therapy • Presence of fungal, bacterial, viral, or other infection that was uncontrolled or requiring IV antimicrobials for management • History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/haemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
Settings and locations where the data were collected	Patients were hospitalised for at least 7 days of observation and management of treatment-emergent acute AEs. Subsequently, subjects returned to the clinic at Week 2 (± 2 days), Week 4 (± 3 days), Month 2 (± 1 week), and Month 3 (± 1 week). Long-term follow-up for disease status (among patients remaining in response) and survival continued every 3 months through Month 18, then every 6 months through 5 years, and then annually for a maximum of 15 years.
Trial intervention **Permitted and disallowed concomitant medication**	Patients received a single infusion of axi-cel at a target dose of 2 x 10^6 anti-CD19 CAR T-cells/kg (± 20%). The minimum dose to be administered was 1 x 10^6 anti-CD19 CAR T-cells/kg. For patients weighing >100kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T-cells was to be administered. The entire bag of axi-cel was to be infused. Axi-cel is administered after a conditioning chemotherapy regimen consisting of cyclophosphamide 500mg/m^2 IV and fludarabine 30mg/m^2 IV on the 5th, 4th, and 3rd day before infusion of axi-cel. Paracetamol 650mg given orally and diphenhydramine 12.5mg IV or orally approximately 1 hour before axi-cel infusion is also recommended. • Corticosteroid therapy at a dose ≥5mg/day of prednisone or equivalent doses of other corticosteroids and other immunosuppressive drugs were to be avoided for 7 days prior to leukapheresis and 5 days prior to axi-cel administration. • Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after axi-cel administration, unless used to manage axi-cel-related toxicities. Other medications that might interfere with the evaluation of the investigational product were also to be avoided for the same period unless medically necessary. • Treatment for lymphoma, such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than the investigational product in this protocol, and other investigational agents, were prohibited, except as needed for treatment of disease progression after the axi-cel infusion.

Primary outcomes	The primary analysis was conducted at the point when 92 patients could be evaluated 6 months after the axi-cel infusion. The primary outcome of the study was ORR, defined as CR or PR per International Working Group (IWG) response criteria for Malignant Lymphoma as determined by the study investigators in the pre-planned set of 92 patients. All patients who did not meet the criteria for an objective response by the analysis cut-off date were considered non-responders.
Other outcomes used in the economic model/specified in the scope	Key secondary endpoints included: • ORR according to central review, based on the IWG 2007 criteria • DoR and PFS according to the investigator's assessment, and by central review, both based on the IWG 2007 criteria • OS • Safety: Incidence of AEs, significant laboratory abnormalities • HRQL, as measured by the EQ-5D-5L in the safety management cohort

The ERG notes the restriction of limiting trial eligibility to patients with an ECOG performance status of 0 or 1, and that the ZUMA-1 clinical study report stated that the ZUMA-1 eligibility criteria were designed to [redacted]

The CS stated that ZUMA-1 was comprised of two patient cohorts - Cohort 1 (DLBCL patients) and Cohort 2 (PMBCL and TFL patients) - and that for both cohorts the study was designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis was that the ORR for patients treated with axi-cel in Cohorts 1 and 2 is significantly greater than 20% (p36 and Table 9 of CS).

Summary of ZUMA-1 effectiveness results

The primary outcome was ORR (i.e. CR or PR) as determined by study investigators. For the updated analysis set, the ORR was 82%; 42% remained in response, including 40% with CR, at the data cut-off (median follow up 15.4 months). The median duration of response was 11.1 months (95% CI 3.9 to could not be estimated).

The CS reported Kaplan-Meier curves for progression free survival and overall survival for the modified intention-to-treat (mITT) population (i.e. patients who received axi-cel) which are presented below in Figure 2 and Figure 3. In a point of clarification response the company justified the use of mITT data rather than ITT data on the basis that the mITT population being considered more suitable for the comparison with SCHOLAR-1 data. The ERG acknowledges the rationale of this decision based on the issue of group comparability since the SCHOLAR-1 data will be mITT (patients had to receive therapy after refractory status). The ERG also notes though that the ITT issue should not be ignored since the period of time between the decision to treat, and receipt of treatment, is likely to be longer for axi-cel when compared to salvage chemotherapy. Consequently, some of the 11 patients

who were assigned axi-cel but were unable to receive it may have missed out on the opportunity of receiving another line of salvage chemotherapy.

The CS reported PFS rates of 49% (95% CI, 39 to 58) at 6 months, 44% (95% CI, 34 to 53) at 12 months, and 41% (95% CI, 31 to 50) at 15 months. The OS rates were 78% (95% CI, 69 to 85) at 6 months, 59% (95% CI, 49 to 68) at 12 months, and 52% (95% CI, 41 to 62) at 18 months. The CS suggests these data support the potential for cure as the curves have long tails after 5 to 6 months for the PFS plot and 10 to 11 months for OS plot. However, the ERG notes that from month 12 onwards the KM plots become heavily influenced by censoring of data. Censoring is indicated by the short, vertical lines in the plots – each line represents a patient for which the event of interest has not occurred up to that time point. Also of note is the difference between the PFS and OS plots in the number of patients 'at risk' – 34 patients at month 12 for PFS versus 63 at month 12 for OS, which is likely a consequence of when PFS follow up data were collected (see Table 1 above). In light of this censoring - which is inevitable when data are immature - it is clear that there is considerable uncertainty as to how the slope of the lines will develop beyond 12 months. This uncertainty will only be resolved when data from longer follow up periods become available for many patients. Two recently published papers of different CAR T-cell therapies (not axi-cel) in patients with relapsed or refractory acute lymphoblastic leukaemia show OS curves still falling at 20 months, highlighting the need for cautious interpretation of the ZUMA-1 data.[11, 12] The ERG's clinical adviser was of the opinion that a minimum of 2-3 years would be an appropriate time frame for considering patients (who are still in remission) to be cured. The median follow up for ZUMA-1 is 15.4 months.

Figure 2 Progression-free survival in the ZUMA-1 updated analysis (n=108, median follow-up 15.4 months)

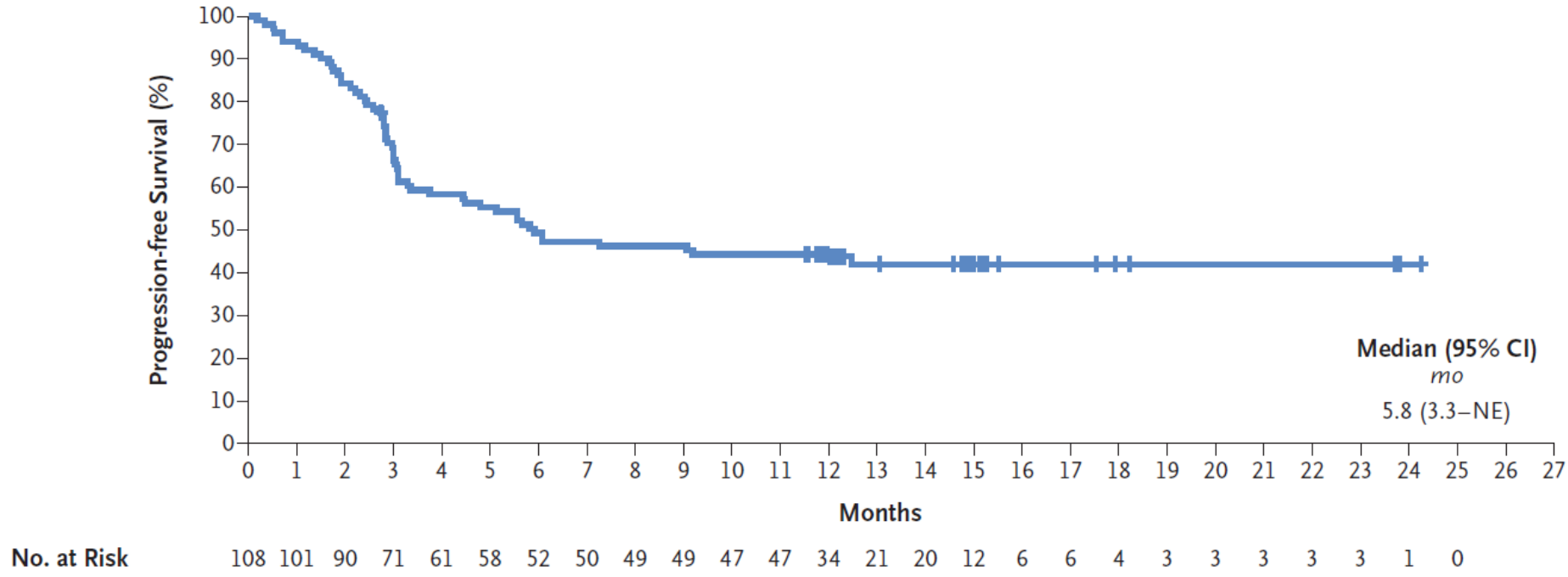
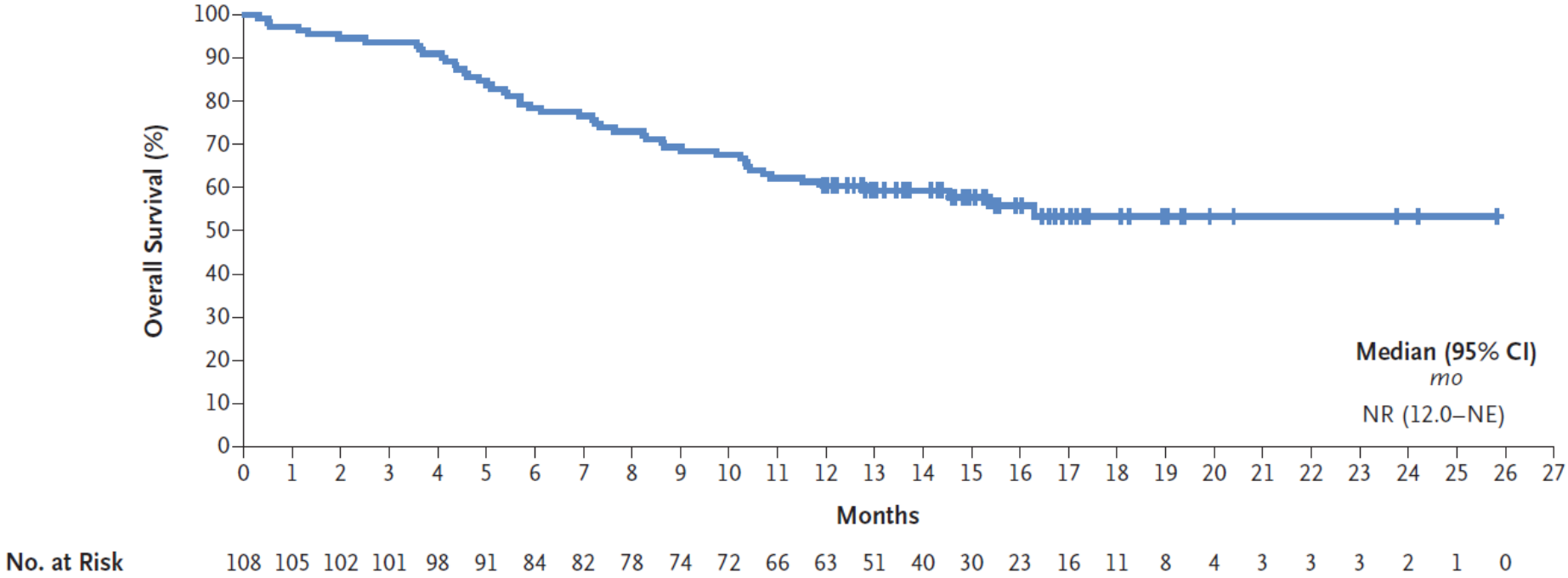


Figure 3 Overall survival in the ZUMA-1 updated analysis (n=108, median follow-up 15.4 months)



The CS reported conflicting data on the number of patients subsequently treated with autologous SCT (after axi-cel treatment). The ERG sought to clarify this; the company responded by stating that [redacted] patients had subsequent autologous SCT, although [redacted] patients had subsequent allogeneic SCT. However, from the CSR it is clear that at least [redacted] received an autologous SCT (p133 of CSR).[5] This was [redacted] patients re-treated with axi-cel. Also, in the CSR table which states that [redacted] allogeneic transplants were given post axi-cel the table footnote states that only transplants received while in remission after axi-cel are included causing some uncertainty about whether allogeneic SCTs were undertaken in other types of patient.

The CS reported (on p117) that 10 patients had been re-treated with axi-cel, in line with the trial protocol. The ZUMA-1 CSR stated that [redacted] [5] The CS also stated that as the quantity of axi-cel initially manufactured is sufficient for the delivery of up to two treatments based on the ZUMA-1 trial protocol, no additional leukapheresis or axi-cel acquisition costs were applied to the re-treated patients (p117-118). However, the ZUMA-1 CSR reported indicated that for [redacted] axi-cel had to be [redacted].[5]

Also, the CS also stated that the expected market authorisation (MA) does not allow retreatment with axi-cel, yet these re-treated patients were not removed or censored for the overall survival outcome. This was reported as not being done to be consistent with subsequent treatments across all ZUMA-1 study patients, i.e. whether patients underwent retreatment or a new anticancer therapy following the initial axi-cel treatment. However, based on the expected MA, this does not reflect future clinical practice and will also inflate the efficacy estimates for axi-cel because some patients changed status from having progressed disease to being complete or partial responders. The CS described results for nine retreated patients from Phase 2: [redacted] patients had complete and partial response, respectively; [redacted] patient had stable disease and [redacted] patients had progressed disease. In a point for clarification the ERG asked for an OS KM plot for the10 re-treated patients, which are presented in Figure 4. The ERG notes that according to this plot 11 patients were re-treated.

Figure 4 Overall Survival Among Retreated Subjects

The CS included pre-specified subgroup analyses (presented in Appendix E of the CS) noting that these were descriptive as the study was not designed to distinguish between subgroups. The ERG also notes that the subgroup results relate only to the primary analysis dataset (median follow up 8.7 months); subgroup analyses were not undertaken by the company for the updated analysis (median follow up 15.4 months). A safety cohort of 34 patients was used to examine the impact of pre-emptive safety management and to capture health-related quality of life data using EQ-5D-5L up to month 6 post axi-cel infusion. The results were converted to EQ-5D-3L (as preferred by NICE) and reported in the CS as shown below in Table 2.

Table 2 EQ-5D-3L utility scores from the ZUMA-1 safety management cohort

Results by time point	**N**	**EQ-5D-3L index score, mean (SD)**
Screening	[redacted]	[redacted]
Week 4	[redacted]	[redacted]
Month 3	[redacted]	[redacted]
Month 6	[redacted]	[redacted]
Total	[redacted]	[redacted]
Results by response category		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
PD	[redacted]	[redacted]
Total	[redacted]	[redacted]

Results by health state		
Progression-free health state	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

ERG summary of ZUMA-1 study

The company's main evidence for effectiveness came from a single-arm study (ZUMA-1). Comparative effectiveness results which are derived from single-arm studies are inherently prone to bias when compared with results from randomised studies. However, the use of single-arm studies can be justifiable when randomisation difficulties are anticipated. These may occur when studying patients from small populations with limited treatment options, such as the relapsed/refractory population in this TA. The importance of this issue is illustrated by the RCT which formed the basis of the clinical effectiveness evidence in NICE TA306.[3] The assessment was of pixantrone - a NICE scope comparator treatment for this assessment - as a third or subsequent line treatment in patients with multiply relapsed or refractory aggressive NHL. The pivotal randomised trial (PIX301) was of pixantrone monotherapy versus (physician's choice of) single chemotherapy agents. Trial enrolment to the PIX301 RCT was stopped early because of slow accrual, with only 140 of a planned 320 recruited. In NICE TA306 concerns were raised by the ERG that PIX301 was likely to be underpowered to detect differences between treatments.

The patients studied in ZUMA-1 appear to be representative of the various lymphoma population sub-groups for which there is a high unmet need for new treatments: nearly all patients had had at least two prior lines of therapy, with 40% of patients having had four or more prior lines of therapy (chemotherapy or ASCT). Appropriate outcomes were assessed in ZUMA-1, but the immaturity of the results data available to date means there is uncertainty regarding the robustness of the OS and PFS results relating to follow up time-points beyond 12 months. Also, the ERG notes that 10% of patients who received a dose of axi-cel were re-treated (due to disease progression) but a re-treatment option is not reflective of future clinical practice, based on axi-cel's expected marketing authorisation. Re-treatment of 10% of the study cohort will also inflate the ZUMA-1 axi-cel efficacy estimates because some patients changed from a progressed disease status to a complete or partial responder status.

3.2.2 Comparator treatment studies

As outlined earlier in section 3.1.3, the company used the SCHOLAR-1 study as the basis for forming a dataset of patients who received relevant comparator treatments. Individual patient data were available from SCHOLAR-1 which were used for comparative analyses with the ZUMA-1 dataset. The ERG concurs with the CS statement that the availability of patient-level data to account for differences between patient characteristics and key prognostic factors is considered to be more rigorous and allows a more appropriate comparison.

SCHOLAR-1 is a retrospective study[13] of 636 patients (mostly from the U.S. with some also from France) with refractory disease (mostly DLBCL). It pools data from four datasets: two RCTs (referred to as CORAL and LY.12) and two retrospective database studies (MDACC and MAYO (the latter is also referred to as IA/MC)). Brief details on these studies were presented in Table 8 of the CS appendices. The CS presented a basic quality assessment of SCHOLAR-1 in Table 11 of the CS appendices. This reports that the treatments given to patients in SCHOLAR-1 were not clearly described. This appears to make it difficult to evaluate how closely the SCHOLAR-1 treatments match with the scope comparators. Notwithstanding this reporting issue, the ERG's clinical adviser was of the opinion that the treatments used in SCHOLAR-1 would likely be representative of current NHS treatments. This is on the basis of the SCHOLAR-1 settings being the U.S. and France and that the studies were published quite recently (so were reflective of current treatments). However, p54 of the CS states that [redacted] of SCHOLAR-1 patients went on to receive ASCT. The ERG notes that ASCT is not in the NICE scope list of comparator treatments. Also, the draft EMA license for axi-cel relates to patients who are ineligible for ASCT. An ideal comparator treatment group should therefore include very few patients who go on to receive ASCT.

The CS reported that since SCHOLAR-1 patients may have been refractory to therapy at multiple times in the treatment course, refractory subgroup was categorised in two ways. The CS described these "First Refractory" and "Last Refractory" categorisations on p 21 of the appendix and mentions the use of "inclusion criteria" to do this. The criteria were not specified. Despite these refractory categorisations being referred to as "subgroups", data from the final column on p56 in Table 11 of the CS implied that the First refractory subgroup is in fact the whole SCHOLAR-1 population (n=636).The ERG sought clarification from the company as to what the refractory categorisations meant. The company response explained that the last refractory categorisation excludes patients without a current line of therapy present in the database after reaching their latest designation of refractory status. Throughout the submission the SCHOLAR-1 analyses were based on the last refractory categorisation. The last refractory categorisation sample size was 593, though fewer patients were evaluable for response (n=508) and survival (n=497).

The outcomes reported in SCHOLAR-1 which were available for comparison with ZUMA-1 were ORR and OS.

Heterogeneity across SCHOLAR-1 studies

The CS reported that Higgin's Q statistic was used to assess the heterogeneity of response rate across the source databases, adding that "a Higgin's Q statistic pre-specified value of P>0.1 was used to determine whether significant heterogeneity was present; the P value was >0.1, and thus the data were pooled for analysis." The actual p-value result was not presented. The ERG is unaware of the "Higgin's Q statistic". It appears likely that Cochran's Q statistic was calculated with Higgins' I^2

possibly also calculated (though if it was, the result - usually expressed as a % - was not presented in the CS). Cochran's Q statistic is known to be poor at detecting true heterogeneity across studies, especially when the number of included studies is low, as is the case with SCHOLAR-1.[14] Table 13 (p60) of the CS presents OS results for each of the four studies which make up SCHOLAR-1. The ERG notes that the smallest study (MAYO) appears to be somewhat of an outlier when comparing the 2-year survival results (10% versus 17%, 22% and 23%) and median survival results (5.0 months versus 6.5, 6.6 and 6.6 months). The MAYO study had a higher proportion of ECOG 2-4 patients (24%) compared with the other studies (15%, 11%, 10%). The ERG considers that this raises questions about the clinical meaning of the pooled SCHOLAR-1 results.

3.2.3 Comparability of ZUMA-1 and SCHOLAR-1 cohorts

The CS includes two tables comparing baseline characteristics across the ZUMA-1 and SCHOLAR-1 studies. Table 11 in the main CS relates to the first refractory categorisation (n=636), which is not used in the submission analyses, though this table does provide individual study details for the four studies which make up SCHOLAR-1. Table 9 in the CS appendices provides the most relevant comparison, as it relates to the last refractory categorisation. It shows that for several covariates there were many missing data in SCHOLAR-1 (listed as 'Not assessed'). For example, ECOG status was missing for 43% of the n=497 survival cohort. Missing data relate to both when covariates were assessed and when the latest refractory status was determined in the component SCHOLAR-1 studies. The CS stated that the determination of refractory status may have been distant in time from the measurement of the covariate (p20 of appendices). If patients did not have a covariate measured within 3 months of determination of refractory status, the covariate was classed as 'Not assessed'.

The covariates reported in the methods section of the published paper of the SCHOLAR-1 study were: IPI risk category, ECOG performance status, disease stage, line of therapy before refractory status, and refractory subgroup (defined as refractory to first-line therapy, refractory to second line or later therapy, or relapsed ≤12 months after ASCT).[13] In this paper subgroup analyses suggest that the following baseline subgroups seem particularly important in predicting longer survival: ECOG 0-1, disease stage I-II, and IPI 0-1. Considering the importance of ECOG status, that ZUMA-1 was restricted to patients with an ECOG status of 0-1, and that some of the SCHOLAR-1 data scenarios for the model did not exclude patients with ECOGs of 2-4 (and none of the scenarios removed patients with missing ECOG data), the ERG requested SCHOLAR-1 ECOG subgroup analyses for OS for the last refractory population, which was more relevant for this assessment. As this analysis excluded patients with missing ECOG data the sample size was not 497 but [redacted]. The results, presented in Figure 5, confirmed the importance of ECOG status on OS in SCHOLAR-1.

Figure 5 Overall survival by ECOG classification for the SCHOLAR-1 last refractory cohort

Refractory subgroup appears to be somewhat less important, with the SCHOLAR-1 paper reporting that "OS rates were similar regardless of refractory subgroup, with a slightly lower median OS among patients who were refractory to 2nd line or later therapy or who relapsed ≤12 months after ASCT (6.1 and 6.2 months, respectively) than among primary refractory patients (7.1 months)".[13] Results were not presented for the 'line of therapy before refractory status' subgroups. Though not listed as a covariate in the methods, the effect of age category was reported, with no differences found when comparing under 65 years with ≥65 years.

Table 3 below presents baseline data on the SCHOLAR-1 covariates. These data are taken from Table 9 in the CS appendices, which compares the ZUMA-1 and SCHOLAR-1 studies; the percentages have been recalculated to include patients classed as 'Not assessed'. Differences are evident across all these covariates and missing data are an issue for all the covariates except refractory subgroup. These imbalances will lead to biased results due to confounding unless they are adjusted using appropriate methods.

Table 3 Comparison of the baseline covariates identified in the SCHOLAR-1 study

Covariate	ZUMA-1 n=101 (%)	SCHOLAR-1 n=497 (%)
ECOG performance status: 0-1	101 (100)	226 (45.5)
2-4	0	55 (11)
Not assessed	0	216 (43.5)
Disease stage: I-II	15 (15)	75 (15)
III-IV	86 (85)	149 (30)
Not assessed	0	273 (55)
Number of previous lines of therapy: 1	2 (2)	100 (20)
2	29 (29)	204 (41)
3	30 (30)	91 (18)
4	28 (28)	11 (2)
5	6 (6)	1 (0)
>5	6 (6)	3 (0)
Not assessed	0	87 (18)
IPI score: 0-1	27 (27)	73 (15)
2	26 (26)	66 (13)
≥3	48 (48)	76 (15)
Not assessed	0	282 (57)
Refractory subgroup: Primary refractory	2 (2)	100 (20)
Refractory to 2nd line or later	78 (77)	310 (62)
Relapse within 12 months of ASCT	21 (21)	87 (18)

3.2.4 Description and critique of the company's approach to creating and analysing a comparative clinical effectiveness dataset

The company's approach to comparing the effectiveness of axi-cel to standard of care treatments was by using individual patient data from the single-arm ZUMA-1 and SCHOLAR-1 studies. Results from such comparisons are inherently prone to bias when compared with equivalent randomised studies. The main bias issue to address when comparing and analysing results from single-arm datasets is the adequate adjustment for important covariates (prognostic indicators). Different methods exist to do this, including regression analysis, propensity scoring, instrumental variables, stratification and matching. Nevertheless, it is known that methods to adjust non-randomized studies for confounding are imperfect and that assessments of cost-effectiveness based on the modelling of such data will be subject to much uncertainty.[15]

In an attempt to address the problem of baseline imbalances across the ZUMA-1 and SCHOLAR-1 studies the CS first presented results from a "standardised" analysis. The methods used in this approach (p25-26 of appendices) describe stratification of two covariates, with weighting of outcomes across the strata. The two covariates described were ECOG performance status and last refractory subgroup (Table 10 CS appendices). The results, which are presented on p63-65 of the CS, also mention standardisation by refractory subgroup and subsequent ASCT, which was not explained in the methods section (nor in Table 10 of the CS appendices). In light of the uncertainty surrounding the inclusion (in the CS analyses) of a large number of patients with missing ECOG data and the standardisation analyses being based on subsequent ASCT but not on subsequent re-treatment with axi-cel, the ERG requested that the company re-run their analyses without standardisation, comparing ZUMA-1 with SCHOLAR-1 patients who had an ECOG of 0-1 (and other results). The results for survival are presented below in Tables 3 to 7.

Table 4 Overall Survival: ZUMA-1 and SCHOLAR-1

	ZUMA-1 mITT (N=108)	**SCHOLAR-1 Survival (N=497)**
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

Table 5 Overall Survival: ZUMA-1 and SCHOLAR-1 ECOG status 0-1 patients

	ZUMA-1 mITT (N=108)	**SCHOLAR-1 Survival (N=226)**
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

Table 6 Overall Survival in primary refractory patients: ZUMA-1 and SCHOLAR-1 ECOG status 0-1 patients

	ZUMA-1 mITT (N=3)	**SCHOLAR-1 Survival (N=65)**
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

Table 7 Overall Survival in patients refractory to second or later line: ZUMA-1 and SCHOLAR-1 ECOG status 0-1 patients

	ZUMA-1 mITT (N=80)	**SCHOLAR-1 Survival (N=121)**
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

Table 8 Overall Survival in patients who had relapsed within 12 Months of ASCT: ZUMA-1 and SCHOLAR-1 ECOG status 0-1 patients

	ZUMA-1 mITT (N=25)	**SCHOLAR-1 Survival (N=40)**
Median OS, months	[redacted]	[redacted]
3-month OS rate	[redacted]	[redacted]
6-month OS rate	[redacted]	[redacted]
12-month OS rate	[redacted]	[redacted]
Cox Model Hazard Ratio (95% CI)	[redacted]	

The SCHOLAR-1 results in Table 4 and Table 5 confirm the importance of the need to adjust for ECOG status. SCHOLAR-1 patients with an ECOG of 0-1 had median OS of [redacted] months versus [redacted] months for the whole last refractory population (which also included patients with ECOG 2-4 and missing ECOG data). The results also suggest that, for the ECOG 0-1 subgroup, primary refractory status appears to have a larger impact on OS in the 'last refractory' cohort than was seen in the full SCHOLAR-1 'first refractory' dataset – see the quotation from the SCHOLAR-1 paper earlier in this section. The median survival for primary refractory patients was [redacted] months compared to [redacted] months (refractory to 2nd line or later) and [redacted] months (relapse within 12 months of ASCT). However, it should be noted that the sample sizes across the SCHOLAR-1 ECOG 0-1 population 'last refractory' subgroups are quite small.

Given that five covariates were identified in the SCHOLAR-1 study, and that SCHOLAR-1 highlighted the prognostic importance of disease stage and IPI (as well as ECOG status), the ERG considers that the CS standardised analyses (stratified for just ECOG and last refractory status) do not adequately adjust for baseline imbalances. The company also adopted a propensity score matching approach to adjusting data, referencing NICE Technical Support Document 17 (on the use of observational individual patient data to inform estimates of treatment effectiveness in technology appraisal).[16] The CS reported minimal details of what the propensity score matching actually involved (p98-99 of the Appendices document), particularly in relation to how covariates were identified for inclusion in the matching and how many unique SCHOLAR-1 patients were used. The CS (appendix O) lists the covariates used in the propensity score matching as age, sex, disease stage, diagnosis and relapsed post-ASCT status. The CS also stated that these covariates had statistically significant differences (between ZUMA-1 and SCHOLAR-1) which became non-significant following "re-weighting". Only two of these covariates match the five covariates explored in SCHOLAR-1.

Moreover, when also considering the various SCHOLAR-1 data sources used in the model base case and scenario analyses (p94 of the CS) the ERG sought clarity from the company on how such decisions were made. The company was asked how covariates were chosen for the propensity scoring analysis and what the sample sizes were, including how many *unique* SCHOLAR-1 patients were included. For clarity, the ERG also requested a baseline characteristics table (same characteristics as detailed in Table 9 of the appendices document) for the propensity score matching dataset. The company response was:

> "Covariates for the propensity score matching were selected using the following criteria: (i) inclusion in both datasets (which is of course necessary); (ii) perceived prognostic relevance; and (iii) the extent to which data were commonly missing for a given variable. Although it would have been preferable to include covariates, such as ECOG or disease stage, in the propensity score analysis, the extent of the missing data in SCHOLAR-1 would have required

> discarding many outcomes. Therefore, it was thought that the approach used provided the most data points and a more robust analysis and you would not expect a difference in the distribution of baseline characteristics from those in Table 9."

The company did not provide the requested baseline characteristics table for the propensity score dataset. The ERG considers that the approach adopted may have been too focused on providing a large dataset rather than the adjusting for imbalances in the known important covariates. In response to the ERGs request for clarity about the sample sizes of the propensity scores dataset the company responded that 521 patients were used from SCHOLAR-1 and 111 patients were used from ZUMA-1 (despite the fact that only 108 patients received axi-cel). The SCHOLAR-1 data sources table from the CS is presented below (Table 9) with added limitations comments from the ERG.

Table 9 SCHOLAR-1 data sources scenarios used in the model

SCHOLAR-1 data source	Description	Justification	Limitation	Additional limitation comments by ERG
Base case: crude adjustment with ECOG 2–4 removed	Subjects with ECOG 2–4 at baseline were removed from the SCHOLAR-1 dataset.	Inclusion criteria of ZUMA-1 only allows ECOG 0–1 patients; The propensity score adjustment performed on all SCHOLAR-1 patients shows little difference compared to unadjusted data (figure 17 of CS). It is not clear from literature if statistical adjustment (e.g. propensity score) would provide a more robust comparison compared with no adjustment	No statistical adjustment (e.g. propensity score analysis) was performed	Although ECOG 2-4 patients were removed, it appears that patients with ECOG data "Not assessed" were included (43.5% of the SCHOLAR-1 population.)
Scenario 1: Unadjusted, all patients	No methods of adjustment were made to the SCHOLAR-1 dataset.	This option is provided as the "raw" SCHOLAR-1 data where no adjustments have been made (i.e. no statistical adjustments or removal of subjects).	No crude or statistical adjustments are performed	
Scenario 2: Propensity score adjusted, all patients	Propensity score adjustment was performed in which weights were generated for each individual SCHOLAR-1 to adjust for the differences in baseline characteristics between SCHOLAR-1 and ZUMA-1 (see appendices).	This follows guidance provided in TSD17, which describes methods to reduce the bias of estimating relative treatment efficacy based on single arm trials or observational studies.	The propensity score adjustment was performed to match SCHOLAR-1 data to ZUMA-1 Phase 2 patients (n=101) only; ECOG 2–4 patients were not removed from SCHOLAR-1	No adjustment for covariates known to be relevant to outcome: ECOG and IPI score.
Scenario 3: Adjustment with ECOG 2–4 and post-refractory SCT removed	Subjects with ECOG 2–4 at baseline and those who had received post-refractory SCT were removed from the SCHOLAR-1 dataset.	In ZUMA-1, only [redacted] of patients (3/108) received allogeneic SCT post treatment compared to almost [redacted] in SCHOLAR-1. The removal of post-refractory SCT patients in SCHOLAR-1 may improve the comparability between ZUMA-1 and SCHOLAR-1	No statistical adjustment was performed; It is not clear if post-refractory SCT patients should be removed from SCHOLAR-1	The 11 (10%) ZUMA-1 patients re-treated with axi-cel were not removed. Patients with "Not assessed" ECOG data at last refractory status were included. The CS is conflating allogeneic SCT with autologous SCT

ERG summary of the company's analyses of comparative effectiveness

To adjust for baseline imbalances between ZUMA-1 and SCHOLAR-1 the CS reported the use of standardised analyses, propensity score matching and crude adjustment methods. Five key covariates were identified from the SCHOLAR-1 paper, although the company's analyses adjusted for only two of these five in any single analysis. Despite having access to individual patient data, the company's approach appears to have been too concerned with maximising sample size and reducing statistically significant baseline differences across the two studies, rather than adjusting for clinically important imbalances (which may not necessarily be statistically significantly different) in covariates known to be important in affecting outcomes. Consequently there is considerable uncertainty about the comparative effectiveness estimates. The CS states that "there remains a large amount of heterogeneity between the study populations which may have biased the results against ZUMA-1" (p82) citing differences in number of prior lines of therapy and in patients receiving subsequent stem cell transplant. However, the ERG thinks this is not a particularly even-handed representation since concern about this bias was not counterbalanced by factors which may have biased the results against SCHOLAR-1, such as differences in ECOG status, re-treatment with axi-cel in 10% of ZUMA-1 patients (which would not happen in clinical practice) and uncertainty relating to the substantial levels of missing covariate data.

3.2.5 Adverse events of axi-cel

Data on adverse events were derived mainly from the earlier ZUMA-1 cohort i.e. the primary analysis (n=101, median follow up 8.7 months) and were reported on pages 67-76 of the CS.

All patients had an adverse event (AE) and 95% of patients had a grade ≥3 AE (Table 19 of CS). [redacted] ([redacted]) had a serious adverse event (SAE) and [redacted] had a grade ≥3 SAE. [redacted] patients died due to an AE ([redacted] of which were deemed to be treatment-related).

The CS stated that cytokine release syndrome (CRS) and neurotoxicity are commonly encountered with CAR T-cell therapies. The CS reported that [redacted] of patients experience CRS, with [redacted] experiencing grade 3 or higher CRS. The most common CRS symptoms (any grade) were pyrexia ([redacted]), hypotension ([redacted]), hypoxia ([redacted]), tachycardia ([redacted]) and chills ([redacted]). In ZUMA-1 64% of patients experienced a neurological adverse event; the most common grade 3 or higher events were encephalopathy (21%) and confusional state (9%).

The CS presented a table (p69 of CS) of grade ≥3 treatment emergent adverse events occurring in at least 10% of patients. Results included [redacted] of patients having grade ≥3 anaemia and [redacted] having grade ≥3 neurological events.

The ERG requested more up-to-date data on B-cell aplasia (an absence of B cells) and how many patients still had detectable CAR T-cells. The company responded stating that at month 12 [redacted] patients ([redacted] had detectable CAR T-cells and no detectable B cells; at month 15, the proportion was [redacted]patients ([redacted]). This suggests that persistence of CAR T-cells and associated B-cell aplasia will be an important adverse event to monitor longer-term.

The CS presented a table (p71) comparing rates of key adverse events across study recruitment phases ('interim analysis' versus 'between interim and primary analysis'). The ERG notes that although it is possible that there may be a reduction in the incidence of ≥ grade 3 events with clinician experience, the absolute reductions in AEs for CRS and neurological events are quite small, and are based on small numbers of events, making it difficult to interpret the real meaning of these results. The CS also reported that a safety management cohort of 34 patients was studied to examine the impact of pre-emptive safety management but results specific to this cohort were not reported in the CS.

Data on adverse events were not presented for the SCHOLAR-1 cohort.

Summary

Adverse events are likely to occur in all patients and serious adverse events in around half of patients who receive axi-cel. Cytokine release syndrome, neurological adverse events and B-cell aplasia often occur following axi-cel treatment. Other adverse events may become evident over time, which may be different from those already observed, but only long-term term follow up data will clarify th

4 Cost Effectiveness

This section focuses on the economic evidence submitted by the company and the additional information provided in response to the points for clarification. The submission was subject to a critical review on the basis of the company's report and by direct examination of the electronic model. The critical appraisal was conducted with the aid of a checklist to assess the quality of the economic evaluation and a narrative review to highlight key assumptions and uncertainties

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

The CS describes the search strategies used to identify relevant cost-effectiveness studies for the treatment of adult patients with R/R DLBCL. The search strategies are briefly described in the main body of the CS (p85-88) and full details are provided in Appendix G.

4.1.1 Searches

The following databases were searched on 27 September 2017: MEDLINE In Process; EMBASE; EconLit and the Cochrane Library (including HTAD and National Health Service Economic Evaluations database NHS-EED). HTA websites and conference proceedings from the last two years were also searched to identify potentially relevant posters and abstracts. The search strategies are reproduced in Tables 22, 23, 24 and 25 in Appendix G of the CS.

4.1.2 Inclusion/exclusion criteria used for study selection

The inclusion/exclusion criteria are summarised in Table 26 (Appendix G) of the CS and follow the usual PICOS framework. In brief, the review included any economic analyses and systematic reviews of pharmacological treatments for adult patients with R/R DLBCL published after (and including) 2007. Articles were independently assessed by two reviewers against each eligibility criteria. Any uncertainty regarding the inclusion of studies were checked and judged by a senior reviewer.

The ERG considers that the inclusion/exclusion criteria appear to be generally appropriate, although some relevant studies in other relevant populations, namely TFL and PMBCL, may have been missed.

4.1.3 Studies included and excluded in the cost effectiveness review

A total of 931 potentially relevant articles were identified in the cost-effectiveness review. 864 of these were subsequently excluded at the primary screening stage. The remaining 53 studies were assessed in full. One additional article was identified and included from conference proceedings and HTA searches.

In total, two studies were extracted from three publications. These studies include a US study on plerixafor and a NICE technology appraisal (TA) on pixantrone. The studies were summarised in

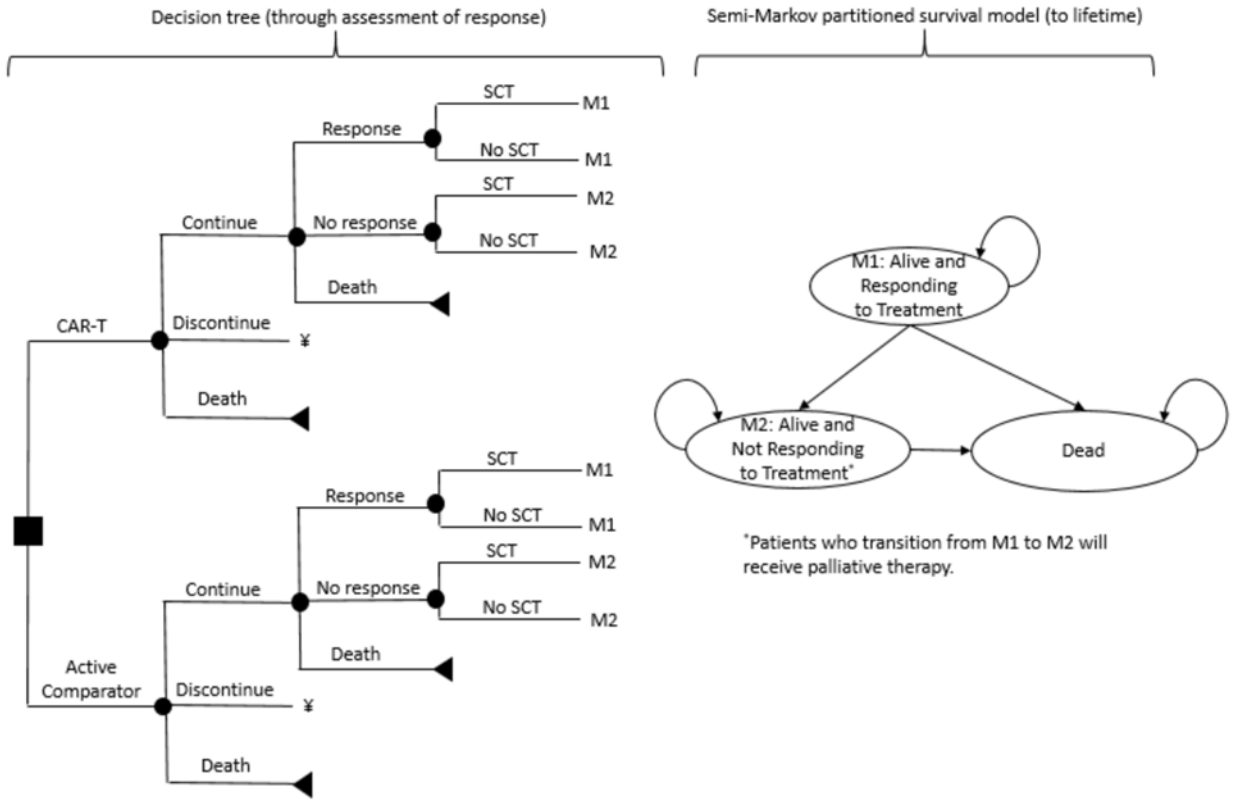
Table 23 in the CS (p87), and a quality check of the studies was reported in Table 29 (Appendix G of the CS). No published cost-effectiveness studies of axi-cel were identified.

Although no studies on the cost-effectiveness of axi-cel were identified by the company, the ERG identified one relevant study recently published by the US Institute for Clinical and Economic Review (US ICER) [17]. This study was not included in the CS as it was published after the company conducted their search. In response to clarification questions, the company provided a short summary and critique of the US ICER study, where it also compared and contrasted the approach used in the company's *de novo* economic analysis and the US ICER analysis (Table 11 of response to clarification questions). Further details of the key similarities and differences in approaches are provided in the validation section of the ERG report. A brief summary of the US ICER study and base-case results are reported below.

The US ICER study evaluated the clinical and cost-effectiveness of axi-cel versus chemotherapy for adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who are ineligible for ASCT. The study was based on a US third-party payer perspective and costs and outcomes were discounted at 3% per year.

The economic model included three-parts: (i) a short-term decision tree characterising the period from the initiation of treatment (axi-cel or chemotherapy) to the initial response assessment (approximately one month); (ii) a partitioned survival analysis model characterising the time period between the initial response assessment and five-years and (iii) a Markov model from five-years until death. The complete model was referred to as a semi-Markov partitioned survival model and a graphical summary of the structure is provided in Figure 6.

Figure 6 US ICER model structure



¥Patients who discontinue due to manufacturing failure will transition to the active comparator. Patients who discontinue due to adverse event will receive no further antileukemic/antilymphomic therapy and will enter the semi-Markov partitioned survival model at M2.
CAR-T: Chimeric antigen receptor T-cell therapies
SCT: Stem cell transplantation

The short-term decision tree was used to determine the costs and outcomes from the initiation of each treatment through to the initial assessment of response (approximately one month) and receipt of stem cell transplantation. The decision tree started from the point that patients were considered eligible for axi-cel and underwent the initial leukapheresis procedure. Following leukapheresis, patients subsequently followed one of three possible pathways: 1) continue with axi-cel and receive the infusion; 2) discontinue axi-cel (before infusion but after leukapheresis) because of adverse events or manufacturing failures; or 3) die before receiving the infusion. Patients who discontinued prior to infusion due to adverse events were assumed to be unable to tolerate other active therapies and were assumed to receive palliative care only. Patients who discontinued due to manufacturing failures were assumed to receive the average costs and outcomes of the active chemotherapy comparator.

Following assessment of response and potential receipt of ASCT, the patient cohort moved from the decision tree to the partitioned survival analysis model which included three health states: 1) alive and responding to treatment; 2) alive and not responding to treatment; and 3) death from B-cell malignancy or other causes. Transitions between health states were based on parametric extrapolations of progression-free survival (PFS) and overall survival (OS) curves up until five years.

PFS and OS data for axi-cel were sourced from the Phase 2 cohort of the ZUMA-1 study (n=101). OS data for the comparator chemotherapy strategy was sourced from the SCHOLAR-1 study. In the absence of PFS data reported in the SCHOLAR-1 study, PFS data was estimated based on assuming a proportional relationship between PFS and OS from an external study. The parametric survival analyses were based on pseudo patient level data (i.e. by recreating individual patient data from published Kaplan Meier curves).

A separate Markov model was then used to characterise the period from five years until death. Patients who were alive and responding to treatment at five-years were assumed to be long-term survivors and effectively 'cured'. Mortality after five years was based on the general population age- and gender-adjusted all-cause risks of mortality, with adjustments made for excess mortality (using a standardised mortality ratio). No excess mortality was assumed in the base-case.

Table 10 summarises the results of the base-case analysis which reported an ICER of $136,078 per QALY gained for axi-cel versus chemotherapy.

Table 10 Summary of base-case results (US ICER model)

Technology	Mean Costs	Mean LYs	Mean QALYs	ICER
Axi-cel	$616,927	7.35	5.87	$136,078
Chemotherapy	$154,884	3.23	2.48	-

One-way sensitivity analyses and scenario analyses were undertaken to identify the key drivers of model outcomes. The key drivers identified were the outcome discount rate, the utility estimate for the "alive and responding to treatment" health state, the standardised mortality ratio and the duration of intravenous immunoglobulins (IVIG) therapy and the survival assumptions.

4.1.4 Conclusions of the cost effectiveness review

The CS reported that there were no previous cost-effectiveness analyses assessing axi-cel. The studies identified for other interventions were not considered appropriate by the company as a basis for modelling axi-cel given the different mechanism of action and the claim of superior efficacy compared to current treatments.

The ERG identified one recently published US study which evaluated the clinical and cost-effectiveness of axi-cel versus chemotherapy for adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who were ineligible for ASCT. The study reported an ICER of $136,078 per QALY gained for axi-cel versus chemotherapy. Inevitably differences

between the US health care system and the NHS makes it difficult to generalise the results. The ERG therefore considers the company's model to provide the most relevant evidence for the decision problem. Nevertheless, the US study provides an important basis for comparing key structural assumptions and parameter uncertainties.

Although not formally included in the company's review, the company also reported that a previously published study (referred to in the CS as the York study) included an assessment, based on a hypothetical data set, of CAR T therapy: (1) as a bridge to stem cell transplantation, and (2) with curative intent.[18] Although the York study was based on hypothetical data, the company considered that the model developed for the CAR T therapy with curative intent was highly relevant to this appraisal. The CS stated that the development of their de-novo model was significantly influenced by the approaches and assumptions used in the York study.

4.2 ERG's summary and critique of company's submitted economic evaluation

The company presents a *de novo* analysis based on a three health state (pre-progression, post-progression and death) partitioned survival model. A summary of the company's economic evaluation is presented on Table 11, with justifications for key aspects and signposts to the relevant sections of the CS. The ERG has considered the methods applied in the company's economic evaluation in the context of a detailed checklist, reported in Appendix 9.1.

Table 11 Overview of the company's economic evaluation

	Approach	**Source / Justification**	**Location in CS**
Model	Cost-effectiveness (cost-utility) analysis using a partitioned survival analysis (PartSA) approach.	Commonly used modelling framework for oncology. Consistent with the model structure proposed in the York study for a hypothetical CAR T technology with "curative" intent.	Section B.3.2; p89-90
States and events	The model contains 3 states: pre-progression, post-progression and death	Health states were aligned with two primary objectives of treatment (avoiding disease progression and prolonging life) and are typical of metastatic oncology models used in previous NICE appraisals.	Section B.3.2; p89-90
Comparators	Axi-cel was compared to: • BSC defined as a blended comparator composed equally of: – Gemcitabine and methylprednisolone (GEM) – Gemcitabine, methylprednisolone and cisplatin (GEM-P) – Rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone (RGCVP) – Rituximab, vinblastine and prednisolone (RVP)	BSC reflected current standard of care for individuals not eligible ASCT. While no single standard of care was identified, the regimens composing the blended comparator were considered to be representative of the current standard of care in the UK and to have equivalent efficacy to the regimens used in SCHOLAR-1 (source of effectiveness inputs for BSC). Pixantrone was not included as a comparator, since it was not considered to be used in clinical practice in the UK, based on advice received from clinicians and BSH guideline.	Section B.3.2; p98-99
Natural History	Based on partitioned survival model. Transitions between states were based on ZUMA-1 (Phase 1 and 2) and the SCHOLAR-1 retrospective database study.	PFS and OS estimates were modelled independently, with the proportion of progressed patients at each cycle, calculated as the difference between the OS and PFS curves.	Section B.3.2; p89-90
Treatment effectiveness	Clinical outcomes included PFS and OS. Axi-cel PFS was extrapolated from ZUMA-1 patient level data using a conventional single parametric survival curve while OS was extrapolated using a mixture-cure model.	In the absence of an RCT, the uncontrolled comparison was made between the mITT population of ZUMA-1 and a subset of SCHOLAR-1 population (excluding patients with baseline ECOG 2-4). The subset was used to increase the comparability between the ZUMA-1 and SCHOLAR-1 populations.	Section B.3.3; p99-116

	Approach	**Source / Justification**	**Location in CS**
	BSC OS was extrapolated based on SCHOLAR-1, while PFS was derived from OS by assuming the same ratio between PFS and OS for axi-cel in ZUMA-1.	Other approaches (including propensity matching) to adjust the survival estimates based on comparability of the ZUMA-1 and SCHOLAR-1 studies were explored using separate scenarios. SCHOLAR-1 did not collect PFS data, so the PFS estimates for BSC required an assumption on the relationship between PFS and OS. The company assumes in the base-case that this relationship was the same as for axi-cel, and varied the assumption using two extreme assumptions in scenario analysis: i) 100% of time spent alive in the BSC arm is spent in the progression-free state or ii) 100% of time spent alive in the BSC arm is spent in the progressed state	
HRQoL	Utilities were estimated from EQ-5D collected in a safety management cohort of ZUMA-1 (n=34). Utility decrements for adverse events were sourced from the published literature.	EQ-5D-5L was collected at screening, week 4, Month 3 and Month 6 in the safety cohort. It is unclear whether these time points were defined from screening or from infusion. EQ-5D-5L responses were converted to EQ-5D-3L using a crosswalk algorithm. The number of observations informing the 'post-progression' is small ([redacted]). The utility value of 'pre-progression' was informed by multiple observations by individual, as the number of observations is greater than the size of the cohort ([redacted] vs n=34). The health state utilities (pre-and post-progression) were assumed the same for both treatment arms. Scenario analyses sourced alternative health state utility estimates from NICE TA306.	Section B.2.6 p48 Section B.3.4.p121-127

	Approach	Source / Justification	Location in CS
		Patients in 'pre-progression' for 2 years were subsequently assumed to have the same utility values as the age and gender matched general population after this point. In scenario analyses, an additional (arbitrary) decrement to the age and gender matched general population utility values was applied. Utility decrements for anaemia, febrile neutropenia, neutropenia, platelet count decrease, pyrexia and thrombocytopenia were sourced from TA306. A disutility equal to the maximum of the identified non-CRS AE disutilities was assumed for AEs where no literature source was identified. CRS was assumed to reduce health state utility to zero for its duration (4 days). AE durations were calculated using patient-level data from ZUMA-1. Durations were calculated as the total number of days that each patient experiences a specific AE, even if that event was experienced more than once. All AE disutilities were applied as a one-off decrement applied to the first cycle of the model, and only to patients receiving axi-cel. No disutility was applied in the model to patients undergoing leukapheresis, conditioning therapy or allogeneic SCT.	
Adverse events	Adverse events were included if they were: • Grade 3 or higher axi-cel-related AEs occurring in ≥10% of subjects in ZUMA-1 • Grade 3 or higher conditioning chemotherapy-related AEs occurring in ≥10% of subjects in ZUMA-1	Adverse event rates for axi-cel were taken from the Phase 2 cohort of ZUMA-1. AEs were not included for BSC. The company considered this approach to be conservative towards axi-cel.	Section B.3.3 p119-120

	Approach	**Source / Justification**	**Location in CS**
	• Grade 3 or higher treatment-emergent CRS occurring in ZUMA-1		
Resource use and costs	Cost categories were: • Treatment costs – Axi-cel: drug acquisition, leukapheresis, conditioning chemotherapy, cell infusion and monitoring – BSC: drug acquisition and administration • Health state medical resource use: – Professional and social services – Health care professionals – Treatment follow-up – Hospital services • AE costs • Allogeneic SCT • Training costs	Categories of cost and resource use were informed by TA306 and the York study. Medical resource use data were derived from TA306 and unit costs sourced from the Personal Social Services Research Unit (PSSRU), NHS reference costs and other published sources. Drug and administration unit costs were sourced from eMIT, MIMS, and NHS reference costs. Resource use was informed by UK hospital chemotherapy protocols. The costs of adverse events grade 3-4 with incidence ≥ 10% were included in the base-case. Following points for clarification, revisions were made for the costs of CRS and B-cell aplasia. It was also assumed that patients in PFS for at least 2 years were long-term survivors and no longer incurred the costs of medical resource use after 2 years in PFS (base-case analysis).	Section B.3.2 p97 Section B.3.3 p116 Section B.3.5 p128-142
Discount rates	Costs and benefits were discounted at 3.5% per annum	In accordance with the NICE reference case. A scenario analysis applied an alternative discount rate of 1.5%, on the basis of the company's base-case suggesting long-term survival for patients receiving axi-cel.	Section B.3.2; p98

	Approach	**Source / Justification**	**Location in CS**
Sensitivity analysis	Probabilistic sensitivity analysis was performed. Deterministic univariate probabilistic analysis was performed on a series of model parameters. A series of scenario analyses was also performed.	In accordance with the NICE reference case.	

4.2.1 The company's economic evaluation compared with the NICE reference case checklist

Table 12 summarises the ERG's assessment of whether the company's economic evaluation meets NICE's reference case and other methodological recommendations.

Table 12 Comparison of company's economic evaluation with NICE reference case

Attribute	Reference Case	Included in CS	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies in the NHS, including those currently regarded as current best practice	Yes	While the blended comparator applied in the economic model does not match the chemotherapy regimens defined in the NICE scope, the ERG's clinical advisor confirmed that the regimens included reflect the current standard of care for patients who are not eligible for ASCT. Despite its inclusion in the NICE final scope, pixantrone was not included in the model, since it was not considered to be standard clinical practice. The ERG's clinical advisor agreed with this view.
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective - costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account.
Perspective - benefits	All health effects on individuals	Yes	QALY benefits to treated individuals were considered.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model uses a lifetime horizon (44 years). Less than 0.01% of patients are expected to survive beyond this period.
Synthesis of evidence on outcomes	Systematic review	Partial	The source of data for BSC (SCHOLAR-1) pooled data from four studies – only two of which (two RCTs) were identified in the company's systematic review.
Outcome measure	QALYs	Yes	EQ-5D was collected in the ZUMA-1 trial.

Health states for QALY measurement	Described using a standardised and validated instrument	Yes	Derived from EQ-5D data.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	Time Trade Off
Source of preference data	Representative sample of the public	Yes	Societal tariffs from EQ-5D.
Discount rate	3.5% on costs and health benefits	Yes	Costs and benefits have been discounted at 3.5% per annum. Scenario analysis was performed applying an annual discount rate of 1.5%, given the given the potential for long-term benefits from the 'cured' proportion of patient who receive axi-cel and the high upfront costs of the technology.
Equity weighting	No special weighting	Yes	No special weighting undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken.

4.2.2 Population

The population defined by the company in the economic evaluation corresponds to the population anticipated to be included in the final marketing authorisation, expected by June 2018. The anticipated license for axi-cel is for [redacted]. This population is considered to be in line with the NICE scope and reflects the population of ZUMA-1.

As previously stated in Section 4.2.1, the ERG concluded that patients in ZUMA-1 appear to be representative of the various lymphoma population sub-groups and that that the ZUMA-1 population should be broadly generalisable to patients seen in NHS settings with baseline ECOG status 0-1.

In Section 3.3 the ERG discusses the four positions in the clinical pathway defined by the company and at which patients are considered eligible for treatment with axi-cel. The ERG considers that it is highly uncertain whether two of these positions, namely for patients refractory to first-line therapy and for patients relapsed to first-line therapy, but ineligible for ASCT following second-line therapy for reasons of age and comorbidities, are reflective of current UK clinical practice and are supported by limited evidence (n=2 and n=0 in ZUMA-1, respectively). The ERG notes that CAR T-cell therapy is an unlikely first line salvage therapy in UK practice while other effective interventions with

long-term evidence are available (including ASCT), and that patients ineligible for ASCT are unlikely to be eligible for CAR T-cell therapies. Therefore, the clinical populations providing evidence relevant to the cost-effectiveness analysis: (i) patients who relapsed after first-line therapy, and would be eligible for ASCT at second-line but who do not respond to salvage therapy; and (ii) patients who relapsed after first-line therapy, were eligible and treated with chemotherapy and ASCT and subsequently relapse. Given that the CS does not present any evidence by treatment position, the ERG cannot examine whether there are any relevant differences in terms of effectiveness, costs or HRQoL between positions or explore how potential differences would impact on the cost-effectiveness estimates.

The main baseline characteristics of the population in the base-case analysis were not reported in the CS. As previously noted in the clinical effectiveness section, all the tables of baseline characteristics from ZUMA-1 reported in the CS (Tables 8 and 11 in the CS and Table 9 in the CS appendices) were based on the 101 patients in the 'primary analysis' phase II cohort, rather than for the updated analysis cohort of 108 patients used in the cost-effectiveness model.

4.2.3 Interventions and comparators

Axi-cel is a CAR T-cell therapy and its administration requires that patients undergo leukapheresis. The patient's T-cells harvested by this process are then engineered to express the CAR with affinity to the antigen CD19; the resulting cell product is axi-cel. Axi-cel is administered as a single intravenous infusion in the hospital setting, after patients have undergone lymphodepleting low-dose conditioning chemotherapy of 500 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine during the three days prior to infusion of anti-CD19 axi-cel.

The most relevant comparator identified by the company was BSC comprising salvage therapy with multi-agent chemotherapy. The BSC comparator applied in the model was justified based on the current NICE treatment pathway and interviews with UK clinicians. BSC was modelled using a blended comparator composed of several gemcitabine and/or platinum-based chemotherapy regimens. These were selected based on a list of regimens used in UK clinical practice provided by the Oxford University Hospitals NHS Foundation. The regimens included in the blended comparator were:

- Gemcitabine and methylprednisolone (GEM)
- Gemcitabine, methylprednisolone and cisplatin (GEM-P)
- Rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone (RGCVP)
- Rituximab, vinblastine and prednisolone (RVP)

While the blended comparator applied in the economic model does not precisely match the chemotherapy regimens defined in the scope, the clinical advisor to the ERG confirmed that the included regimens reflect the current standard of care for patients who are not eligible for ASCT. The regimens included in the blended comparator were assumed to have equal efficacy to the regimens used in SCHOLAR-1, which is the source of the effectiveness inputs for BSC.

Pixantrone monotherapy was not included as a comparator despite being included in the NICE scope. The company argued that pixantrone is not commonly used in UK's clinical practice due to disappointing clinical experience. The clinical advisor to the ERG confirmed that pixantrone is rarely used and that it was perceived in the clinical community to be of limited effectiveness.

4.2.4 Perspective, time horizon and discounting

A 3.5% discount rate was applied for costs and health benefits, in line with NICE guidance. A scenario analysis using a lower discount rate on costs and benefits (1.5% per annum) was also presented. The company stated that this scenario would be relevant if the NICE committee considers that axi-cel meets the criteria for the use of a lower discount rate based on the NICE methods guide.[19]

The time horizon was described as a lifetime horizon and comprised 44 years (528 monthly cycles). The ERG considered the time horizon appropriate, as less than 0.01% patients in the model were expected to remain alive beyond 44 years. However, the long time horizon is driven by the extrapolation and 'cure' assumptions within company's model, which the ERG consider to be subject to significant uncertainties.

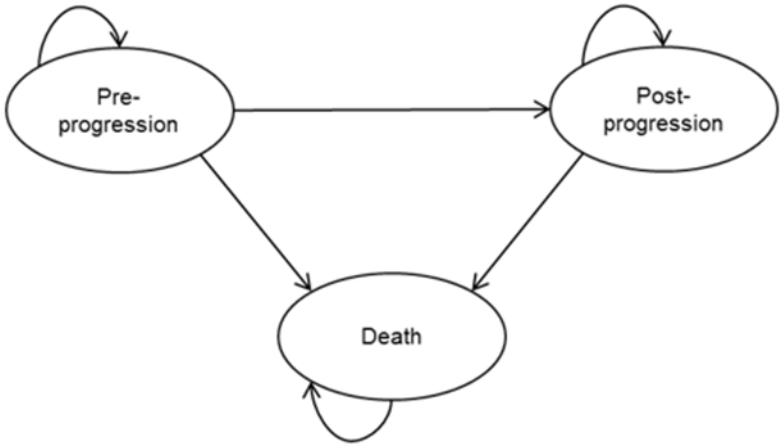
The CS did not formally state a perspective, but the costs and benefits included are consistent with a NHS and Personal Social Services (NHS & PSS) perspective.

4.2.5 Model structure

The company's cost-effectiveness analysis was based on a three state model (pre-progression, post-progression and death) informed using a partitioned survival analysis (PartSA) approach. Patients enter the model in the pre-progression health state, having progressed on previous treatment(s) for DLBCL, PBCL or TFL. Patients remain in the pre-progression state until disease progression or death. Following a transition to disease progression, patients remain in this state until death.

A schematic of the model structure is shown in Figure 7.

Figure 7 Model structure



The use of partitioned survival analysis means that PFS and OS survival curves are modelled independently and are used to directly inform state membership of the 'Pre-progression' and 'Death' states over time, respectively. The proportion of patients in the 'Post-progression' state during each model cycle is determined by the difference between the modelled OS and PFS survival curves. The model uses a cycle length of one month with a half-cycle correction applied.

The choice of model structure was justified by the company based on the common use of this approach in oncology modelling, noting that the same structure was used to model a 'hypothetical' CAR T therapy with 'curative' intent in the York study.[18] The selection of a partitioned survival model over a state-transition model was further justified by the company given the lack of PFS data reported in the study (SCHOLAR-1) which informed the clinical effectiveness inputs for BSC in the model. The lack of PFS precluded the direct estimation of pre- and post-progression survival necessary to inform a state-transition model.

The OS and PFS Kaplan Meier (KM) data for axi-cel was based on the latest ZUMA-1 combined Phase 1 and 2 data cut (n=108, August 2017). As previously highlighted in Section 4.2, the KM data for axi-cel is based on the mITT population (i.e. patients who received axi-cel). As a result, model entry for patients receiving axi-cel occurs from the time point of infusion of axi-cel, rather than from the time point of the initial leukapheresis procedure. While the ERG previously acknowledged the rationale of this decision based on the issue of group comparability since the SCHOLAR-1 data will be mITT, the ERG also concluded that this issue should not be ignored since the period of time between the decision to treat, and receipt of axi-cel infusion, is likely to be longer for axi-cel when compared to salvage chemotherapy.

The ERG notes that the company incorporated the costs of leukapheresis and conditioning chemotherapy of those patients who were selected for axi-cel treatment in ZUMA-1, but did not

subsequently receive at least one dose of axi-cel. The approach taken to incorporate these costs was based on applying multipliers to the costs of leukapheresis and conditioning chemotherapy in the first cycle to reflect the costs of the patients who underwent these procedures but did not subsequently receive axi-cel. However, this approach did not quantify the potential impact on survival and HRQoL outcomes of the 11 patients out of 119 enrolled to ZUMA-1 who received leukapheresis but were not subsequently infused (e.g. due to adverse events, death or manufacturing failure).

Following a request in the point for clarification, the company adapted the model to explore an additional scenario which explores the potential impact of including the Full Analysis Set population (ITT); this scenario is discussed at the end of Section 5.

Based on visual inspection of the axi-cel KM curves for PFS and OS, the company identified a plateau occurring from around 6 months in the PFS data and after around 10-12 months for OS (Figures 15 and 16, CS). The plateauing of PFS and OS was considered by the company to indicate a proportion of patients experiencing long-term remission and survival. In order to appropriately capture the plateau in the OS data, the company investigated the use of more complex survival models (mixture cure models) as well as standard parametric models.

In situations where a proportion of patients experience long-term durable remissions for their illness, there can be significant heterogeneity in survival data. Standard parametric models group all patients together and provide a single prediction of survival for the entire group. In contrast, the mixture-cure model assumes that for a proportion of patients (the cure fraction), axi-cel will have a curative effect, and therefore, these patients will have the same mortality rate as the UK general population. The mixture-cure model estimates the cure fraction based on the observed data and fits a single parametric curve to the observed survival of 'non-cured' patients. The 'cured' patients are assumed to not progress over the model time horizon, and can only remain in 'Pre-progression' or transition to 'Death' due to non-lymphoma causes.

The mixture-cure approach was not applied to BSC in the base-case analysis, where a single standard parametric curve was fitted to extrapolate OS in the decision model. The appropriateness of the survival modelling approach for both treatments is discussed in more detail in Section 4.2.6.2.

The model also included a further important structural assumption, specifically that those patients' who remain in the 'Pre-progression' health state for at least two years (in either treatment group), will subsequently revert to the same HRQoL as the general population and will not incur any further costs related to their previous condition. This is equivalent to a separate structural 'cure' assumption

applied in the model that prevents transitions from the 'Pre-progression' to the 'Post-progression' state after two years.

The concept of 'cure' and the associated assumptions are central to the cost-effectiveness estimates generated by the model but are also subject to considerable uncertainty. There are three key aspects to the cure assumption: (i) the estimated cure fraction; (ii) the time point at which cure is assumed to occur; and (iii) whether patients cured from lymphoma may still differ from the general population in terms of excess mortality, costs, and HRQoL.

It is important to recognise that mixture-cure models require long follow-up times well beyond the point of cure in order to robustly estimate a cure fraction and sufficient numbers of patient at risk at the end of follow-up.[20, 21] The short-follow-up of ZUMA-1 (median 15.4 months) cannot exclude the possibility of late relapses occurring that may not have been captured in the OS extrapolation. As previously stated, the ERG's clinical adviser was of the opinion that a minimum of 2-3 years would be an appropriate time frame for considering patients (who are still in remission) to be cured.

The assumption that patients who remain in the 'Pre-progression' health state for at least two years in either treatment group, will subsequently revert to the same HRQoL and medical resource use cost of the general population does not appear to be robustly supported by evidence. The assumption of cure at two years is based on one US study where no statistical difference could be found between the mortality of DLBCL survivors and that of the general population after two years post-diagnosis.[22] However, the ERG identified several other studies that suggest that significant excess mortality remains up until at least five years post-diagnosis.[23, 24]

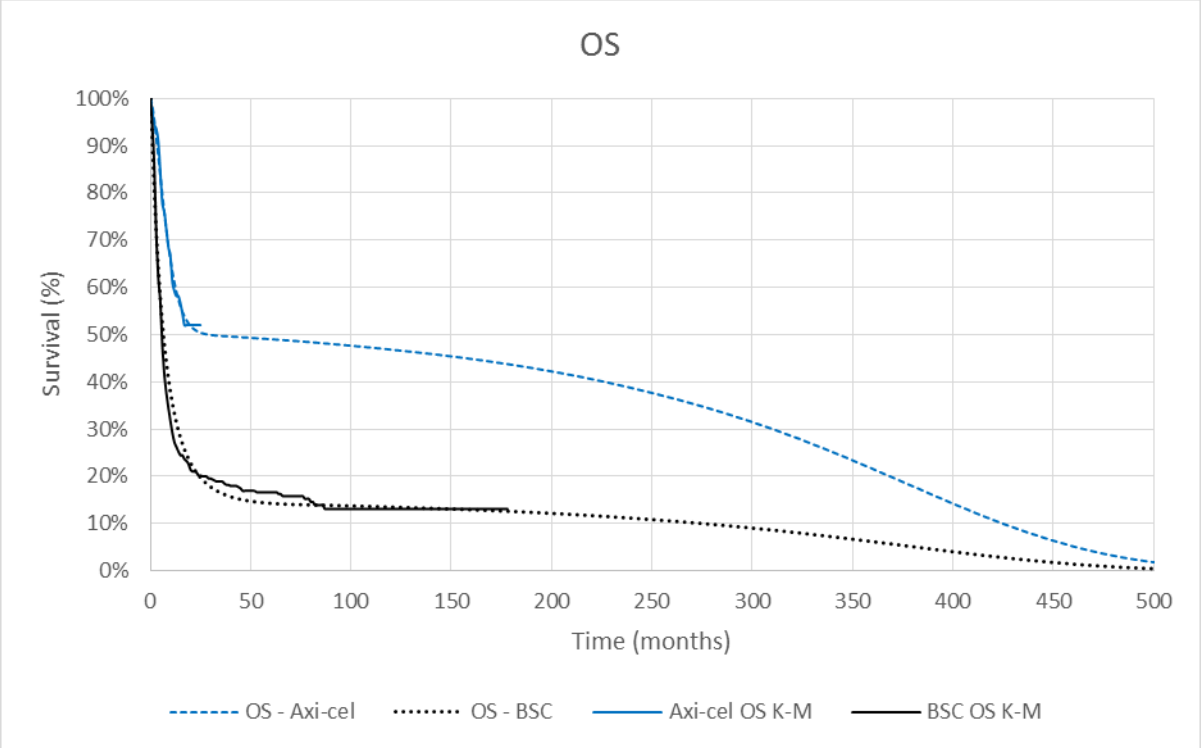
The ERG does not consider that the uncertainties to which the cure assumption is subject have been fully addressed in the company submission, and discusses this further in Section 4.2.6.2.

4.2.6 Treatment effectiveness and extrapolation

PFS and OS were the main effectiveness inputs included in the company's economic model. OS survival estimates were derived from the ZUMA-1 single arm trial mITT population (n=108) for axi-cel and from patients in SCHOLAR-1 study. For the model base case, the SCHOLAR-1 data was adjusted by removing patients with an ECOG score of 2–4 to increase comparability between the ZUMA-1 and SCHOLAR-1 populations. Only patients with ECOG 0–1 were recruited in ZUMA-1 trial based on the trial protocol.

Figure 8 illustrates the KM curves and extrapolated OS curves for axi-cel and BSC. The KM data from ZUMA-1 is evidently less mature than the SCHOLAR-1 study.

Figure 8 Overall survival in the model: K-M curves with base-case extrapolation (adapted from company model)



The majority of survival benefits of axi-cel are conferred during the extrapolation period. Therefore, it is important to consider the assumptions underlying the extrapolation of survival (PFS and OS), and their impact on the magnitude of survival benefits.

4.2.6.1 Uncontrolled comparison of treatment effectiveness

In Section 4.2, the appropriateness of using a historical control to establish relative effectiveness of axi-cel compared to BSC was discussed. OS data for the BSC treatment group was sourced from SCHOLAR-1. The baseline characteristics of the population in SCHOLAR-1 were not considered by the company to be directly comparable to ZUMA-1, particularly in terms of number of previous lines of treatment (ZUMA-1 patients more heavily pre-treated) and ECOG status (ECOG 0-1 only in ZUMA-1). Patients in SCHOLAR-1 also received subsequent SCT in higher proportion than those in ZUMA-1 ([redacted] vs [redacted]).

The company explored a range of alternative approaches to attempt to adjust for differences in population characteristics between ZUMA- 1 and SCHOLAR-1. The four adjustments proposed for the SCHOLAR-1 were:

1. Base-case analysis: Removal from SCHOLAR-1 of patients with known ECOG 2-4 at baseline;
2. Scenario 1: Unadjusted, all patients in SCHOLAR-1 included;
3. Scenario 2: Propensity score matching used to adjust survival data for all patients in SCHOLAR-1
4. Scenario 3: Removal from SCHOLAR-1 of patients with ECOG 2-4 at baseline and those who had received post-refractory SCT

The KM curves for each of the above described adjustments to the SCHOLAR-1 population are depicted in the CS (Figure 17; CS, p95), and show mostly overlapping curves, with the exception of the adjustment described for scenario 3 (removal of ECOG 2-4 and post-refractory SCT) where survival outcomes considerably worse than for the other adjustments. The selection of the crude adjustment to SCHOLAR-1, by removing ECOG 2-4 patients, was considered by the company to be the most appropriate approach for their base-case. The company considered that other alternative adjustments including the use of propensity score would make minimal difference to the survival outcomes.

The ERG's key concern with the base-case approach is that while this removes patients with known ECOG 2-4 ([redacted]), patients with unknown ECOG status appear to be retained. Figure 9 shows that the KM for OS in the subgroup of patients with known ECOG 0-1 status (provided with the company's response to points for clarification) appears to plateau at approximately [redacted] In contrast, the OS Kaplan-Meier used for the company base case (excluding ECOG 2-4 only) appears to plateau at a lower survival estimate (approximately [redacted]).

The comparison of the KM data from the difference subgroups indicates that the subgroup of patients in SCHOLAR-1 with known ECOG 0-1 status has a better prognosis than the population used in the company base-case, which excludes patients with known ECOG 2-4 at baseline. The ERG concludes that restricting the patient population for BSC to patients with known ECOG 0-1 status in SCHOLAR-1 (n=226) may provide a more appropriate basis for comparison with the ZUMA-1 population, which only included patients with known ECOG 0-1 status.

Figure 9 Kaplan Meier curves for OS by ECOG status from SCHOLAR-1 (from company's response to clarification question, p10).

The appropriateness of the statistical adjustment by propensity score matching of the SCHOLAR-1 full population was also discussed in Section 3.2.4. As previously noted, the exclusion of covariates associated with prognostic in the statistical model on the basis of missing data and reduction of sample size, is likely to have compromised the method's ability to reduce any important bias on survival outcomes. Furthermore, by performing the method on the full population in SCHOLAR-1, more comorbid patients are likely to have been included in the matching population. The variables selected by the company to estimate the propensity scores were limited to baseline age, disease stage, diagnosis (i.e. DLBCL versus PMBCL and TFL), and relapse post-ASCT status.

Despite the company's claims that the different adjustment methods explored for the SCHOLAR-1 data did not make a significant difference, the ERG remains concerned that none of the approaches were appropriate to ensure the comparability of the SCHOLAR-1 and ZUMA-1 data.

4.2.6.2 Overall survival

Table 13 summarises the survival models investigated for each treatment along with the main justification provided by the company for use in their base-case analysis.

Table 13 Summary of company justification for selected OS extrapolation curves

Treatment	Type of survival model	Cure fraction	Parametric curve	Goodness of visual fit	Best statistical fit	Clinically plausible
Axi-cel	Single parametric	NA	Exponential	No comment	Yes	No
			Gamma		No	
			Gompertz		No	
			Loglogistic		Yes	
			Lognormal		No	
			Weibull		No	
	Mixture-cure	**0.50**	**Weibull**	**No comment**	**Yes**	**Yes**
		0.53	Gamma		No	Yes
		0.01	Lognormal		No	No
BSC	**Single parametric**	**NA**	Exponential	No comment	No	No comment
			Gamma	No comment	No	No comment
			Gompertz	**Yes**	**Yes**	**Yes**
			Loglogistic	No comment	No	No comment
			Lognormal	No comment	No	No comment
			Weibull	No comment	No	No comment
	Mixture-cure	0.19	Weibull	Yes	Yes	No comment
		0.18	Gamma	Yes	No	No comment
		0.17	Lognormal	Yes	No	No comment

Survival models used in the company base-case are reported in bold

Axi-cel

The company fitted a number of standard single parametric and mixture-cure models to the OS data of the mITT population in ZUMA-1. The base-case survival model selected was a mixture-cure model where the survival of 'not-cured' patients is modelled with a single parametric Weibull curve and the mortality of the 'cured' patients is considered equal of the age and gender matched general population mortality rate.

The estimated cure fraction suggests that approximately 50% of patients receiving axi-cel achieve a long-term remission. The company states that the mixture-cure approach was selected for the base-case axi-cel OS analysis because there is "*a biomedical rationale for believing a proportion of those patients treated with axi-cel will have an excellent long-term prognosis (with a risk of mortality similar to the general population)*" and that the extrapolation based on single parametric curves was

not clinically plausible. The company placed particular emphasis on the ability of the mixture-cure model to more accurately model the tail of the KM curve. However, in light of the extensive censoring there is considerable uncertainty as to how the survival data and associated KM curves will develop over longer time horizons. As previously noted by the ERG, this uncertainty will only be properly resolved when data from longer follow-up periods become available for more patients.

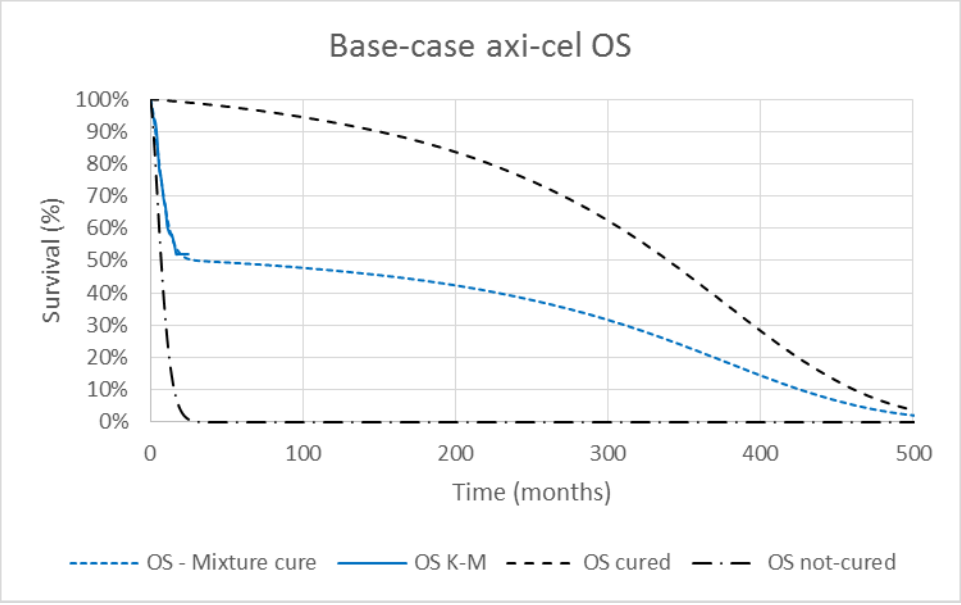
The ERG considers that the axi-cel OS extrapolation is affected by significant uncertainties that have not been fully explored in the company submission, and highlights below the key uncertainties associated with the cure assumption.

Mixture-cure models vs single parametric

The base-case modelling approach for axi-cel OS effectively defines two separate survival cohorts representing 'cured' and 'not-cured' patients. The OS curve for axi-cel patients is therefore a weighted average of the age and gender matched general all-cause mortality and the OS parametric curve fitted to the 'not-cured' patients, where the weights correspond to the cure fraction and the proportion of 'not-cured' patients, respectively.

Figure 10 illustrates the company's base-case axi-cel OS for the entire group and by cured status, alongside the axi-cel OS KM data.

Figure 10 Axi-cel observed and base-case extrapolated OS by cure status (adapted from CS model)

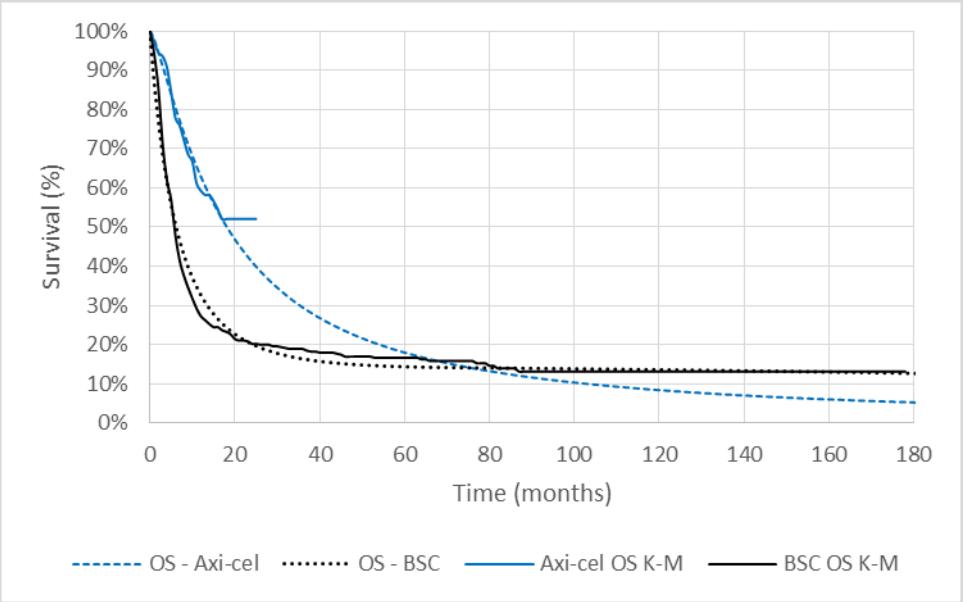


The extrapolation of OS based on standard single parametric curves for axi-cel was dismissed by the company as providing clinically implausible estimates. The main argument against the use of standard single parametric curves was that over the extrapolation period, the predicted OS based on all

standard parametric curves for axi-cel eventually becomes lower than the observed OS for BSC based on the more mature SCHOLAR-1 data.

Figure 11 shows the extrapolation of axi-cel OS with the best fitting single parametric curve (loglogistic), demonstrating how it intercepts the observed survival of BSC after approximately five years.

Figure 11 Overall survival in the model: K-M curves with base-case extrapolation for BSC and loglogistic extrapolation for axi-cel (adapted from CS model)



The company also justified not applying spline models to extrapolate axi-cel OS on the basis that these models rely strongly on data observed towards the end of the curve. Since observed data is sparse towards the end of the KM, the extrapolations were considered to also be highly uncertain. Furthermore the company considered that the spline models lack a strong clinical rationale.

The ERG acknowledges that the use of single parametric curves over the entire model time horizon does not appear to provide clinically plausible lifetime extrapolations for OS. However, the ERG considers that there remains considerable uncertainty surrounding the extrapolated OS data using the mixture-cure model.

Cure assumption

The OS extrapolation assumes cure for a fixed proportion of the patients on axi-cel that occurs immediately on infusion and that restores patients to the age and gender-matched mortality of the general UK population. A separate cure assumption is further built into the model via the model constraint that patients in the 'pre-progression' state move from the health state utility to general

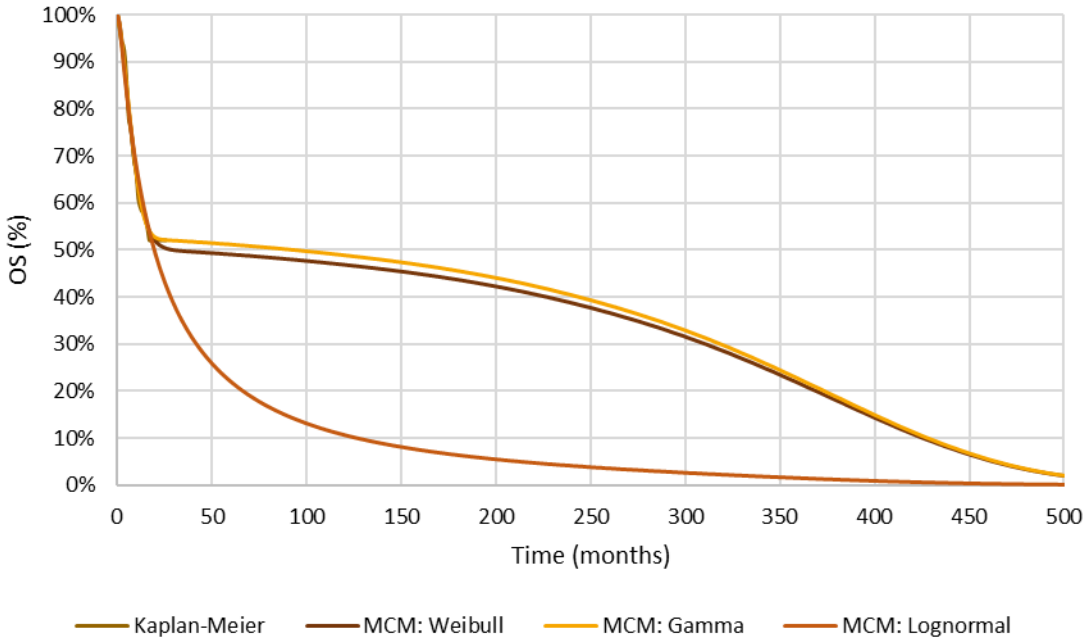
population utility after two years in the state, and also have no medical costs after that time point. The two year time point was based on one clinical study,[22] which compared the mortality risk of DLBCL patients at one and two years after diagnosis with that of the US general population.

There is no accepted clinical definition of cure. It is considered that the observed survival data suggest the occurrence of statistical cure for a given treatment when there is a flattening of the OS KM curve which forms a plateau. The OS KM curve for axi-cel shows the beginning of plateau on its distal portion from 10-12 months onward (Figure 6, CS p45), however the number of patients at risk by this time point is small (n=23). To provide robust estimates of cure fraction, mixture-cure models requires both a sufficiently long follow-up and numbers of patient at risk at the end of follow-up.[20, 21] A previous study exploring cure in DLBCL with a follow-up of 11 years concluded that even this follow-up period may not be sufficient to estimate a cure fraction accurately.[23]

A key issue to consider is whether the existing evidence for axi-cel can robustly demonstrate the cure fraction, given the limited duration of follow-up (median follow up = 15.4 months) and high levels of censoring. The company fitted three mixture-cure models to the axi-cel OS data. Although the implied cure fraction from the Weibull (0.50) and gamma (0.53) distributions were similar, the cure fraction estimated from the lognormal mixture-cure model was close to zero (0.01). As a result, the OS extrapolation for the lognormal mixture-cure model was similar to the standard single parametric lognormal model.

Figure 12 summarises the overall survival estimates for the alternative mixture-cure models compared to the observed OS KM data.

Figure 12 Overall survival for axi-cel – comparison of alternative mixture cure models (CS)



The company concluded that only the Weibull and Gamma mixture-cure models provided clinically plausible OS and hazard predictions. The ERG considers that the difference in the cure fractions across the alternative models suggest that the OS data may not be sufficiently mature to be able to estimate a robust cure fraction for OS.

The company also assumed that the cured population would be subject to the mortality risk of the general UK population. Again this relates to the definition of cure, and whether it is reasonable to assume that a long-term survivor would not experience any excess mortality compared to the general population. Howlader et al (2017),[23] a large study on long-term outcomes of DLBCL survivors (n=18,047) after rituximab become part of the standard of care, suggests that patients are at an elevated mortality risk from vascular disease, infections, and blood diseases for at least 5 years after diagnosis. The clinical advisor to the ERG also considered it unlikely that 'cured' patients would have the same mortality as the general population, due to prior treatment related toxicity, predominantly cardiac related. The company explored this in a scenario analysis, by applying a multiplier which arbitrarily increased the general population mortality risk by 10%. The ERG considers that this adjustment is arbitrary and hence may not adequately capture the impact of uncertainty in the longer term survival estimates.

The timing for the cure is also uncertain. As mentioned previously, the company assumes implicitly that cure occurs at two years post-treatment start (although the mortality of 'cured' patients is that of the general population from model entrance for axi-cel), by assuming that health state utility for

patients who have not progressed after two years subsequently reverts to that of the general population. The ERG considers that the follow-up of ZUMA-1 is too short to ascertain this. Previous cost-effectiveness studies have assumed cure after 5 years[18] [17] on their base-case or in scenario analyses. This appears more consistent with the findings from the largest study identified by the ERG reporting on long-term outcomes of DLBCL survivors (n=18,047).[23]

The ERG concurs with the company that to rely exclusively on a single parametric survival curve to model axi-cel OS for the entire model time horizon would produce results inconsistent with the longer term observed survival data assumed for BSC. However, the cure assumption as implied by the base-case mixture-cure model is also considered overly optimistic by the ERG as a basis for the lifetime extrapolation of OS for axi-cel, given that:

i. Survival data in ZUMA-1 is too immature to robustly estimate the size of the cure fraction;
ii. Median follow-up is shorter than the two years that the company considers to be the time point at which cure can be observed;
iii. Cure at two years is in itself highly uncertain, as excess mortality risk appears likely to persist for at least 5 years.[23]

There are considerable uncertainties surrounding the company's base-case OS extrapolation. The two modelling approaches presented in the company's submission, the mixture-cure and single parametric over the entire time horizon, are considered by the ERG to reflect the most optimistic and pessimistic assumptions for the OS estimates for axi-cel, respectively.

The ERG explores alternative assumptions for the extrapolation of OS for axi-cel in Section 6.

Best Supportive Care

Similar to the approach taken by the company to extrapolate the OS of axi-cel, a number of standard single parametric and mixture-cure curves (see Table 13) were fitted to the OS outcomes of the subset of patients in SCHOLAR-1 with unknown ECOG status or ECOG 0-1. Mixture-cure models were not included in the base-case analysis for BSC because the Gompertz single parametric curve was considered to have a good statistical and visual fit.

The ERG considers the OS modelling approach for the BSC to be inconsistent with that of axi-cel. The good statistical and visual fit of single parametric curves to the observed BSC OS is likely to be due to the greater maturity of the SCHOLAR-1 to ZUMA-1. Since SCHOLAR-1 has a much longer follow-up and a greater sample size, the survival data are more likely to allow the fitting of mixture-cure models with stable cure fractions. The mixture-cure models explored by the company for the

BSC OS, all fit the observed data reasonably well and the estimates of cure fraction are fairly robust across different distributions (0.17-0.19). Furthermore, if it is clinically plausible that cure occurs for patients on axi-cel, the same considerations should apply to the BSC group (albeit at a lower rate). Therefore, the ERG considers that the use of two different modelling approaches for each treatment group to be inconsistent and that this may bias the cost-effectiveness estimates against BSC. When the company base-case is modified so as to incorporate the Weibull mixture-cure model for BSC, the ICER of axi-cel vs BSC increases to [redacted] per additional QALY. When the best fitting BSC mixture-cure model (lognormal) is applied, the ICER of axi-cel vs BSC increases to [redacted] per additional QALY.

As previously highlighted, there is a risk that the comparison between axi-cel and BSC is biased due to the use of uncontrolled evidence to establish the comparison. The ERG is particularly concerned that the base-case BSC population includes more comorbid patients than those in ZUMA-1. The ERG's preferred approach would have been to include only patients of known ECOG 0-1 in the base-case comparison, in line with the inclusion criteria of ZUMA-1.

In Section 6, the ERG presents an alternative analysis where the survival outcomes of SCHOLAR-1 patients with ECOG 0-1 are applied in the decision model and used to estimate OS for BSC.

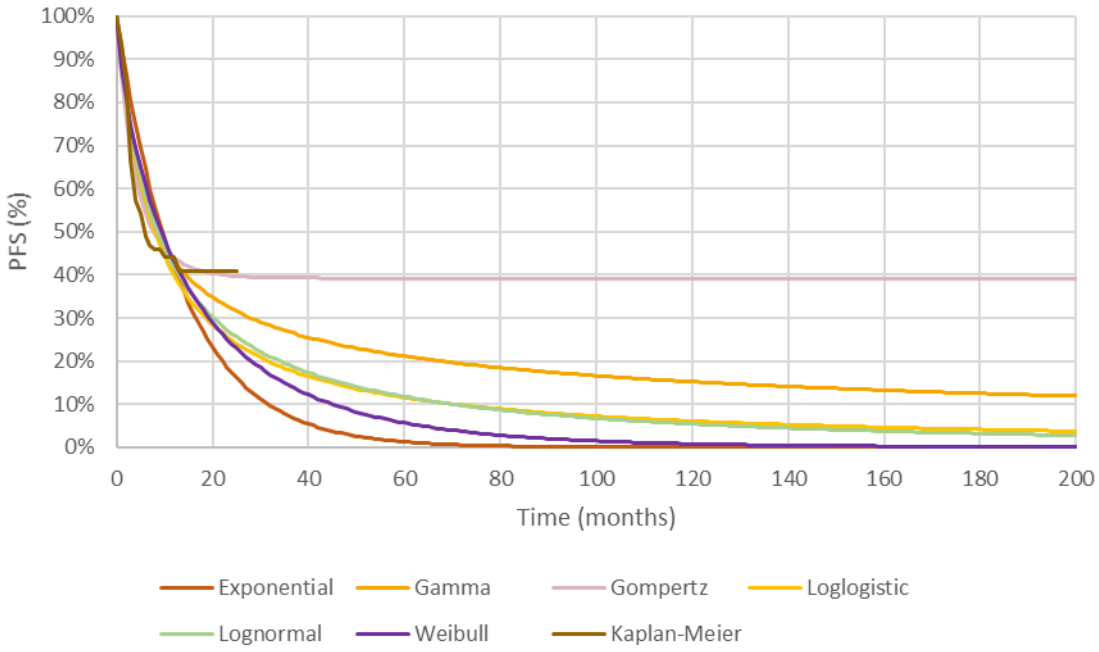
4.2.6.3 Progression free survival

PFS data from ZUMA-1 was used to model state membership for the 'Pre-progression' state. PFS was extrapolated through the fitting of conventional single parametric curves for axi-cel. In the absence of PFS data collected on SCHOLAR-1, the company relied on assumptions on the relationship between OS and PFS for axi-cel to estimate PFS for BSC.

Axi-cel

Figure 13 summarises the graphical fit of the alternative single parametric curves applied to the axi-cel PFS data in the model. The Gompertz distribution was selected for the base-case based on goodness of fit statistics, visual fit and the log cumulative hazard plot.

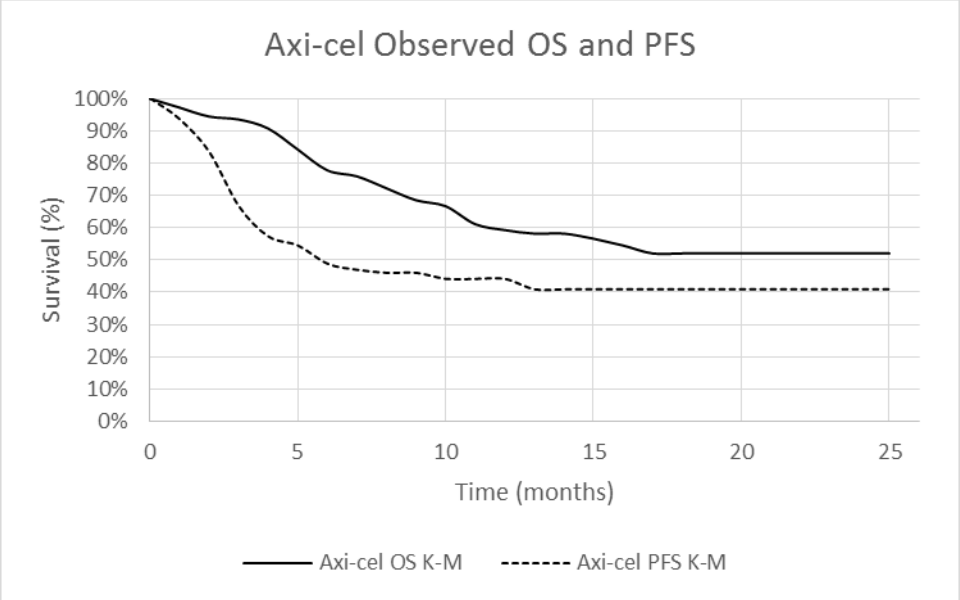
Figure 13: PFS for axi-cel: KM and single parametric curves



The ERG considers that none of the PFS curves appear to fit particularly well to the entire KM data, suggesting that more complex survival distributions may have provided a better statistical fit. Of the fitted distributions, only the Gompertz distribution appears to capture the plateauing evident in the PFS KM data. While the alternative PFS curves imply marked differences in longer term PFS estimates for axi-cel, the separate structural 'cure' assumption imposed at year 2 limits the impact of these differences beyond 2-years within the economic model.

The PFS KM curve also shows similar plateauing to the OS data, albeit at an earlier time point and at a lower survival probability (Figure 14). The ERG considers that the use of different survival models used for PFS and OS results in an important disconnect, implying that patients can be cured in terms of survival but not from disease progression. During the clarification stage, the company was requested to justify why the mixture-cure models were not also explored for PFS and to provide analyses using the mixture-cure approach.

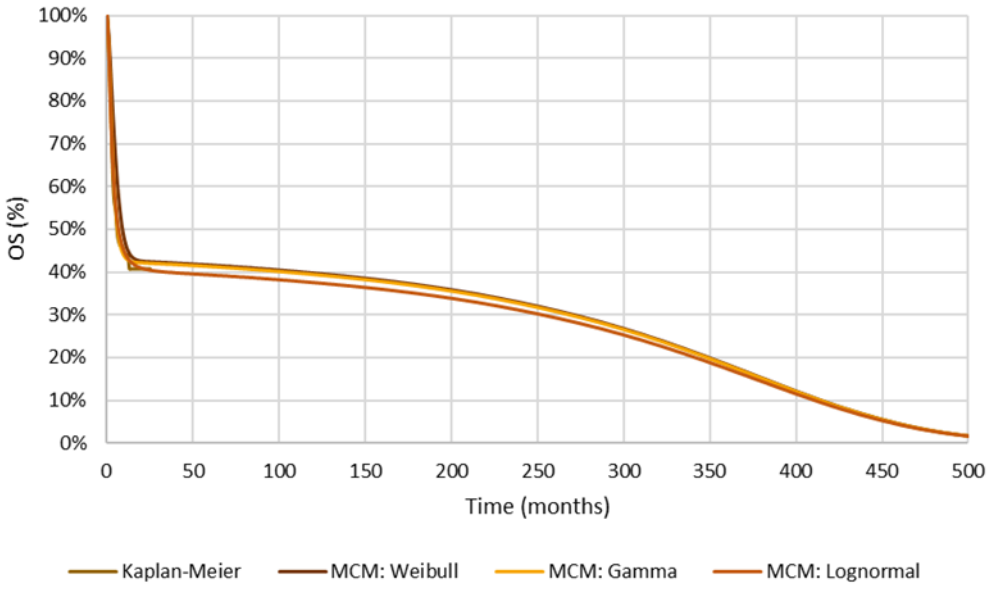
Figure 14 Kaplan-Meier (OS and PFS) curves for axi-cel (adapted from CS model)



The implied cure fractions estimated for PFS by the company for axi-cel (Table 12, company response) showed less variation across the three alternative distributions compared to OS, varying between 40% (lognormal) and 43% (Weibull).

Figure 15 shows the overall estimated PFS for each mixture-cure model compared to the observed ZUMA-1 PFS KM. The similarity in the implied cure fractions for PFS across the distributions is evident in the small differences between the subsequent PFS extrapolations. This is in marked contrast to the differences reported for OS based on the alternative mixture-cure models.

Figure 15 Progression-free survival for axi-cel: KM with mixture cure model parametric curves (CS)



In their response the company argued that while there is substantial precedent for using mixture-cure models for the outcome of overall survival, similar consensus has not been reported concerning the validity of this method for PFS and how the cure fracture should be interpreted. The company concluded that the PFS cure results should be treated with caution given a lack of clarity concerning how the cure method should be implemented and interpreted for PFS.

The ERG does not consider that the concerns expressed by the company provide sufficient grounds for dismissing the difference in the implied cure fraction estimates. The ERG also notes that PFS has been used in other studies in the context of mixture-cure models.[25] The ERG concludes that the differences in the estimate cure fractions for PFS and OS potentially suggest either: (i) that there are a significant number of patients who become cured following progression (i.e. due to subsequent therapies) or (ii) the OS data may not be sufficiently mature to robustly estimate the cure fraction for OS.

In relation to the first issue, there were ten patients in ZUMA-1 underwent retreatment with axi-cel after disease progression. Since the anticipated marketing authorisation is not expected to allow for retreatment, any subsequent 'cures' achieved in ZUMA-1 following retreatment would not be realised in clinical practice. The CS states that *"based on best overall responses per investigator, among the 9 retreated patients from the Phase 2 trial,* [redacted] *patients had complete and partial response, respectively;* [redacted] *patient had stable disease and* [redacted] *patients had progressed disease. It is therefore assumed that including the retreated patients in ZUMA-1 would have minimal impact on the OS for the axi-cel arm".* The ERG notes that the [redacted] response rate reported in patients

retreated with axi-cel appears markedly higher than the pooled response rate reported in SCHOLAR-1 of 20% (CR, 3%; PR, 17%) among primary refractory patients and 34% (CR, 15%; PR, 19%) among patients who progressed ≤12 months post-ASCT. Although only a small number of patients were retreated with axi-cel, the ERG considers that this leads to a potentially positive bias in the subsequent OS data, compared to that which would be expected if retreatment is not permitted in clinical practice.

For the second issue, and given the uncertainty surrounding the extrapolation of OS more generally, the ERG considers that a plausible explanation for the differences could be the more limited time at risk for mortality (i.e. follow up for survival may not be sufficient to capture the mortality of patients experiencing a late progression) and that with longer follow-up the cure fraction for OS for axi-cel may converge towards the cure fraction for PFS. The implications of this are explored by the ERG in Section 6.

Best supportive care

PFS data was not collected in SCHOLAR-1. In the company's base-case analysis, BSC PFS was modelled by assuming that the ratio between the extrapolated OS and PFS of axi-cel can be directly applied to the extrapolated BSC OS to estimate BSC PFS. Two alternative assumptions were also evaluated using scenario analysis: (i) PFS=0, i.e. all patients in BSC enter the model via the 'Post-progression' state; and (ii) PFS is the same as OS, i.e. all time alive in the model is spent in 'Pre-progression'.

The company did not provide a rationale to the approach used to model BSC PFS other than it being necessary due to lack of PFS data in SCHOLAR-1. The scenarios tested correspond to the two extremes concerning the timing of disease progression; immediately at the time point of model entry or never. While these approaches are helpful in determining the potential limits of the ICER to relatively extreme assumptions, neither is based on a clear clinical rationale. Furthermore, it is possible that the relationship between PFS and OS on BSC is different from that for axi-cel, given the different mechanisms of action of the two treatments.

The ERG notes that an alternative modelling approach for estimating PFS for BSC not considered in the company's submission and applied in the US study[17] would have been to assume the proportional relationship from a published PFS and overall OS for R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone) in the same disease state. The US study did not explicitly report what relationship was subsequently assumed and so the ERG has not been able to explore this issue further. While the ERG highlights the assumption made by the company is subject to uncertainty, the ERG does not consider this to be a major driver of the ICER and that this assumptions appears less critical than the uncertainties expressed in the previous section regarding the disconnect between the modelling

approaches for PFS and OS applied for axi-cel and the separate structural 'cure' assumption imposed at 2-years.

4.2.6.4 Adverse events

The company's decision model only incorporates adverse events for the axi-cel treatment due to the lack of data reported in SCHOLAR-1. The company considered this approach to be conservative towards axi-cel.

The adverse event rates for axi-cel were sourced from an earlier data cut-off (January 2017) of the Phase-2 ZUMA-1 trial (n=101). The CS did not justify the use of this subset of ZUMA-1, rather than using the population from which OS and PFS were estimated (n=108). All adverse events included in the model were Grade 3 or higher, occurring in 10% or more of subjects in ZUMA-1. The submission considered treatment adverse events associated with conditioning therapy and axi-cel infusion. Adverse events associated with leukapheresis were not included, as none of the grade 3 and higher had an incidence over 10%. The ERG notes that the 10% incidence cut-off for adverse events inclusion was not justified and appears to be largely arbitrary. The previous US study used a 5% incidence cut-off but also included adverse events for both BSC and axi-cel.[17]

After response to clarification questions, the company revised the model to also include grade 1-2 hypogammaglobulinemia, as this adverse event requires treatment associated with potentially significant resource use consumption. The model was also updated to reflect the costs of treatment of CRS with tocilizumab, as this was not restricted to grade 3-4 events in ZUMA-1.

4.2.7 Health related quality of life

The main source of utility estimates was the safety management cohort from ZUMA-1 (n=34), which collected EQ-5D-5L from trial participants. The company also undertook a separate systematic literature search and review of utility studies which reported other relevant health-state values.

4.2.7.1 Systematic review of utilities and HRQoL

The CS describes the search strategies used to identify relevant studies of utility values/HRQoL for the treatment of adult patients with R/R DLBCL. The search strategies were briefly described in the main body of the submission and full details were provided in Appendix H of the CS.

The electronic databases used for the HRQoL review were reported as MEDLINE, MEDLINE In Process, EMBASE, EconLit, and the Cochrane Library (including HTAD and National Health Service Economic Evaluations database NHS-EED) and were searched on 7 September 2017. Additional searches of conference websites from the last two years were also searched. The search strategies used

in MEDLINE, Embase, the Cochrane Library and EconLIT are fully reproduced in the CS (Appendix H). Although the company states that "*the same literature search strategy, in terms of the data sources investigated, was performed as was done for the SLR of published cost-effectiveness studies"*, the ERG notes that the search strategy was modified to fit the requirements of each review.

The systematic search identified one publication, and three more were identified from the cost-effectiveness review, corresponding to three unique studies. The characteristics and results of the included studies are summarised in tabular form (Table 41, CS). The company did not apply any of the utility estimates from the identified studies in the model, nor compare them to the utility values sourced from ZUMA-1. No justification was provided for this. Utility estimates sourced from a previous NICE TA,[3] which was not one of the identified studies, were applied in a scenario analysis.

4.2.7.2 *Health state utilities*

HRQoL is reflected in the company's model by assigning utility estimates to each of the three health states. Base-case estimates for the 'Pre-progression and 'Post-progression' health states were derived from EQ-5D data collected within the safety management cohort from ZUMA-1, and no differences in health state utilities were assumed by treatment group. Since the single arm trial collected EQ-5D-5L, a crosswalk algorithm was applied to convert estimates to EQ-5D-3L. The company applied alternative utility estimates sourced from NICE TA306 in a scenario analysis.

Table 14 provides a summary of the utility values used within the model. The utility estimates applied in the base-case were broadly similar to those used in the scenario analysis, which correspond to those of patients with renal cell carcinoma and receiving 2nd line treatment in TA306.

Table 14 Summary of health state utility values applied in the model

State	Base-case Mean utility (SE)	Scenario analysis Mean utility (95% CI)	Source/Justification
Pre-progression	[redacted]	0.76 (0.70-0.82)	Base-case: ZUMA-1 safety management cohort. EQ-5D data in the same population. Scenario analysis: Utility estimates from TA306[3] are considered to be more plausible than those identified in the systematic literature review.
Post-progression	[redacted]	0.68 (0.60-0.76)	
Pre-progression after 2 years in health state	General population	10% percentage decrement to general population utility	Base-case: To reflect the assumption that long-term survivors have the same mortality as the general population, as per Maurer et al (2014)[22]

The safety management cohort of ZUMA-1, the only source of EQ-5D data in the relevant population, has a small sample size, and it is not clear from the submission how data was used to estimate the health state utilities. The 'Post-progression' estimate was informed by very few observations ([redacted]), and only [redacted] observations inform the 'Pre-progression' state. The company also does not explain the rationale for selecting the ZUMA-1 safety management cohort. Compared to the Phase II ZUMA-1 population the safety management cohort was generally younger (median age [redacted] vs 58 years), and had a higher proportion of: (i) males ([redacted]% vs 33%), (ii) patients at an earlier stage of disease (disease stage I-II [redacted] vs 15%) and (iii) patients with better prognostic (IPI 0-1 [redacted] vs 27%).

Given the small sample size informing the 'Post-progression' estimate and that this is likely to have been measured close to the progression event, the subsequent estimate may not be reflective of the entire period of progressive disease. However, the ERG considers that the uncertainty surrounding the utility of progressive disease is unlikely to be a key driver of cost-effectiveness, given that the majority of patients who experience progression will die within a relatively short time frame. The majority of QALY gains is the model are driven by QALYs accrued in the extrapolation of OS and the HRQoL of 'cured' patients. In particular, the uncertainty surrounding the assumption that patients in 'Pre-progression' state revert to the same HRQoL of the general population at 2-years appears a more critical area of uncertainty.

As discussed previously, there appears to be only limited evidence to support cure at two years post-treatment, and excess mortality appears to persist for up to five years post-treatment.[23] Importantly, if the survival of 'cured' patients remains affected by excess mortality this is also likely to be reflected in lower HRQoL than that of the general population for the period where excess mortality applies. The company presents a scenario analysis whereby after 2 years patients in 'Pre-progression' experience the utility of the general population affected by an arbitrary multiplier of 0.90 (reduction of 10% from the population norm) resulting in an ICER of [redacted] (9.1% increase from company's base-case).

The ERG explores alternative assumptions on HRQoL of long-term survivors in Section 6.

4.2.7.3 Adverse events disutilities

Table 15 summarises the data applied in the model to estimate disutility from adverse events associated with conditioning chemotherapy and axi-cel infusion. Utility decrements associated with adverse events were applied as a one-off 0.03 QALY decrement in the first cycle of the model for axi-cel patients.

The duration of adverse events was stated to have been calculated using patient-level data from ZUMA-1. The majority of utility decrements values were sourced from NICE TA306. The disutility assumed for a CRS was assumed to reduce a patient's utility to zero for the duration of the adverse event, in line with the York report.[18] The CS stated that for adverse events for which no utility estimates were identified, a disutility equal to the maximum of the identified non-CRS AE disutilities was assumed, as per NICE TA306.[3]

Details on the estimation of the duration of adverse events were not provided in the CS. The only reference provided was in the Excel model which referred to data on file. Hence, it is unclear to the ERG whether the durations were derived from the earlier data cut-off (January 2017) of the Phase-2 ZUMA-1 trial (n=101) or the combined Phase-1 and -2 population (n=108). The ERG examined the clinical study report for further information of the duration of adverse events, with a particular focus on CRS events. The ERG noted a discrepancy between the duration of 4 days assumed in the model and the median time to resolution of symptoms of [redacted] days for CRS reported in the clinical study report.

The assumption that in the absence of other published estimates, the disutility associated with encephalopathy, hypophosphatemia, hypotension, leukopenia, decreased lymphocyte count, decreased neutrophil count and decreased white blood cell count is equal to the maximum of the identified non-CRS adverse events disutilities lacks a clinical rationale. Similarly, the inclusion of adverse events that had an incidence equal or greater than 10% is also arbitrary. However, the disutility associated with adverse events is not considered by the ERG to be an important driver of cost-effectiveness. Alternative assumptions would potentially have a limited impact on the cost-effectiveness estimates. Furthermore, the ERG notes that the exclusion of adverse events for BSC appears potentially conservative.

Table 15 Summary of adverse events data applied in the model to estimate disutilities. AE, adverse events; CSR, cytokine release syndrome.

Adverse events Grade 3-4	**Proportion on axi-cel infusion %**	**Proportion on conditioning chemotherapy %**	**Proportion in the model %**	**Duration (days)**	**Utility decrement**	**Source of utility estimate**
Anaemia	0	41	41	14	-0.12	Swinburn et al., 2010, as per TA306 [3]
CRS	13	0	13	4	[redacted]	Assumed to reduce utility of 'Pre-progression' state to zero, state, as per York study [18]
Neutropenia	13	35	48	47	-0.09	Nafees et al., 2008, as per TA306 [3]
Platelet count decreased	0	13	13	50	-0.11	Tolley et al., 2013, as per TA306 [3]
Thrombocytopenia	0	23	23	63	-0.11	Tolley et al., 2013, as per TA306[3]
Pyrexia	12	0	12	2	-0.11	Beusterien et al., 2010, as per TA306[3]
Febrile neutropenia	17	29	46	6	-0.15	Lloyd et al., 2006, as per TA306[3]
Encephalopathy	21		21	9	-0.15	Assumed equal to the maximum of other, non-CRS AE disutilities in the absence of other data, as per TA306[3]
Hypophosphatemia	0	11	11	16	-0.15	
Hypotension	11	0	11	5	-0.15	
Leukopenia	0	15	15	21	-0.15	
Lymphocyte count decreased	0	19	19	64	-0.15	
Neutrophil count decreased	0	28	28	17	-0.15	
White blood cell count decreased	0	27	27	40	-0.15	

4.2.8 Resources and costs

The CS provided a detailed description of resource use and cost. These included: drug acquisition costs, drug administration costs, monitoring costs, costs related to the health states and adverse events, training costs and the cost of subsequent treatments (e.g. allogeneic SCT).

4.2.8.1 Systematic review of resource use and costs

The company conducted a systematic review of the literature to identify published studies on cost and healthcare resource use data in adult patients with R/R DLBCL. The systematic literature review was only referred to in the main body of the CS and full details were provided in Appendix I.

The electronic databases searched were: MEDLINE, MEDLINE In Process, EMBASE, EconLit, and the Cochrane Library (including HTAD and NHS-EED). These were searched on 7 September 2017. HTA websites and conference proceedings from the last two years were also searched.

The search identified two publications, and one more was identified from the utilities review, corresponding to two unique studies. The characteristics and results of the included studies were presented in Appendix I (Tables 41 and 42), accompanied by a study quality assessment in Table 43 in the CS. The CS did not discuss the relevance of the studies and why this evidence was not incorporated in the model. The estimates of the majority of resource use in the model were informed by NICE TA 306 and the York study.

4.2.8.2 Axi-cel treatment costs

The cost of axi-cel treatment included the costs of the following elements: leukapheresis, conditioning chemotherapy, axi-cel acquisition, cell infusion with axi-cel, monitoring and retreatment. These costs were assumed to be incurred in the first model cycle.

Table 16 summarises the costs per patient and the sources and associated assumptions.

Table 16 Summary of axi-cel treatment costs applied in the model

Element of cost	**Cost**	**Adjusted cost in the model**	**Source/Assumption**
Leukapheresis	£1,284.77	£1,415.63	NHS reference costs 2015/16, weighted average of all HRGs for stem cell and bone marrow harvest (currency codes SA34Z, SA18Z), as per York study. Adjusted cost estimated using a multiplier of 1.102 applied to reflect the 11 patients who underwent leukapheresis, but not axi-cel infusion
Conditioning chemotherapy	Hospital admission £5,062.63 Chemotherapy acquisition £208	£5,856.77	Hospital admission: • NHS reference costs 2015/16, weighted average of non-elective long-stay HRGs for malignant lymphoma (currency codes SA31A-F), as per York report Chemotherapy acquisition: • 3 infusions of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 • Source of unit costs: eMIT • BSA percentile from Phase 2 ZUMA-1(n=101), used to estimate dose and vial combination. Assumed drug wastage Adjusted cost estimates using a multiplier of 1.019 to reflect the 2 patients who underwent conditioning therapy, but not axi-cel infusion
Acquisition of axi-cel	[redacted]	Not adjusted	Company submission Assumes that cost of the drug will only be reimbursed if axi-cel is administered to the patient, so is only applied to patients who received axi-cel (no multiplier).
Cell infusion and monitoring	£6,760.37	Not adjusted	NHS reference costs 2015/16, weighted average of elective inpatient HRGs for malignant lymphoma (currency codes SA31A-F) and NHS reference costs 2015/16, weighted average of elective excess inpatient bed days HRGs for malignant lymphoma (currency codes SA31A-F) Assumed to incur hospitalisation for 17.6 days. The average elective inpatient stay for malignant lymphoma was 10.4 days. The remaining 7.2 days were costed as excess bed days

Retreatment	£12,031.47	£1,114.02	9.25% of the unadjusted costs of conditioning chemotherapy and cell infusion to reflect the add on cost of the 10 patients who underwent retreatment
Training	£83	Not adjusted	NHS reference costs 2015/16, medical consultant time (£104) Assumes 2 days (16 hours) of healthcare professional time per centre, 10 patients per centre and 2 years before retraining.
Total cost in the model	[redacted]		
Key: BSA, body surface area; eMIT, electronic market information tool; HRGs, healthcare resource groups; NA, not applicable			

Since the model population only includes patients that received at least one dose of axi-cel (mITT, n=108), the costs per patient were adjusted by applying multipliers reflecting the costs incurred by the patients who only underwent the preparation procedures (leukapheresis and conditioning therapy). The costs of retreatment were included as an add-on cost in the model's first cycle, to reflect the 10 patients in ZUMA-1 who underwent a second infusion after disease progression. The company justified the exclusion of the costs of leukapheresis and axi-cel acquisition costs from retreatment costs by stating that the initial manufacturing process for axi-cel produces sufficient cell product for up to two treatments.

The costs associated with axi-cel treatment appear to be generally well implemented within the decision model. The ERG identified two specific areas of uncertainty. Firstly, an adjustment is proposed to account for the costs of conditioning chemotherapy and cell infusion (excluding the acquisition cost of axi-cel) to reflect the additional cost of the 10 patients who underwent retreatment with axi-cel in ZUMA-1. The ERG notes that if the marketing authorisation stipulates that patients are not permitted to receive a subsequent infusion with axi-cel, then the relevant costs that should have been applied would appear to be the treatment costs that they would receive in practice (i.e. the acquisition and administration for salvage therapy with BSC). The ERG does not consider that this is likely to constitute an important source of bias since the costs of conditioning chemotherapy and the extended hospitalisation for infusion result in similar total management costs to those assumed for the acquisition and (shorter) administration assumed for BSC.

The second area of uncertainty concerns the assumptions associated with the costs of training. The CS assumes that training would require 16 hours of consultant time per centre infusing twenty patients every two years. In the US, where axi-cel is commercially available, all physicians, mid-level providers, pharmacists and nurses who will interact with CAR T-cell patients must undergo FDA mandated training as part of a Risk Evaluation Mitigation Strategy (REMS)[26]. REMS aims to reduce the risks associated with axi-cel related adverse events, particularly CRS and neurological events. The company states in response to clarification questions that "*A Risk Management Plan (RMP) is likely to be mandated by regulatory authorities, similar to the REMS required by FDA in the US*". The company also states that it will help train staff "*in all specialties likely to be involved in the patient management on the identification and management of axi-cel related AEs*".

The ERG considers that the cost of training included in the model appears unlikely to reflect the level of training required by the RMP. Importantly, the effectiveness and safety of axi-cel is dependent on the provision of appropriate training.[27] The ERG explores alternative assumptions on the cost of training in Section 6.

4.2.8.3 BSC treatment costs

The costs of BSC treatment included chemotherapy drug acquisition and administration costs. BSC represented as a blended comparator, comprised of equal proportions of four different regimens: GEM, GEM-P, RGCVP and RVP.

Table 17 presents a summary of the acquisition costs of each individual chemotherapy regimen included in the blended BSC comparator.

Table 17 Summary of acquisition costs of the chemotherapy regimens composing BSC

Regimen	Drug	Cost per day	Chemotherapy cycles			Cost per month
			Days/cycle	Duration	Number/course	
GEM	Gemcitabine[a]	£17.87	3	28 days	3	£90
	Methylprednisolone[b]	£7.24	5			
GEM-P	Gemcitabine[a]	£17.87	3	28 days	3	£109
	Methylprednisolone[b]	£7.24	5			
	Cisplatin[a]	£18.90	1			
RGCVP	Rituximab[c]	£2,080.50	1	21 days	6	£2,156
	Gemcitabine[a]	£17.87	2			
	Cyclophosphamide[d]	£28.08	1			
	Vincristine[e]	£10.13	1			
	Prednisolone[f]	£0.29	5			
RVP	Rituximab[c]	£2,080.50	1	28 days	3	£2,139
	Vinblastine[g]	£28.97	2			
	Prednisolone[f]	£0.29	1			
[a]1000 mg/m^2/day, [b]1000 mg/day, [c]375 mg/m^2/day, [d]750 mg/m^2/day, [e]1.4 mg/m^2/day, [f]100mg/day, [g]6 mg/m^2/day						

Table 18 summarises the average acquisition and administration costs of the blended comparator.

Table 18 Summary of BSC treatment costs applied in the model

Element of cost	Cost	Source/Assumption
Drug acquisition	Month 1: £1,415 Month 2: £1,415 Month 3: £1,264 Month 4: £781 Month 5: £111	Drug unit costs from eMIT and MIMS BSA percentiles from Phase 2 ZUMA-1(n=101), used to estimate dose and vial combination. Assumed drug wastage Number of treatment cycles and days per cycle for drug of each regimen were informed by UK hospital chemotherapy protocols [28, 29]. Costs applied to all alive patients in the cycle ('Pre-progression' and 'Post-progression')
Administration	Hospital admission £5,062.63	NHS reference costs 2015/16, weighted average of non-elective long-stay HRGs for malignant lymphoma (currency codes SA31A-F), as per York report [18]. As for administration of conditioning therapy for axi-cel. One-off cost in first cycle of the model.
Total cost in model	[redacted]	
Key: BSA, body surface area; eMIT, electronic market information tool; MIMS, monthly index of medical specialties; HRGs, healthcare resource groups; NA, not applicable.		

The ERG acknowledges the rationale for using a blended comparator since it is not clear that one specific regimen would be displaced if axi-cel was to be recommended. However, the ERG also notes that there are marked differences between the costs assumed for rituximab and non-rituximab based regimens. The current blend assumes an equal proportion of patients receive each of the 4 individual regimens. Rather than assuming an equal proportion, the ERG considers that it would have been more appropriate to base the blend on the proportion of patients receiving rituximab and non-rituximab based regimens in clinical practice.

The ERG also notes that the CS assumes that the salvage chemotherapies regimens will be administered in an inpatient setting. While it seems reasonable to assume that axi-cel conditioning chemotherapy requires hospital admission, given that the treatment is likely to be delivered only in specialised centres to where patients will have to travel, the same is not anticipated for conventional chemotherapy. The ERG reports sensitivity analyses on the impact of delivering BSC on an outpatient setting in Section 6.

4.2.8.4 Health state costs

In addition to the acquisition and administration costs assumed for axi-cel and BSC, the model also included resource and cost estimates for the pre- progression and progression health states. The same health state costs were assumed for each treatment and hence differences between treatments are determined by differences in the proportion of patients residing in each state over time.

Medical resource use and associated costs included the following categories: (i) professional and social services, (ii) health care professionals, (iii) treatment follow-up, and (iv) hospital resource use. Resource use estimates for all categories are based on a previous NICE appraisal in the same disease area [3] with estimates of resource use estimated based on a survey of three key opinion leaders.

Table 19 summarises the health state costs included in the decision model.

Table 19 Summary of health state costs applied in the model

	Resource use elements	Cost per cycle		Unit costs	Assumptions
		Pre-progression	Post-progression		
Professional and social services	Residential care Day care Home care Hospice	£406.54	£607.89	PSSRU 2016 National Audit Office End of Life Care	Resource use sourced from TA306[3], which was informed by a survey of three key opinion leaders. Since PFS was modelled in two separate health states in TA306, "PFS on 3rd (or 4th) line treatment" and 'PFS, discontinued 3rd or 4th line treatment', the company averaged resource use across this health states to derive the costs for the 'Pre-progression' state. Resource use in 'Post-progression is assumed to be the same as for the 'Progressed disease' state of TA306. 'Pre-progression' health state costs are assumed to be incurred for the first two years only.
Healthcare professionals	Oncologist Haematologist Radiologist Nurse Palliative care team Specialist nurse GP District nurse CT scan	£571.28	£1,255.90	NHS reference costs 2015/16 PSSRU 2016	
Treatment follow up	Full blood counts LDH Liver function Renal function Immunoglobulin Calcium phosphate	£29.60	£8.58	NHS reference costs 2015/16	
Hospital resource use	Inpatient days Junior haematologist visits Senior haematologist visits Radiologist visits Specialist nurse visits Nurse visits Oncologist visits GP visits	£160.38	£134.03	NHS reference costs 2015/16 PSSRU 2016	
Total cost per cycle		£1,168	£2,006		

The company's base-case assumes that patients remaining in 'Pre-progression' for two years are in long-term remission, and no longer incur the costs of medical resource use after this period. A similar assumption was also taken for the 'Pre-progression' health state with the utility of patients in the state shifting to that of the general population after the first two years in 'Pre-progression'. As highlighted in section 4.2.7.2, these assumptions on the costs and HRQoL of PFS patients in the model appear to be overly optimistic and lacking robust evidence to support them.

The CS notes that the population addressed by pixantrone differs to that of axi-cel, and that the estimates were only based on the opinions of three clinicians. The CS also notes that estimates for PFS in the pixantrone submission were reported separately according to whether patients were actively receiving treatments in the PFS health state or had discontinued treatment. Since discontinuation was not modelled in the BSC arm, the model assumed a crude average of the PFS costs reported in the pixantrone submission.

The CS stated that the uncertainties arising due to differences in populations, the small number of clinicians surveyed and the use of a crude average were considered in separate scenarios, specifically:

1. Two scenario analyses where the costs of medical resource use were doubled and halved to explore the uncertainty associated with using resource use estimates sourced from a different population[3];
2. Scenario analyses where the time point at which costs in 'Pre-progression' are assumed to return to zero are varied.

However, none of these scenario analyses results were subsequently reported in the CS. The ERG considers the first set of analyses to be of limited interest, as these simply explore how responsive the cost-effectiveness estimates are to extreme variations in the parameter estimates. The second set of analyses aims to explore the impact of varying the time point for cure, which is one of the elements of uncertainty surrounding the cure assumption (see section 4.2.6.2). Alternative assumptions on the time point for cure are likely to have significant impact on cost-effectiveness, as the survival benefits in the model are being driven by the extrapolation for long-term survivors. It would be more informative, however, to vary the time point for cure according to explicit assumptions on cure, rather than across an arbitrary range of time points. The ERG explores alternative assumptions on the costs of long-term survivors in the context of the cure assumption in Section 6.

4.2.8.5 Adverse events costs

AE costs for Grade 3-4 events were only included for the axi-cel treatment arm. These costs were applied as a one-off mean cost (£358) in the first cycle of the model for axi-cel patients.

The company states that each of the grade 3-4 AEs with incidence ≥10% in ZUMA-1, except CRS and B-cell aplasia, were assumed to require an extension of hospitalisation by 1 day. An assumption of one day (as opposed to the entire AE duration) was used to avoid potential double counting, as some aspects of these may already be included in the hospitalisation costs used for administration and monitoring. However, the ERG notes that the single excess bed day cost for 1 day does not appear to have been included in the company model. Assuming an excess bed day cost of £473 as for axi-cel infusion (see section 5.2.7.3) and the proportions of adverse events reported in Table 15, the resulting mean cost omitted from the model amounts to £1,332.

The ERG also identified a potential inconsistency between the approach for adverse event costs stated in the CS and the same approach summarised in their response to the points for clarification (Table 11 p13, company response document). In their response document, the company stated that all AE costs were assumed to be covered in the costs assumed for hospitalisation and administration of axi-cel, except for CRS - where tocilizumab and intensive care unit (ICU) stay costs were applied. Hence, the ERG considers that the company may have revised their assumption during the preparation of the submission but did not alter the accompanying text. Given that the costs of axi-cel administration are based on the actual length of stay reported for ZUMA-1 patients, the ERG considers that the costs of any extension to the hospitalisation period due to Grade 3-4 AEs (with the exception of those requiring ICU stay) should be captured within the costs of administration. Hence, although some uncertainty exists regarding the company's intentions, the ERG considers that it was probably reasonable not to assume additional excess bed day costs for other AEs.

The costs of B-cell aplasia were not included in the initial submission by the company because the primary manifestation, hypogammaglobulinemia, did not present as a Grade 3-4 AE in any patients in ZUMA-1. Following points of clarification, the company updated the model to include the cost of IVIG treatment and administration for the [redacted] of patients in ZUMA-1 who experienced Grade 1 or 2 hypogammaglobulinemia and subsequently received IVIG. A weighted average monthly cost of IVIG treatment of £204 for 12 months was assumed, based on the cost of a monthly intravenous administration (£1,257), an acquisition cost of IVIG of £19 per 0.4g dose and an estimate of the required dose (0.5g/kg; mean weight of [redacted] kg from ZUMA-1).

The cost of CRS was based on an assumption that patients with Grade 3-4 CRS required management with cytokine inhibitor drugs and an intensive care unit (ICU) hospitalisation. The cost of cytokine inhibitor drugs (£1,392) was derived from NHS reference costs (currency code XD31Z, cytokine inhibitor drugs, band 1). The cost of an ICU hospitalisation was calculated as the weighted average of HRGs for non-specific, general adult critical care in the NHS national schedule of reference costs (£1,363). Following points of clarification, the company updated the model to include the cost of

cytokine inhibitor drugs for all patients (all AE grades) that received these in ZUMA-1 ([redacted] vs [redacted] Grade 3-4 only).

The unit costs and resource use of managing CRS and B-cell aplasia are summarised in Table 20 for both the initial and updated company's model (revised after clarification questions).

Table 20 Summary of adverse event costs

Adverse events	Resource use	CS model	Updated model	Unit cost	Source of unit cost
CRS	% tocilizumab	[redacted]	[redacted]	£1,257	NHS Reference Costs 2015/16, Cost of cytokine inhibitor drug (currency code: XD31Z)
	% grade 3-4	[redacted]	[redacted]	£1,363	NHS Reference Costs 2015/16, Weighted average of HRGs for adult critical care (currency codes: XC01-7Z)
B-cell aplasia	% IVIG	0	[redacted]	£19 £1257 per infusion	Cost per 0.4 g dose from TA359 NHS Reference Costs 2016/17, Cost of immunoglobulins band 1 (currency code: XD34Z)

The ERG considers that the inclusion of treatment with tocilizumab and IVIG in the updated company's model is an important correction. However, concerns remain that important elements of costs may not been fully captured. The unit costs used for critical care (£1,363) from NHS reference costs[30] are assumed in the CS to represent the cost of an ICU hospitalisation. However, the ERG understands that the NHS reference costs for critical care represent a cost per diem as opposed to the average ICU hospitalisation period. Hence, the ERG considers that the unit cost should have been applied to the duration of the Grade 3-4 CRS AE event. The ERG also highlights two important areas of uncertainty in the CS:

1. The ERG previously noted a discrepancy between the duration of 4 days assumed in the model for the mean duration of a CRS AE for utility assumptions and the median time to resolution of symptoms of [redacted] days for CRS reported in the clinical study report.
2. Given concerns regarding CRS, the ERG considers that it is possible that the provision of axi-cel in specialist centres may require an ICU bed to be available during the period a patient is considered to be at risk of CRS, regardless of whether they then actually experience a serious AE. This would have broader infrastructure and resource implications for the NHS than reflected in the CS. As part of the response to points for clarification (p41), the company

states that "*based on trial experience a minority require ITU admission*, *retaining an empty bed available for each and every patient to be treated with CAR T therapy is not required*".

The ERG considers that these uncertainties have not been fully addressed in the CS, and explores alternative assumptions in Section 6.

4.2.8.6 Stem cell transplant costs

The cost of SCT was included for both treatment groups. The proportion of patients undergoing SCT was sourced from ZUMA-1 for axi-cel (~[redacted]) and from SCHOLAR-1 ([redacted]) for BSC. For the scenario analysis where the BSC effectiveness data corresponded to different subsets/adjustments of SCHOLAR-1 data, the proportion of patients receiving stem cell transplant was adjusted accordingly. The company's base-case assumed that patients who received SCT post-treatment all underwent allogeneic SCT.

The cost of allogeneic SCT includes two elements: (i) the initial cost of transplant (cost of the procedure and associated hospitalisation) and (ii) the cost of long-term care post-transplant. The unit cost for the initial costs of transplant (£34,783.96) is the weighted average (by frequency of HRG) of all adult allogeneic transplantations from NHS reference costs 2015/16[30]. The costs of long-term care refer to the period between discharge and two years after transplant and sourced from the UK Stem Cell Strategy Oversight Committee Report[31].

Table 21 summarises the costs of follow-up care for allogeneic SCT from discharge. A weighted cost (£40,601) per transplant patient was estimated for each period based on the proportion of surviving patients.

Table 21 Cost of allogeneic SCT long-term care by follow-up period

Follow-up period	Average cost per living patient	% alive	Weighted costs per transplant patient	Inflated cost per transplant patient*
Discharge to 6 months after transplant	£28,390	90	£25,551	£26,414
6 to 12 months after transplant	£19,502	48	£9,361	£9,677
12 to 24 months after transplant	£14,073	31	£4,363	£4,510
Cost applied in the model				£40,601
*2015/16 price year				

The total cost of transplant in the CS (initial and follow-up costs) was £75,385, applied as a one-off cost to the first-cycle in the model. The ERG notes that while the application of a one-off cost simplifies the inclusion of the cost in the model, the follow-up costs for each period should also have also been discounted. This is addressed in section 6.

As discussed in section 4.2.2., there is uncertainty surrounding the actual number of patients in ZUMA-1 who received a SCT. Although fewer than [redacted] of axi-cel patients are assumed in the model to undergo SCT reflecting the number of patients in response to axi-cel in ZUMA-1 (CS, p140), at least [redacted] patients who were retreated with axi-cel underwent SCT (CSR, p133). The ERG considers that it is unclear how many patients in ZUMA-1 received a SCT post-treatment with axi-cel. Given that in the ERG additional analyses, the axi-cel OS estimates are adjusted so that the cure fractions in OS and PFS are consistent, the potential survival benefits of retreatment with axi-cel are likely to not be reflected on the model outcomes (see section 4.2.6.3). Therefore, the ERG does not consider it appropriate to correct the model further by including additional costs of patients who were retreated with axi-cel and received SCT.

Another issue identified in section 4.2.2, is that patients on BSC who received SCT post-treatment underwent ASCT[13]. In the model, these patients are assumed to receive allogeneic SCT, which is more costly than ASCT[32]. In section 6, the ERG addresses this issue in a scenario analysis where it is assumed that all BSC patients who received SCT underwent ASCT as in SCHOLAR-1.

The ERG also notes that while the cost of SCT was considered, the potential impact of SCT on HRQoL was not formally captured. Given the higher rate of SCT assumed for BSC, the ERG considers that the approach used by the company is potentially conservative towards axi-cel.

4.2.9 Discounting

Both costs and benefits were discounted at an annual rate of 3.5%, as per the NICE reference case. The CS also presents a scenario analysis using a discount rate of 1.5% per annum for costs and benefits. The company highlights that it might be appropriate for the NICE appraisal committee to consider a lower discount rate, given the potential for long-term benefits from the 'cured' proportion of patient who receive axi-cel and the high upfront costs of the technology.

The NICE methods guideline states that a non-reference-case discount rate for costs and outcomes may be considered when a treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)[19]. In these cases, a discount rate of 1.5% may be considered by the Appraisal

Committee, provided that the evidence base supporting cure is robust and that the technology does not commit the NHS to significant irrecoverable costs.

As highlighted in section 4.2.6.2, the ERG considers that the evidence submitted is not sufficiently mature to robustly demonstrate that cure occurs, and the duration of health benefits is driven by a highly uncertain extrapolation of survival estimates. Furthermore, the sustainability of the health benefit over at least 30 years appears unlikely given that the age of the population who is likely to receive this treatment in this specific indication.

The Appraisal Committee will also have to consider if the NHS investment required to implement this technology is of a magnitude that is constitutes an irrecoverable cost. In the US, CAR T-cell therapies can only be provided by specialised centres certified by the manufacturers[26]. The company assumes that future CAR T delivery centres commissioned by NHS England and validated by Kite are likely to be large allogeneic-SCT centres experienced in apheresis, cell processing and tracking of cells for transplantation. It is unknown whether CAR T-cell delivery can be incorporated into existing centres or whether additional capacity will have to be built into the NHS with associated infrastructure costs.

4.2.10 Cost effectiveness results

4.2.10.1 Base-case results

The base-case results are summarised in Table 22.

Table 22 Company base-case deterministic cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

CS, Table 60 – p147

Axi-cel was more costly (mean incremental cost difference of [redacted]) but also more effective (mean incremental difference of [redacted] LYG and [redacted] QALYs) compared with BSC. The resulting deterministic ICER for axi-cel vs BSC was [redacted] per QALY gained.

The majority of QALY gains for axi-cel were generated within the 'Progression-free' state as shown in Table 23. Graphical traces are reported in the CS (Figure 33 and 34, p148 CS). The ERG notes that the high % absolute increment for this state is driven by the cure assumptions applied in the model.

Table 23 Summary of QALY gains by health state

Health state	QALY Axi-cel	QALY BSC	Increment	Absolute increment	% absolute increment
Progression-free	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE decrements	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; BSC, best supportive care; QALY, quality-adjusted life year

CS appendix J, Table 46 – p82

A summary of disaggregated costs is shown in Table 24. A similar table was reported in the CS appendices (Table 47, p82). However, the ERG identified a number of reporting errors in the table in the CS. These errors included incorrect labelling of the intervention and comparator columns, differences between the individual cost items reported in the table and those reported in the Excel model and differences in total costs compared to those presented in the main ICER tables.

On further examination of the Excel model, the ERG also identified an error in discounting formula applied to one individual item (axi-cel costs). The error in the discounting formula only affected the reporting of the individual item and not the total costs estimates informing the base-case analysis results. The results presented in Table 24 are based on the ERG's revised estimates, correcting the formula.

Table 24 Summary of disaggregated costs

Item	Cost intervention (axi-cel)	Cost comparator (BSC)	Increment	Absolute increment	% absolute increment
Axi-cel costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allogeneic SCT costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Training costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; BSC, best supportive care; QALY, quality-adjusted life year; SCT, stem cell transplant

The summary of disaggregated costs demonstrates the majority of the difference in total costs is due to the higher acquisition costs of axi-cel. The higher acquisition costs of axi-cel and partially offset by reductions in the costs of salvage chemotherapy and a lower rate of SCT. However, the potential cost offsets are limited due to a similar increase in medical resource use cost. The higher medical resource cost for axi-cel is driven by the higher proportion of patients surviving over the initial 24 month period during which health state costs for pre- and post-progression are applied.

4.2.10.2 Sensitivity analyses

Deterministic sensitivity analysis

The CS presented a series of one-way deterministic sensitivity analyses to assess the impact of varying key model input parameters on the net monetary benefit (NMB) at a willingness to pay threshold of £50,000. The range over which parameters were varied was not stated. The one-way deterministic sensitivity analysis was conducted on a subset of model parameters but their selection was not justified.

Results are presented in Figure 16, a tornado diagram summarising the 10 most influential parameters reported by the company. Given that cost-effectiveness results in the submission are presented in terms of ICERs, the ERG updated the tornado diagram to output the ICER of axi-cel vs BSC (from the company's model). Results are shown in Figure 16.

Figure 16 Company's deterministic sensitivity analyses results – ICER of axi-cel vs BSC (adapted from company model)

Key: AC, axi-cel; BSC, best supportive care; MCM, mixture cure model; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; SCT, stem cell transplant.

The one-way deterministic sensitivity analyses show that the base-case cost-effectiveness results appear most sensitive to the mean cure fraction (pi) used in the mixture cure model for modelling axi-cel OS with the ICER varying between [redacted] and [redacted] per additional QALY when the cure fraction decreases from 37% to 64%. The base-case results are also sensitive to changes in the constant of the standard parametric curves (Gompertz) fitted to axi-cel for PFS and OS for BSC. This is less intuitive, but the increase of a negative constant on Gompertz survival function implies that the risk of the event will decrease at a higher rate for the lower value of the parameter. For axi-cel PFS a lower value of the constant favours axi-cel, as it increases the time that axi-cel patients remain in PFS. For BSC OS, a lower value of the Gompertz constant, will increase survival on BSC and, thus reduce the survival benefit of axi-cel.

The company also conducts a number of scenario analyses to check the robustness of the model results to uncertainty relating to survival data, duration of time horizon, discount rate, and utility estimates. Scenario analyses results are summarised in Table 25.

Table 25 Company's scenario analyses results

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change base-case ICER
Base-case		[redacted]	[redacted]	[redacted]	0%
Time horizon = 10 years	44 years	[redacted]	[redacted]	[redacted]	107%
Time horizon = 20 years		[redacted]	[redacted]	[redacted]	25%

Discount rates = 1.5%	3.5%	[redacted]	[redacted]	[redacted]	-22%
Mixture cure model for BSC	PSM with single curves	[redacted]	[redacted]	[redacted]	7%
100% progression-free in BSC	Based on ZUMA-1 OS/PFS ratio	[redacted]	[redacted]	[redacted]	4%
100% progressed in BSC		[redacted]	[redacted]	[redacted]	-23%
Unadjusted, all	Unadjusted, excl. ECOG 2–4	[redacted]	[redacted]	[redacted]	0%
Unadjusted, excl. ECOG 2–4 and SCT		[redacted]	[redacted]	[redacted]	-10%
Propensity score adjusted		[redacted]	[redacted]	[redacted]	0%
Utility from literature (pixantrone)	ZUMA-1 safety population	[redacted]	[redacted]	[redacted]	-1%
AC PFS distribution: gamma	Gompertz	[redacted]	[redacted]	[redacted]	32%
BSC OS distribution: exponential	Gompertz	[redacted]	[redacted]	[redacted]	-21%
BSC OS distribution: gamma		[redacted]	[redacted]	[redacted]	-13%
BSC OS distribution: loglogistic		[redacted]	[redacted]	[redacted]	-20%
BSC OS distribution: lognormal		[redacted]	[redacted]	[redacted]	-18%
BSC OS distribution: Weibull		[redacted]	[redacted]	[redacted]	-19%
AC OS distribution (MCM): Gamma	Weibull	[redacted]	[redacted]	[redacted]	-3.5%
Multiplier for DLBCL/PMBCL/TFL patients in long-term remission (general population utility values): 0.9	1	[redacted]	[redacted]	[redacted]	9.1%
Multiplier for DLBCL/PMBCL/TFL patients in long-term remission (life tables): 1.1	1	[redacted]	[redacted]	[redacted]	1.7%
Key: AC, axi-cel; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; QALY, quality adjusted life year.					

Table 61 CS, p153

ICERs from the scenario analyses ranged between [redacted] (scenario where BSC patients were assumed to progress upon model entrance) and [redacted] per QALY (time horizon of 10 years). The key drivers of cost-effectiveness across the scenarios were:

1. Time Horizon

2. Discount rate
3. PFS for BSC and axi-cel
4. OS for BSC

The impact of these drivers relate to the extrapolation of treatment effectiveness, which the ERG considers relies on immature data and potentially optimistic structural assumptions. Shorter time horizons reduce the QALY gains of axi-cel compared to BSC, which are driven by the long-term survivors. Since the majority of the costs for axi-cel are incurred in the first cycle of the model, there will be fewer QALY gains from axi-cel to offset this. For a lower discount rate, future costs and benefits have a higher present value compared to the base-case assumption, which favours axi-cel again because the QALY gains are accrued steadily over a long time horizon due to the long-term survivors, but long-term costs are fairly small. The modelling of axi-cel PFS with a generalised gamma distribution (second best fitting) also increases the ICER, by reducing the time spent in PFS for patients receiving axi-cel (mean PFS reduces from [redacted] to [redacted] months). As this is the state where the majority of QALY gains are accrued for axi-cel, reduction of time on health state increases the ICER considerably.

The scenarios where alternative parametric assumptions on the OS of BSC all favour axi-cel, since the corresponding extrapolated survival curves all predict lower survival for BSC and, thus, increase the relative survival increase from treatment with axi-cel. However, these curves have a worse statistical and visual fit than the base-case assumption. The scenario assuming that patients in BSC are all in progressive disease upon model entrance also favours axi-cel, as 86% of QALY gains for BSC in the base-case are accrued in the 'Pre-progression' state. In this scenario, the relative gains from axi-cel compared to BSC increase considerably, lowering the ICER to [redacted] per additional QALY.

Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) where parameters were sampled probabilistically from distributions based on 10,000 simulations. No justification is presented as to why only a selection of parameters are not varied in the PSA. Furthermore, parameters such as the rates of adverse events and some elements of costs varied between an arbitrary range of 15% around the mean, and it is not clear whether such value ranges actually represent the true uncertainty around the given parameters.

The mean probabilistic ICER was [redacted] per QALY ICER which is marginally higher than that of the deterministic analysis, as shown in Table 26.

Table 26 Company base-case probabilistic cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	--	-	-
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

The company also presents the cost-effectiveness plane and acceptability curve (CS, Figure 35 and 36). The probability of axi-cel being cost-effective at £50,000 per QALY is [redacted] The equivalent probability at a £30,000 per QALY threshold was not reported.

The ERG was not able to fully validate the company's Visual Basic for Applications (VBA) code used to programme the PSA. The VBA coding was opaque and it was unclear whether or not parameter values were being sampled from the full range of distributions to which they were assigned. The PSA also appears to be inefficiently programmed, which results in long computation times for each 10,000 run of the model (over three hours).

4.2.11 Model validation and face validity check

The company states that the cost-effectiveness model was internally quality checked by an independent health economist who was not involved in the development the model, and that any errors and issues identified were addressed following the model quality check. The key assumptions and face validity of the model was reported to have been validated with UK clinical experts, although only one expert was subsequently named. Comparisons between the clinical trial and undiscounted model results for the median and mean OS and PFS of axi-cel and BSC patients were presented in the CS appendices.

In the absence of any previously published studies identified by the company, comparison of the results of the de-novo model were not compared with other studies. Following points for clarification, the company provided a summary of the similarities and differences in the approaches used in the US

ICER report and the submitted NICE model. A detailed summary table (Table 11, company response document p13-15) was provided.

Key differences were noted between the approaches in the following areas:

- Axi-cel survival data – The use of pseudo patient level data derived from the digitisation of OS and PFS KM data from the Phase 2 ZUMA-1 dataset (US ICER study) vs individual patient data from the combined Phase 1 and 2 ZUMA-1 dataset (submitted NICE model). The company argued that their submitted model used a more accurate source of survival data and the combined data allowed for a larger sample to be utilised.
- BSC (survival data) – The use of pseudo patient level data derived from the digitisation of OS KM data from the overall SCHOLAR-1 population and the assumption of a proportional relationship between PFS and OS reported for RDHAP in the same disease area (US ICER study) vs individual patient data from SCHOLAR-1 with adjustments (removing ECOG 2-4 patients) and the assumptions of a proportional relationship between PFS and OS based on the ZUMA-1 trial of axi-cel (submitted NICE model).
- Extrapolation – The use of a piece-wise parametric modelling approach up until 5-years and general population survival after 5-years (US ICER study) vs the use of a mixture cure model and use of general population mortality data for cured patients together with additional structural assumptions concerning the HRQoL and costs from 2-years (submitted NICE model).
- Adverse events – Any grade 3-4 AE that occurred in ≥5% of patients with axi-cel or BSC (ICER study) vs any grade 3-4 AE that occurred in ≥10% of patients with axi-cel only (submitted NICE model).
- Utilities – Utilities assumed to equal those of age and gender matched population after 5-years (US ICER study) vs utilities assumed to equal those of age and gender matched population after 2-years (submitted NICE model). The company considered the 2-year to be a more relevant estimate as it was based on an external study based on a similar patient population.
- Axi-cel acquisition costs – List price plus $100k ‘mark-up’ for hospital administration (US ICER study) vs list price (submitted NICE model).
- Resource use and costs – Monthly healthcare costs assigned to the entire time horizon including patients responding to treatment (US ICER study) after 5 years vs no costs assumed after 2 years for progression-free patients (submitted NICE model).
- ZUMA-1 patients who did not receive axi-cel – ITT approach and use of a decision tree to capture costs and outcomes of patients who received leukapheresis but were not subsequently infused with axi-cel (i.e. due to death, adverse events or manufacturing failure) in the US ICER study vs mITT approach (with multipliers used to account for some cost elements such as leukapheresis

and conditioning chemotherapy in patients who did not subsequently receive axi-cel) in the submitted NICE model. As part of the response to points for clarification, the company included an additional scenario analysis using a similar approach to the US ICER study.

4.3 Additional analyses presented by the company as part of their response to points for clarification

In response to the points for clarification, the company revised their base-case assumptions to include additional costs associated with the treatment of CRS and B-cell aplasia. The revisions to CRS included the costs for cytokine inhibitors (tocilizumab) for any patient who received these in ZUMA-1. This increased the mean cost of managing CRS from £358 to £414. The costs of B-cell aplasia were revised to include the cost of IVIG acquisition and administration, applied as a monthly cost of £204 over 12 months to [redacted] of patients in the model.

The combined costing revisions increased the mean total costs of axi-cel by [redacted] and the ICER of axi-cel vs BSC to [redacted] per QALY gained. The revised deterministic base-case results are presented in Table 27. The company did not report probabilistic results.

Table 27 Company revised base-case results (mITT)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As part of the points for clarification, the company were also requested to provide an additional scenario which explored the impact of using the ITT data from ZUMA-1 Phase 1 and 2 for PFS and OS.

Table 28 summarises the reasons for patients not receiving axi-cel.

Table 28 ITT patients in ZUMA-1 (combined Phase1 & 2) including reasons for not receiving axi-cel

Patient categories	N	%	OS events	OS censored

mITT	108	90.8%		
Not receive axi-cel (death)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (due to AE)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (due to disease progression)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (due to non-measurable disease)	[redacted]	[redacted]	[redacted]	[redacted]
Total ITT population	119	100%		

Replication of Table 18, company's response doccumeny

The following assumptions were applied within the updated model for the ITT scenario analysis (summarised in Table 29):

- For patients who did not receive axi-cel due to death or adverse events, a one-off QALY (0.19 QALY) was estimated by using their average OS ([redacted]) and post progression utility ([redacted]); and a one-off cost (£7,002) based on post-progression monitoring cost (£2,006 per month)
- For patients who did not receive axi-cel due to disease progression or non-measurable disease, the discounted QALYs and costs from the BSC arm were used.
- The median time from leukapheresis to delivery of axi-cel to the treatment facility was 17 days. The base-case mITT analysis used axi-cel infusion as the model start time. With the ITT analysis where the model start time for axi-cel starts at leukapheresis, a one-off QALY ([redacted]) was added to the mITT patient group by assuming a progression-free utility ([redacted]) over 17 days
- The ITT population overall costs and QALYs were calculated using the weighted average of the three categories of patients (mITT, not receive axi-cel due to death and AE, not receive axi-cel due to other reasons)

Table 29 ITT scenario analysis assumptions

Patient categories	**N**	**%**	**One-off costs**	**One-off QALYs**
mITT			[redacted]	[redacted]
mITT (adjusted for ITT scenario)	108	90.8%	[redacted]	[redacted]

Not receive axi-cel (death or due to adverse events)	[redacted]	[redacted]	[redacted]	[redacted]
Not receive axi-cel (other reasons)	[redacted]	[redacted]	[redacted]	[redacted]
Total	119	100%	[redacted]	[redacted]

Table 30 summarises the results for the scenario analysis based on the ITT population analysis. The resulting ICER for the ITT scenario was marginally increased to [redacted] per QALY compared to the revised mITT base case [redacted] per QALY). The company stated in their response that they considered the mITT population to provide a more appropriate approach for the base-case analysis.

Table 30 Company scenario analysis results for ITT population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.4 Conclusions of the cost effectiveness section

The ERG considered the company's economic submission to meet the requirements of the NICE reference case. However, the ERG identified a number of key uncertainties. The main concerns identified by the ERG include:

1. *The uncontrolled comparison and the subset of SCHOLAR-1 study used for BSC*

The comparison between axi-cel and BSC is based on an uncontrolled comparison between the mITT population of ZUMA-1 and a subset of the SCHOLAR-1 study population which excluded patients with baseline ECOG 2-4 (company base-case analysis).

A comparison of the KM data reported for the different subgroups indicates that the subgroup of patients in SCHOLAR-1 with known ECOG 0-1 status appears to have a better prognosis than the base-case population from SCHOLAR-1. The ERG considers that restricting the patient population in

SCHOLAR-1 to patients with known ECOG 0-1 status (n=[redacted]) may provide a more appropriate basis for comparison with the ZUMA-1 population.

2. *The use of the mITT population for axi-cel*

The OS and PFS data for axi-cel were informed using the latest ZUMA-1 combined Phase 1 and 2 data cut (n=108, August 2017). The data was based on the mITT population (i.e. patients who received axi-cel). As a result, model entry for patients receiving axi-cel occurs from the point of infusion of axi-cel, rather than from the point of the initial leukapheresis procedure. The ERG considers that the period of time between the decision to use axi-cel and subsequent axi-cel infusion (i.e. the time between the initial leukapheresis procedure and receipt of axi-cel infusion, is likely to be longer for axi-cel) is likely to be significantly longer than the decision to use salvage chemotherapy and the start of chemotherapy.

Although the CS attempts to quantify the additional costs of leukapheresis and conditioning chemotherapy, the company base-case analysis did not attempt to quantify the potential impact on survival and HRQoL outcomes of the 11 patients out of 119 enrolled to ZUMA-1 who received leukapheresis but were not subsequently infused (e.g. due to adverse events, death or manufacturing failure) and potentially biases the analysis against BSC.

In response to the points for clarification, the company subsequently submitted an additional scenario analysis which attempted to quantify the impact on costs and outcomes.

3. *Significant uncertainties remain concerning the company's base-case OS extrapolation for axi-cel*

The ERG considers that the difference in the cure fractions across the alternative mixture cure models suggest that the OS data for ZUMA-1 is not sufficiently mature to be able to estimate a robust cure fraction for OS. This leads to significant uncertainties surrounding the company's base-case OS extrapolation approach.

The base-case mixture-cure model was considered overly optimistic by the ERG as a basis for the lifetime extrapolation of OS for axi-cel. The two modelling approaches presented in the company's submission, the mixture-cure and single parametric over the entire time horizon, are viewed by the ERG as the most optimistic and pessimistic assumptions for the OS estimates for axi-cel, respectively.

The ERG also considers that the differences in the cure fraction for PFS and OS have not been fully addressed by the company. The ERG considers that a plausible explanation for the differences is the

limited time at risk for mortality (i.e. follow up for survival may not be sufficient to capture the mortality of patients experiencing a late progression) and that with longer follow-up the cure fraction for OS for axi-cel might converge towards the cure fraction for PFS.

4. *The inclusion of additional structural assumptions related to cure*

The ERG does not consider that the assumption made that patients who remain in the 'Pre-progression' health state for at least two years in either treatment group, will subsequently revert to the same HRQoL and medical resource use cost of the general population is robustly supported by evidence. The assumption of cure at two years is based on one US study (n=767) where no statistical difference was reported between the mortality of DLBCL survivors and that of the general population after two years post-diagnosis [22]. However, the ERG identified several other studies that suggest that significant excess mortality remains up until at least five years post-diagnosis. This included a recent US study examining survival after diagnosis for DLBCL based on 18,047 cases during 2002-2012 from the Surveillance, Epidemiology and End Results Data[23].

5. *Uncertainties surrounding the HRQoL and costs of adverse events associated with axi-cel (specifically for B-cell aplasia and CRS)*

The ERG identified a number of uncertainties concerning the HRQoL and costs of adverse events. The most important uncertainties related to the assumptions for CRS and B-cell aplasia, whose occurrence is specifically associated with CAR T technologies.

In terms of HRQoL assumptions, the ERG identified a discrepancy between the duration of CRS (4 days) assumed in the model and the median time to resolution of symptoms of [redacted] days reported in the clinical study report. The ERG also identified two other uncertainties surrounding the cost of CRS within the company base-case analysis.

- Firstly, the company base-case analysis only considered the cost of Grade 3-4 CRS which was assumed to require management with cytokine inhibitor drugs (tocilizumab) and an ICU hospitalisation. However, cytokine inhibitor drugs are also used for the management of lower grade CRS events. Following points of clarification, the company updated the model to include the cost of cytokine inhibitor drugs for all patients that received these in ZUMA-1.
- Secondly, the ERG believes that the unit costs assumed for the cost of an ICU hospitalisation (£1,363) are actually per diem costs. Hence, these per diem costs should have been applied to the duration of CRS. The discrepancies noted in the assumed duration of the Grade 3-4 CRS events combined with the unit cost assumptions raise uncertainties concerning whether the costs of CRS events have been fully quantified in the company base-case analysis.

The ERG also noted that the occurrence of B-cell aplasia in patients treated with CAR T-cells is an expected consequence and is linked to the proliferation of CAR T-cells and the associated durability of the clinical effect. The costs of B-cell aplasia were not included in the initial submission, but this was corrected by the company following points of clarification. The ERG considers the company's revisions appropriate and uses the updated the model to conduct additional analyses in section 6.

6. *Uncertainty surrounding post-treatment SCT*

There are two important areas of uncertainty regarding post-treatment SCT. First, there is uncertainty surrounding the actual number of patients in ZUMA-1 who received a SCT, as the numbers in the submission differ depending on data categorisation. The second issue relates to whether patients received autologous or allogeneic SCT post-treatment. While the company assumes that only allogeneic SCT was performed in both treatment groups, evidence suggests that BSC patients only underwent ASCT, which is less costly than allogeneic SCT. Given that the costs of SCT are an important element of cost for BSC due to higher rates of transplant for this treatment, this is likely to have a significant impact on estimates of cost-effectiveness.

7. *Uncertainty surrounding broader infrastructure and training requirements*

Given the complexity of the intervention and the lack of a clear service specification for the provision and administration of axi-cel, the ERG considers that important uncertainties remain concerning whether the additional resource/cost implications for the NHS have been fully quantified. The ERG notes that particular consideration should be given to whether there are additional infrastructure requirements for the NHS which have not been captured. The ERG noted specific uncertainties whether ICU beds may need to be made available (even if not used) to ensure that patients receiving axi-cel can be guaranteed access to appropriate services if and when required (and without detriment to other patients). Although the company dismissed these concerns in their response, the ERG considers that uncertainties remain.

The ERG also considers that the cost of training included in the model appears unlikely to reflect the level of training required by the risk management plan likely to be mandated by the regulatory authorities.

8. *Uncertainty surrounding whether the criteria are met relating to the application of end-of-life considerations and the appropriate discount rate*

A key issue regarding the cost-effectiveness results is whether the NICE appraisal committee consider that the existing criteria for end-of-life considerations and 1.5% discounting (applied to costs and

health outcomes) are met. The ERG notes that the company base-case deterministic [redacted] per QALY) and probabilistic ICERs [redacted] per QALY) exceed NICE's conventional threshold range (£20,000-£30,000) as well as the upper bound of the threshold range (£50,000 per QALY) which is applied when end-of-life criteria are met. The CS also included a separate scenario analysis using a discount rate of 1.5% per annum for costs and benefits, which reduces the base-case deterministic ICER of axi-cel vs BSC from [redacted] to [redacted] per QALY.

Given the importance of these issues, additional analyses requested by the ERG from the company and independently undertaken by the ERG are presented in Section 6.

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

5.1 Overview

This section focuses on the additional analyses undertaken by the ERG to explore the key areas of uncertainty highlighted in Section 5. These analyses are undertaken using the revised model submitted by the company following the points for clarification which includes revisions to the cost assumptions for CRS and B-cell aplasia.

The ERG notes that the company's VBA code required substantial modifications to ensure that the ERG's model revisions were included in the simulation, since the original code restored a number of model parameters to default values. Given time constraints, the ERG was unable to ensure that these modifications were appropriately sampling the revised values. As a result, all of the revised ERG analyses reported are based on deterministic cost-effectiveness estimates.

5.2 ERG corrections and adjustments to the company's base case model

In Section 5, the ERG identified a range of uncertainties to which the company's base-case cost-effectiveness results were subject. The ERG performed a number of adjustments to the company's revised model (post-clarification questions) to address several of these uncertainties.

The following sections describe the model adjustments and report the results of the additional exploratory analyses performed by the ERG to explore the areas of uncertainty identified in Section 5. The assumptions varied for each scenario are summarised in Table 31.

Table 31 Overview of ERG's additional analyses

Scenario	Variation from company's base-case assumptions
i. BSC OS for ECOG 0-1	BSC OS is based on SCHOLAR-1 ECOG 0-1 patient subgroup survival data.
ii. Consistent PFS and OS cure fraction	Axi-cel OS is based on a loglogistic parametric model constrained by the PFS curve, with general population mortality risk applied at the point of convergence.
iii. Combined consistent PFS and OS cure fraction and BSC OS for ECOG 0-1	The two previous assumptions on OS are combined.
iv. Combined alternative assumptions on survival extrapolation and cure	An additional assumption of cure in terms of costs and HRQoL at 52 months and onward is added to scenario iii.
v. Combined alternative assumptions on survival extrapolation and cure on axi-cel ITT population	Scenario iv is applied to the axi-cel ITT population.
vi. Cost of managing Grade 3-4 CRS	Varies alternative durations of stay and proportion of patients requiring an ICU stay due to CRS.
vii. Long-term costs of SCT	Costs are discounted at 3.5% *per* annum, and one scenario is explored where SCT for BSC patients is assumed to be autologous.
viii. BSC delivery setting	BSC is assumed to be delivered in outpatient setting
ix. Composition of BSC blended comparator	The proportion of the BSC chemotherapy regimens is varied to extreme values.
x. Training costs	Costs are calculated based on the time of 5 and 10 healthcare professionals.
xi. ERG alternative base-case	Combines alternative assumptions on survival extrapolation and cure, as per scenario iv and corrects the CS base-case by: – Applying the cost of ICU stay to the average ICU hospitalisation period (4 days); – Discounting long-term costs of SCT; – Assuming that BSC patients who receive SCT all undergo ASCT. The alternative base-case results are presented for axi-cel mITT and ITT population, and at a 3.5% and 1.5% annual discount rate on costs and QALYs.

5.2.1 The uncontrolled comparison and the subset of SCHOLAR-1 study used for BSC

The company base-case analysis was based on OS estimates for BSC from a subset of the SCHOLAR-1 study population (excluding patients with baseline ECOG 2-4). The ERG considers that the subgroup of patients in SCHOLAR-1 with known ECOG 0-1 status (n=226) may provide a more appropriate basis for comparison with the ZUMA-1 population.

The ERG digitised the KM data from SCHOLAR-1 for patients with known ECOG 0-1 status (Figure 3, Company response document) and fitted single parametric models. Further details are reported in

Appendix 9.2. Figure 17 shows the digitised KM data and the ERG's preferred distribution (Gompertz) which was selected based on statistical and visual fit.

Figure 17 BSC observed and extrapolated survival data for ECOG 0-1 subgroup

Table 32 reports the cost-effectiveness results using the subgroup of patients with ECOG 0-1 in SCHOLAR-1. The survival outcomes for the ECOG 0-1 subgroup of patients from SCHOLAR-1 are more favourable than those of the company's BSC base-case population. The improved survival outcomes for BSC result in higher mean QALYs (vs) but also higher mean costs (vs). The combined impact on these changes for BSC increases the ICER for axi-cel compared to BSC to per additional QALY.

Table 32 Cost-effectiveness results for scenario with BSC OS based on ECOG 0-1 SCHOLAR-1 subgroup

Scenario Analysis	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
	BSC					

BSC OS for ECOG 0-1	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2.2 Uncertainties concerning the company's axi-cel OS extrapolation

In Section 5.4, the ERG concluded that the company's OS extrapolation for axi-cel was potentially optimistic given the immaturity of ZUMA-1 data. Equally the ERG also considered that the use of single parametric analyses for the entire extrapolation period was overly conservative and generated implausible longer term predictions.

The differences in the cure fraction estimated for axi-cel PFS and OS may result from the survival follow-up not being sufficient to capture the mortality of patients experiencing a late progression, and with longer follow-up it is plausible that the cure fraction for OS for axi-cel might converge towards the cure fraction for PFS. Given the high uncertainty surrounding the extrapolation of OS for axi-cel the ERG considers that this scenario provides a plausible alternative to the alternative optimistic and conservative approaches considered by the company.

To assess the impact of this scenario, the ERG selected the best fitting single parametric OS curve for axi-cel (loglogistic) in the model and constrained it so that patients receiving axi-cel transitioned to mortality risk of the age and gender matched general population once the OS curve converged with the PFS curve. This is illustrated by Figure 18.

Figure 18 Axi-cel PFS and OS curves assuming convergence of OS and PFS

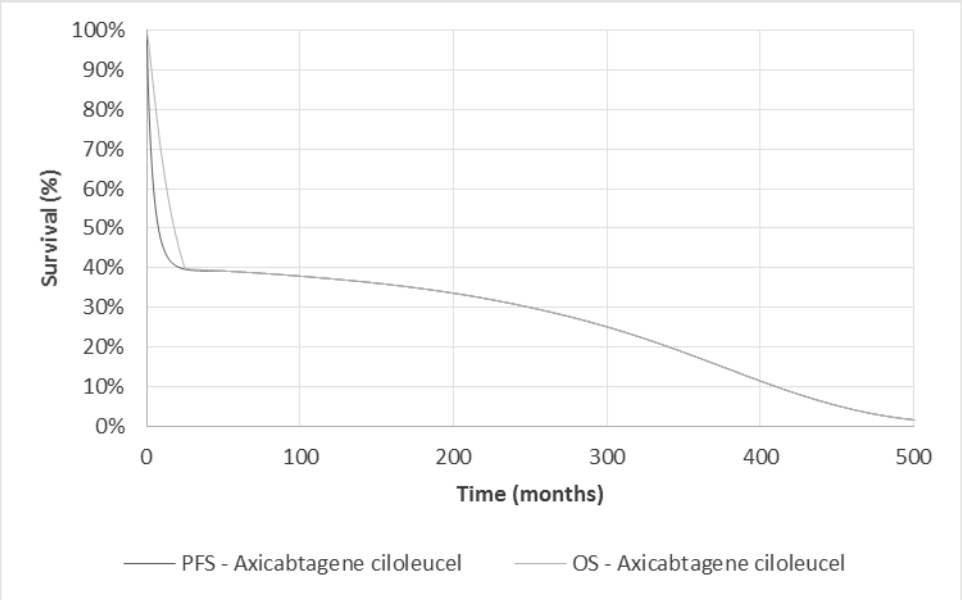


Table 33 shows cost-effectiveness results for the scenario where the axi-cel OS is based on a loglogistic parametric model constrained by the PFS curve, with general population mortality risk applied at the point of convergence.

Table 33 Cost-effectiveness results for scenario with alternative axi-cel OS extrapolation assumptions

Scenario Analysis	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Consistent PFS and OS cure fraction	BSC	[redacted]	[redacted]			
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

This assumption still allows for long-term survival in the model, but for a smaller cure fraction (approximately 40%) and occurring around 52 months in the model, which results in smaller survival gains from axi-cel compared to BSC than in the company's base-case ([redacted] vs [redacted] life years gained). By applying an extrapolation approach that allows for long-term survivors but with a consistent cure fraction for axi-cel PFS and OS, the ICER of axi-cel vs BSC increases to [redacted] per additional QALY.

5.2.3 Combination of ERG alternative survival assumptions for axi-cel and BSC

Table 34 presents the results for a scenario where the alternative assumptions on the survival extrapolation of BSC and axi-cel cost-effectiveness explored in the two previous scenarios are combined.

Table 34 Cost-effectiveness results for scenario with alternative axi-cel and BSC OS extrapolation assumptions

Scenario Analysis	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Consistent PFS and OS cure fraction	BSC	[redacted]	[redacted]			
	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC OS for ECOG 0-1						

When the ERG scenarios are combined this significantly reduces the mean incremental QALYs for axi-cel compared to the company base-case ([redacted] vs [redacted] QALYs) and the ICER increases to [redacted] per additional QALY.

5.2.4 Uncertainties concerning the company's additional structural assumptions related to cure

Another key area of uncertainty relates to the company's assumptions on the costs and HRQoL of long-term survivors. The company assumed pre-progressed patients alive at two years post-treatment, would subsequently revert to the same HRQoL and medical resource use cost of the general population. The ERG considers that the assumption of cure at two years is overly optimistic and not robustly supported by evidence, as discussed in Section 5.

The ERG updated the previous combined scenario by applying the separate structural assumption at the point that the axi-cel OS curve converged with the PFS curve (approximately 52 months), after which pre-progressed patients were assumed to switch to the same HRQoL and costs as the age and gender matched general population.

Table 35 shows the cost-effectiveness results for this scenario analysis combining the ERG's exploratory analyses for the related cure assumptions. The ICER of axi-cel compared to BSC increases to [redacted] per additional QALY.

Table 35 Cost-effectiveness results for scenario combining alternative axi-cel and BSC OS extrapolation assumptions and cure at 52 months

Scenario Analysis	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Consistent PFS and OS cure fraction	BSC	[redacted]	[redacted]			

BSC OS for ECOG 0-1 Structural cure assumption at 52 months	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.2.5 The use of the mITT population for axi-cel

The previous ERG exploratory scenario analyses explore alternative assumptions on the survival extrapolation and the timing of cure in the model, which are the key drivers of axi-cel cost-effectiveness. Another important area of uncertainty relates to the use of the mITT population for axi-cel, rather than the full ITT population of ZUMA-I (Phase 1 and 2). The ERG discussed in Section 5 that using the mITT population potentially biases the analysis against BSC, by ignoring the survival outcomes and HRQoL of patients who received leukapheresis but did not subsequently receive axi-cel.

In Table 36 the ERG presents the cost-effectiveness result for a scenario analysis where the ITT population of ZUMA-1 is considered, as per the company's scenario presented in Section 5.3, and the ERG's assumptions on OS extrapolation and timing for cure are included.

Table 36 Cost-effectiveness results for the ERG's alternative survival and cure assumption with ZUMA-1 ITT population

Scenario Analysis	Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Consistent PFS and OS cure fraction BSC OS for ECOG 0-1	BSC	[redacted]	[redacted]			
Structural cure assumption at 52 months ITT ZUMA -1	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG's combined assumptions on survival extrapolation and timing of cure based on the ITT population increase the ICER to [redacted] per additional QALY.

5.2.6 Other cost related uncertainties in the model

The ERG conducted a number of scenario analyses varying cost assumptions on the company's revised base-case for which results are summarised in Table 37. Further details on the assumptions of each scenario are presented in Appendix 9.3.

Table 37 Summary of cost-effectiveness results for the ERG cost scenarios

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	% change base-case ICER
Company's revised base-case		[redacted]	[redacted]	[redacted]	0%
CRS management: 4 days ICU stay for [redacted] of axi-cel patients	CRS management: 1 day ICU stay for [redacted] of axi-cel patients	[redacted]	[redacted]	[redacted]	0.2%
CRS management: [redacted] days ICU stay for [redacted] of axi-cel patients		[redacted]	[redacted]	[redacted]	0.4%
CRS management: 4 days ICU stay for all axi-cel patients		[redacted]	[redacted]	[redacted]	1.8%
CRS management: [redacted] days ICU stay for all axi-cel patients		[redacted]	[redacted]	[redacted]	3.7%
Discounted SCT long-term costs	Undiscounted SCT long-term costs	[redacted]	[redacted]	[redacted]	0.01%
Discounted SCT long-term costs and BSC SCT assumed autologous	All SCT assumed allogeneic	[redacted]	[redacted]	[redacted]	3.8%
BSC administered in outpatient setting	BSC administered in inpatient setting	[redacted]	[redacted]	[redacted]	1.4%
Blended comparator consisting of 50:50 of the 2 rituximab containing regimens	Blended comparator consisting of equal proportions of 4 chemotherapy regimens	[redacted]	[redacted]	[redacted]	-1.3%
Blended comparator consisting of 50:50 of the 2 non-rituximab containing regimens		[redacted]	[redacted]	[redacted]	1.3%
Training costs for 5 healthcare professionals	Training costs for one healthcare professional	[redacted]	[redacted]	[redacted]	0.1%
Training costs for 10 healthcare professionals		[redacted]	[redacted]	[redacted]	0.3%

Overall, the scenario analyses had a marginal impact on the estimates of cost-effectiveness with the ICERs of axi-cel vs BSC varying between [redacted] (for a blended comparator composed equally of non-rituximab containing regimens) and [redacted] per additional QALY (for discounted long-term SCT costs and BSC SCT assumed autologous).

5.2.7 ERG alternative base-case

The assumptions and approaches applied for the OS and cure related assumptions (Section 6.2.4) were combined and used as part of an ERG alternative base-case. A number of further amendments are also proposed including:

1. The cost of ICU (£1,363) is assumed to represent a per-diem estimate and is applied to the average ICU hospitalisation period (4 days);

2. The follow-up costs assumed for patients receiving SCT are discounted;

3. The proportion of BSC patients who received SCT are assumed to have all undergone ASCT.

The results are presented in Table 38 for the mITT and ITT populations and for the alternative discount rates (3.5% and 1.5%). At a 3.5% discount rate, the ICER based on the alternative ERG base-case varied between [redacted] and [redacted] per QALY (mITT vs ITT approach). At a 1.5% discount rate, the ICER varied between [redacted] and [redacted] per QALY (mITT vs ITT approach).

Table 38 Cost-effectiveness results - ERG alternative base-case

Population	Scenario	BSC		Axi-cel		Inc. Costs	Inc. QALYs	ICER (£/QALY)
		Total costs	Total QALYs	Total costs	Total QALYs			
mITT	Discount rate 3.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Discount rate 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT	Discount rate 3.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Discount rate 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.3 Conclusions from ERG analyses

A series of alternative assumptions were explored by the ERG. The main scenarios addressed uncertainties related to: (i) the uncontrolled comparison and the subset of SCHOLAR-1 study used for BSC; and (ii) the company's axi-cel OS extrapolation and (iii) the additional structural assumptions related to cure. The combined impact of the alternative assumptions proposed by the ERG increased the ICER increases to [redacted] per additional QALY (mITT population, 3.5% discounting).

Further exploratory analyses assessed the impact of using an ITT population, altering the model on a range of alternative cost assumptions.

Several of the assumptions were combined within the ERG alternative base-case. At a 3.5% discount rate, the ICER based on the alternative ERG base-case varied between [redacted] and £[redacted] per QALY (mITT vs ITT approach). At a 1.5% discount rate, the ICER varied between [redacted] and [redacted] per QALY (mITT vs ITT approach).

While the ERG aimed to address the key uncertainties identified throughout section 5, there are a number of uncertainties that have not been fully addressed due to data limitations. First, the ERG notes that while the restricting the patient population in SCHOLAR-1 to patients with known ECOG 0-1 status may provide a more appropriate basis for comparison with the ZUMA-1 population, this remains an uncontrolled comparison and is, therefore affected by unquantifiable bias. The ERG approach may reduce this bias, but cannot account for other relevant variables (e.g. different rates of SCT between treatments). Second, the axi-cel ITT population scenarios represented an approximation based on a weighted approach of cost-effectiveness estimates, rather than formal modelling based on the effectiveness, costs and HRQoL of this population. Third, the ERG's approach to OS extrapolation and cure assumptions provides a plausible alternative to the optimistic and conservative approaches considered by the company, but remains affected by uncertainty given the lack of mature data. Finally, there are wider issues regarding how CAR T-cell therapies will be provided in the UK context and the resulting implications in terms of potential additional resource use/costs to the NHS, which cannot be fully quantified within the scope of this review.

6 End of life

The CS (Table 22, p84 CS) presents evidence to support axi-cel as an end-of-life therapy.

Criterion 1: The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

The median OS in the standard of care group (BSC) reported in the overall SCHOLAR-1 study population (n=636) was 6.3 months (95% CI 5.9 to 7.0). The median OS reported across each of the 4 individual studies included within the SCHOLAR-1 study varied between 5 months (MAYO study; n=82) and 6.6 months (MDACC; n=165 and LY12; n=219). A standardised comparison of the SCHOLAR-1 study, based on refractory subgroup and ECOG status, reported a median OS of [redacted] months.

While the SCHOLAR-1 data suggests that the first criterion is met, the ERG notes a marked difference between the median and the mean estimates for survival predicted over the entire lifetime horizon of the model. The modelled (discounted) mean overall survival for BSC was [redacted] years in the company base-case and model and [redacted] years in the ERG's alternative base-case. While the extrapolations of OS are subject to uncertainty, the lifetime survival estimates for BSC are based on more mature evidence from the SCHOLAR-1 data.

Criterion 2: 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.

The CS states that although the median OS for axi-cel in the ZUMA-1 study has not been reached, the lower 95% confidence interval was 12.0 months. This suggests that the extension of survival with axi-cel should exceed 5.7 months. The modelled (discounted) increase in the mean overall survival for axi-cel, compared to BSC, was [redacted] years in the company base-case and [redacted] years in the ERG's alternative base-case. Although the extrapolations of OS are subject to considerable uncertainties, the ERG considers that there is sufficient evidence to indicate that the second criterion is met.

The ERG concludes that there is some uncertainty surrounding whether the first criterion for end-of-life considerations is met and depends on judgements concerning the use of the median or mean OS estimates. The ERG also highlights that, in circumstances where one of the criteria does not appear to meet the exact level described in the policy, previous NICE committees have applied discretion in determining whether it reasonable to apply a weight to the QALYs gained,. For example, in NICE TA509 [33], the NICE committee acknowledged that the survival benefit with pertuzumab (median survival gain of 15.7 months), far exceeded the 3 month extension to life criteria and represented a step-change in treatment.

While the predicted survival gains for axi-cel are subject to significant uncertainties, the ERG considers that axi-cel appears to represent a similar step-change in the management of R/R adult patients with DLBCL, PMBCL or TFL who are ineligible for ASCT.

7 Overall conclusions

Although the company made attempts to adjust for differences in important covariates across the ZUMA-1 and SCHOLAR -1 datasets, the ERG considers that none of these were adequately robust to minimise the impact of confounding on the comparative effectiveness results. Moreover, although the company took account of the use of ASCT subsequent to axi-cel, they did not take account of re-treatment with axi-cel, causing further uncertainty in the results.

The key drivers in the cost effectiveness of axi-cel are the separate cure assumptions applied to the OS estimates for axi-cel and which cohort from SCHOLAR-1 provides a more appropriate basis for estimating OS for BSC. Given the high uncertainty surrounding the extrapolation of OS for axi-cel, the ERG considers that their alternative base-case provides a plausible alternative to the alternative optimistic and conservative approaches considered by the company.

Given the complexity of the intervention and the lack of a clear service specification for the provision and administration of axi-cel, the ERG considers that important uncertainties remain concerning whether the additional resource/cost implications for the NHS have been fully quantified.

There is some uncertainty surrounding whether the first criterion for end-of-life considerations is met and depends on judgements concerning the use of the median or mean OS estimates. The ERG did not consider that the criteria for applying a 1.5% discount rate were met. The ERG considers that the evidence submitted is not sufficiently mature to robustly demonstrate that cure occurs, and the duration of health benefits is driven by a highly uncertain extrapolation of survival estimates. Furthermore, the sustainability of the health benefit over at least 30 years appears unlikely given that the age of the population who is likely to receive this treatment in this specific indication. The ERG also concludes that the NICE Appraisal Committee will also have to consider if the NHS investment required to implement this technology is of a magnitude that is constitutes an irrecoverable cost.

7.1 Implications for research

Long-term follow up of ZUMA-1 patients is essential to more accurately evaluate the effectiveness and safety of axi-cel.

8 References

1. Chaganti S, Illidge T, Barrington S, McKay P, Linton K, Cwynarski K, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol* 2016;**174**:43-56.

2. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;**26 Suppl 5**:v116-25.

3. National Institute for Health and Care Excellence. *Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma*. London: NICE; 2014.

4. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;**52**:377-84. Available from: <Go to ISI>://MEDLINE:9764259

5. Kite Pharma Inc. *KTE-C19-101. A phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1). Clinical study report*; 2017.

6. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med* 2017;**377**:2531-44.

7. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Mol Ther* 2017;**25**:285-95.

8. Kochenderfer JN, Somerville RP, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. *J Clin Oncol* 2017;**35**:1803-15.

9. Kochenderfer JN, Dudley ME, Kassim SH, Somerville RP, Carpenter RO, Stetler-Stevenson M, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol* 2015;**33**:540-9.

10. Kochenderfer JN, Somerville RPT, Lu T, Yang JC, Sherry RM, Feldman SA, et al. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. *Mol Ther* 2017;**25**:2245-53.

11. Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N Engl J Med* 2018;**378**:449-59. Available from: <Go to ISI>://MEDLINE:29385376

12. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med* 2018;**378**:439-48. Available from: <Go to ISI>://MEDLINE:29385370

13. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017;**130**:1800-8.

14. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed)* 2003;**327**:557-60. Available from: <Go to ISI>://MEDLINE:12958120

15. Woolacott N, Corbett M, Jones-Diette J, Hodgson R. Methodological challenges for the evaluation of clinical effectiveness in the context of accelerated regulatory approval: an overview. *J Clin Epidemiol* 2017;**90**:108-18. Available from: <Go to ISI>://MEDLINE:28709997

16. Faria R, Hernandez Alava M, Manca A, Wailoo AJ. *The use of observational data to informa estimates of treatment effectiveness in techmology appraisal: methods for comparative individual patient data*. Sheffield: School of Health and Related Research, University of Sheffield; 2015.

17. Tice Sea. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value - Evidence report. 2018.

18. Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess* 2017;**21**:1-204.

19. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013*. London: NICE; 2013.

20. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics* 2007;**8**:576-94.

21. Yu X, De Angelis R, Andersson T, Lambert P, O'Connell D, Dickman P. Estimating the proportion cured of cancer: some practical advice for users. *Cancer epidemiology* 2013;**37**:836-42.

22. Maurer MJ, Ghesquieres H, Jais JP, Witzig TE, Haioun C, Thompson CA, et al. Event-free survival at 24 months is a robust end point for disease-related outcome in diffuse large B-cell lymphoma treated with immunochemotherapy. *J Clin Oncol* 2014;**32**:1066-73.

23. Howlader N, Mariotto AB, Besson C, Suneja G, Robien K, Younes N, et al. Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunochemotherapy era. *Cancer* 2017;**123**:3326-34.

24. Jakobsen L, Bøgsted M, Brown P, Arboe B, Jørgensen J, Stauffer Larsen T, et al. Minimal loss of lifetime for patients with diffuse large B-cell lymphoma in remission and event free 24 months after treatment: a Danish population-based study. *J Clin Oncol* 2017;**35**:778-84.

25. Othus M, Barlogie B, LeBlanc ML, Crowley JJ. Cure models as a useful statistical tool for analyzing survival. *Clin Cancer Res* 2012;**18**:3731-6.

26. Perica K, Curran KJ, Brentjens RJ, Giralt SA. Building a CAR garage: preparing for the delivery of commercial CAR T cell products at Memorial Sloan Kettering Cancer Center. *Biol Blood Marrow Transplant* 2018.

27. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol* 2018;**15**:47-62. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28925994

28. London Cancer Alliance. *Non-Hodgkin's Lymphoma. TWG Agreed Regimens*. Available from: http://www.londoncanceralliance.nhs.uk/information-for-healthcare-professionals/forms-and-guidelines/south-east-london-cancer-network/haematology/non-hodgkins-lymphoma/

[accessed 23rd April 2018].

29. NHS England. Thames Valley Strategic Clinical Networks. *Lymphoma group. R-VP*. Available from: http://nssg.oxford-haematology.org.uk/lymphoma/pdf-protocols/L-40-r-vp.pdf [accessed 23rd April 2018].

30. Department of Health. *NHS National Schedule of Reference Costs 2015 to 2016*. 2016. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [accessed 23rd April 2018].

31. NHS Blood and Transplant. Unrelated Donor Stem Cell Transplantation in the UK: effective, affordable, sustainable. A report from the UK Stem Cell Strategy Oversight Committee. 2014. Available from: http://docplayer.net/7404866-Unrelated-donor-stem-cell-transplantation-in-the-uk.html

32. Majhail NS, Mau L-W, Denzen EM, Arneson TJ. Costs of autologous and allogeneic hematopoietic cell transplantation in the United States: a study using a large national private claims database. *Bone Marrow Transplant* 2013;**48**:294-300.

33. National Institute for Health and Care Excellence. *Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer*. London: NICE; 2018.

34. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**:1-158.

35. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;**12**.

9 Appendices

9.1 Quality assessment using the Philips economic modelling checklist

Table 39 Quality assessment of the company's cost-effectiveness submission using the Philips checklist [34]

Description of quality	Response (✓,× or NA)	Comments	Reference
Structure			
S1 Statement of decision problem objective			
Is there a clear statement of the decision problem?	×	The decision problem was stated in the first table of the CS using the PICOS framework, but it is unclear whether patients refractory to first line therapy for aggressive non-Hodgkin's lymphoma are part of the relevant population.	CS, Table 1, p8-9
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	×	The objective is not explicitly stated but it is broadly consistent with the NICE scope.	
Is the primary decision-maker specified?	×	Not specified	
S2 Statement of scope/perspective			
Is the perspective of the model clearly stated?	×	No, the perspective of the company's analysis is not stated, but costs and health benefits included are consistent with the NHS and Personal Social Services (NHS & PSS) perspective.	
Are the model inputs consistent with the stated perspective?	NA		
Has the scope of the model been stated or justified?	✓	The scope set by NICE and that used for the company's de novo analysis was clearly stated in the first table of the CS. The two scopes are broadly similar although one comparator	CS, Table 1, p8-9& p98-99

		defined by the NICE scope, pixantrone monotherapy, was excluded from the company's scope on the basis of not being part of routine clinical practice in the UK.	
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	NA	Outcomes relate to life-years, quality adjusted life years based on EQ-5D and costs.	
S3 Rationale for structure			
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	The decision model is based on a partitioned survival approach containing 3 states: pre-progression, post-progression and death. Health states were aligned with two primary objectives of treatment (avoiding disease progression and prolonging life) and are typical of metastatic oncology models used in previous NICE appraisals.	CS,p89-90
Are the sources of data used to develop the structure of the model specified?	✓	The model was designed in line with the NICE reference case. No details were provided in the main submission concerning the model conceptualisation process. Only one clinician is named as having performed the clinical validation of model inputs and assumptions, although it is stated that the key assumptions of the model had been validated by *"UK clinical experts"*.	CS, p155-156
Are the causal relationships described by the model structure justified appropriately?	×	The causal relationship was justified, but the lack of RCT data renders the causal relationship between axi-cel and outcomes highly uncertain. THE ERG considers that approaches to increase the comparability of the study populations for each treatment are likely to bias cost-effectiveness estimates in favour of axi-cel. The company did not provide a rationale to the approach used to model BSC PFS, i.e. assuming a proportional relationship between OS and PFS of BSC as for axi-cel, other than it being necessary due to lack of PFS data in SCHOLAR-1	CS, p93-97
S4 Structural assumptions			
Are the structural assumptions transparent and justified?	✓	Yes.	CS, Table 59, p144-145
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	Yes	
S5 Strategies/comparators			

Is there a clear definition of the options under evaluation?	✓	Yes.	CS, p98-99
Have all feasible and practical options been evaluated?	×	Comparators not evaluated from the NICE scope include: • DHAP, cisplatin, cytarabine, dexamethasone (with or without rituximab) • GDP, cisplatin, gemcitabine, dexamethasone (with or without rituximab) • ICE, ifosfamide, carboplatin, etoposide (with or without rituximab) • IVE, ifosfamide, epirubicin and etoposide (with or without rituximab) • pixantrone monotherapy	
Is there justification for the exclusion of feasible options?	✓	**Pixantrone monotherapy:** "*While the final scope issued by NICE also included pixantrone monotherapy (in people who have had 2 of more prior therapies, including rituximab) as a potential comparator, clinicians confirmed at a recent clinical ad-board that very few patients are treated with pixantrone monotherapy in NHS England as it does not improve outcomes.[1, 2] Therefore, pixantrone is not seen as a relevant comparator and has not been included in this submission. Furthermore, recently published BSH Guidelines (2016) on the management of DLBCL do not recommend pixantrone as a treatment option for DLBCL."* **Other chemotherapy regimens (DHAP, GDP, ICE, IVE; with or without rituximab):** different chemotherapy gemcitabine and/or platinum-based chemotherapy regimens (with or without rituximab) were applied in the model. Although these did not match those of the NICE scope the ERG's clinical advisor confirmed that the regimens included reflect the current standard of care for patients who are not eligible for ASCT.	CS, p8-9, p20-21, & p98-99
S6 Model type			
Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	✓	Yes.	
S7 Time horizon			
Is the time horizon of the model sufficient to reflect all important differences between options?	✓	The time horizon used in the model was 44 years, which is assumed to represent a lifetime horizon.	CS, p97
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	**Time horizon:** The time horizon is in line with NICE guidance. **Duration of treatment:** The schedule of treatment used in the model is consistent with the expected marketing authorisation.	CS, p103-104 & p116-117

		Duration of treatment effect: Axi-cel is stated to have a curative effect for a proportion of patients, mostly those who achieve CR, based on observed flattening of KM curves at the end of follow-up. The ERG considers that the survival data is too immature to robustly support the cure fraction estimated by the company (approximately 50%).	
S8 Disease states/pathways			
Do the disease states or the pathways reflect the underlying biological process of the disease in question and the impact of interventions?	✓	The ERG remains concerned that the assumptions around OS extrapolation and cure are insufficiently supported by the data, given immaturity and short follow-up, and that uncertainty was not explored by the company.	
S9 Cycle Length			
Is the cycle length defined and justified in terms of the natural history of disease?	✓	The cycle length was set at one month in the model, which was "*anticipated to capture all the relevant changes in the modelled cohort, considering the median OS in the BSC arm is expected to be approximately 6 months".*	CS, p97-98
Data			
D1 Data identification			
Are the data identification methods transparent and appropriate given the objectives of the model?	✓	Yes	CS, Sections B. 3.3, B. 3.4, B. 3.5, & B. 3.6
Where choices have been made between data sources, are these justified appropriately?	×	Data was mostly scarce and few alternative choices were available. However, there were isntances when alternative sources were available and justifications were not provided (e.g. relationship between BSC OS and PFS; excess mortality of long-term survivors).	CS p 143-144
Has particular attention been paid to identifying data for the important parameters in the model?	×	Insufficient attention was given to identifying comparable data for the OS of BSC and axi-cel	
Has the quality of the data been assessed appropriately?	✓	**Clinical Effectiveness:** "*ZUMA-1 was considered to be a good quality study and was conducted according to Good Clinical Practices (GCP)".* **Cost and Cost-effectiveness Studies:** "*A quality assessment of the two included studies was performed using the Drummond and Jefferson checklist"* **HRQoL Studies**: No quality assessment is described.	CS appendices D, G & I

Where expert opinion has been used, are the methods described and justified?	×	Resource use data collected via a survey of 3 key opinion leaders that was conducted for a previous NICE TA was applied in the model, but no details were provided on the methods used.	CS, P134
D2a Baseline data			
Is the choice of baseline data described and justified?	✓	Yes.	
Has a half-cycle correction been applied to both cost and outcome?	✓	Yes.	CS, p98
D2b Treatment effects			
If the relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	NA	Relative treatment effectiveness was derived from non-randomised data.	
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓	Partly. The choice of parametric curve was informed through visual inspection, assessment of clinical plausibility, and metrics of statistical fit in line with NICE Decision Support Unit guidelines. The use of a mixture-cure model to extrapolate axi-cel OS is considered to not be appropriate given the immaturity of OS data and the short-follow-up of ZUMA-1.	CS, section B.3.3
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓	See S7 (duration of treatment).	
Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓	Partly. The ERG considers that the scenario analysis conducted by the company do not sufficiently explore the uncertainty around the OS extrapolation and cure assumptions.	CS, Table 61
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis.	NA	Treatment effect duration was not modelled explicitly in the company's economic analysis.	
D2c Costs			
Are the costs incorporated into the model justified?	✓	Yes.	
Has the source of the costs been described?	✓	Unit costs were based on the literature, the company's proposed list price, NHS Reference costs, the monthly index of medical specialties (MIMS), Personal Social Services Research Unit (PSSRU) 2016 and the Department of Health's electronic market information tool (eMit). Where appropriate, unit costs were inflated to 2015/2016 prices. All sources were explicitly stated and described.	CS, Section B.3.5
Have the discount rates been described and justified given the target decision maker?	✓	Conventional 3.5% annual discount rates were presented for the base-case scenario. The company has given justification for applying an annual discount rate of 1.5% to costs and outcomes as a scenario	CS, p98

		analysis: "*Due to the potential for axi-cel to provide long-term survival (the model estimates a mean undiscounted OS of >10 years) and HRQL benefits, and given that the total acquisition cost of axi-cel is incurred within the first model cycle, an alternative discount rate of 1.5% was used in a scenario analysis. This scenario analysis is especially relevant if the NICE committee decides that axi-cel qualifies for the use of a 1.5% discount rate based on the NICE method guide (section 6.2.19).*"	
D2d Quality of life weights			
Are the utilities incorporated into the model appropriate?	✓	Partly. The utilities incorporated into the model are in line with the NICE reference case. However, the utilities are sourced from a small subset of ZUMA-1 population (n=34) and it is unclear how these were derived.	CS, Section B.3.4
Is the source of the utility weights referenced?	✓	All sources are referred and described.	CS, Section B.3.4
Are the methods of derivation for the utility weights justified	✓	EQ-5D-5L was collected and responses were converted to EQ-5D-3L using a crosswalk algorithm. National tariffs were applied to derive utility weights.	CS, p121-127
D3 Data incorporation			
Have all data incorporated into the model been described and referenced in sufficient detail?	×	Not all parameters are included in the CS.	
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	NA		
Is the process of data incorporation transparent?	×	Some data are referenced explicitly in the company's model and incorporated with the value and the distributions. Measures of variance (standard errors, ranges, etc.) are not presented,	CS, Table 58
If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	✓	The chosen distributions have been described but not justified.	
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	×	Upon model inspection, the ERG identified a number of parameters (rates of adverse events and some elements of costs) which had been varied between an arbitrary range of 15% around the mean, and it is not clear whether such value ranges actually represent the true uncertainty around the given parameters.	
D4 Assessment of uncertainty			
Have the four principle types of uncertainty been addressed? If not, has the omission of particular forms of uncertainty been justified?	✓	See below.	

D4a Methodological			
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	×	Alternative methods of axi-cel OS extrapolation and of estimating BSC PFS were insufficiently explored.	
D4b Structural			
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	×	Key structural uncertainties in terms of cure timing and cure fraction were not sufficiently explored.	
D4c Heterogeneity			
Has heterogeneity been dealt with by running the model separately for different subgroups?	NA	No relevant subgroups were defined by the NICE scope. However, there is uncertainty as to whether the effectiveness, cost and HRQoL data is equally reflective of the populations defined by the four positions in the clinical pathway (as claimed by the company).	
D4d Parameter			
Are the methods of assessment of parameter uncertainty appropriate?	✓	In line with the NICE reference case deterministic sensitivity analyses were performed on a series of model parameters. Probabilistic sensitivity analyses were also performed.	CS, Section B.3.8
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	×	See D3	
Consistency			
C1 Internal consistency			
Is there any evidence that the mathematical logic of the model has been tested thoroughly before use?	✓	The company states that *"The cost-effectiveness model has been internally quality checked by an independent health economist who was not involved in the development the model. The errors and issues identified were addressed following the model quality check."*	CS, p155-156
C2 External consistency			
Are any counterintuitive results from the model explained and justified?	NA		
If the model has been calibrated against independent data, have any differences been explained and justified?	NA		
Have the results of the model been compared with those of previous models and any differences in results explained?	×	The company compares and contrasts the assumptions and data sources of their submitted model against those of the ICER report one, but does not compare results. However, the ICER report model is a US study, and differences between the US health care system and the NHS makes it difficult to	Company response to clarification

		generalise the results. The company could nevertheless have compared the differences in predicted survival outcomes between models.	questions, Table 11

9.2 Selection of parametric distribution to model the OS of the SCHOLAR-1 subgroup of patients with ECOG 0-1

The ERG digitised the KM curve for the subgroup of patients in SCHOLAR-1 with ECOG 0-1 provided by the company in response to clarification questions (Figure 3, company response document, p10). The online software WebPlotDigitizer was used to digitise the KM curve and the algorithm developed by Guyot and colleagues (2012)[35] and colleagues was applied to reconstruct the IPD data in R. The ERG fitted standard parametric models (exponential, Weibull, lognormal, loglogistic, Gompertz and generalised gamma) in Stata® using the *streg* package. Goodness of fit statistics, in terms of AIC and BIC, are presented in Table 40 for each parametric model and visual representation of each curve is shown alongside the KM curve in Figures 20-25.

The parametric OS curves with better statistical fit are the generalised gamma followed by the Gompertz function. In addition to good statistical fit, the Gompertz is the only distribution that captures the distal part of the KM where flattening of the curve is observed. Thus, the Gompertz parametric curve was selected as the best fitting survival model and implemented in the company's revised model.

Table 40 Goodness of fit measures for BSC OS curves based on SCHOLAR-1 patients with ECOG 0-1

Parametric model	AIC	BIC
Exponential	871.37	874.80
Weibull	808.44	815.28
Lognormal	735.48	742.32
Loglogistic	731.24	738.08
Gompertz	**695.55**	**702.39**
Generalised gamma	**675.44**	**685.70**
Models with best statistical fit in bold		

Figure 19 BSC OS based on SCHOLAR-1 patients with ECOG 0-1: KM with fitted exponential curve

Figure 20 BSC OS based on SCHOLAR-1 patients with ECOG 0-1: KM with fitted Weibull curve

Figure 21 BSC OS based on SCHOLAR-1 patients with ECOG 0-1: KM with fitted lognormal curve

Figure 22 BSC OS based on SCHOLAR-1 patients with ECOG 0-1: KM with fitted loglogistic curve

Figure 23 BSC OS based on SCHOLAR-1 patients with ECOG 0-1: KM with fitted Gompertz curve

Figure 24 BSC OS based on SCHOLAR-1 patients with ECOG 0-1: KM with fitted generalised gamma curve

9.3 ERG's additional cost scenarios assumptions

The ERG explored a number of costing scenarios to address the unresolved uncertainties around resource use and costs in the company's base-case, as identified in Section 5. These areas of uncertainty are:

1. Cost of managing Grade 3-4 CRS;
2. Undiscounted long-term costs of allogeneic SCT;
3. BSC delivery setting;
4. Composition of BSC blended comparator;
5. Additional resource use/cost implication of providing training in the context of a mandatory risk management plan.

Table 41 summarises the assumptions and rationale for varying the company's base-case.

Table 41 Overview of ERG's cost scenarios

Company's base-case assumptions	**ERG Scenario assumptions/rationale for variations on the base-case**
CRS management: 1 day ICU stay for [redacted] of axi-cel patients	CS assumes the duration of CRS to be 4 days when estimating the AEs disutility, but does not state the source of this duration. The median duration to CRS resolution of symptoms reported in the clinical study report was [redacted] days. The cost of hospitalisation in an ICU for CRS management applied in the model correspond to a HRG cost per diem, thus implicitly assuming that duration of stay is one day. The ERG conducts scenario analyses, where the duration of ICU stay is varied to 4 and [redacted] days. The company also assumed that the ICU would only be required for [redacted] of axi-cel patients, as for the proportion of patients in ZUMA-1 with CRS grade 3 and above. The ERG highlights in section 5 that provision of axi-cel may require an ICU bed to be available during the period a patient in considered to be at risk of CRS, regardless of whether they then actually experience a serious AE. Thus, the scenario analysis, also consider the assumption that all axi-cel patients will require an ICU bed. Four alternative CRS management scenarios are considered: i. 4 days ICU stay for [redacted] of axi-cel patients ii. [redacted] days ICU stay for [redacted] of axi-cel patients iii. 4 days ICU stay for all axi-cel patients iv. [redacted] days ICU stay for all axi-cel patients
Undiscounted SCT long-term costs and all SCT assumed allogeneic	The ERG conducted two scenario analysis updating the costs of SCT in the model: i. SCT long-term costs are discounted at 3.5% per annum ii. SCT long-term costs are discounted at 3.5% per annum and the BSC patients who received SCT ([redacted]) are assumed to have all undergone ASCT. The cost of ASCT comprised two elements: – Initial cost of transplant: £17,343.99 (NHS Reference Costs 2015/16, Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over [currency codes: SA26A) [30] – Long-term follow-up costs: £20,300.52 (assumed to be half of allogeneic SCT long-term follow-up cost, based on a study comparing the short and long-term costs of allogeneic vs autologous SCT) [32]
BSC administered in inpatient setting	A monthly cost for outpatient visits for chemotherapy administration is applied to BSC patients, instead of a one-off inpatient admission cost as per CS. The

	unit cost is derived from NHS reference costs (currency codes SB14Z and SB15Z) [30] and applied to the number of cycles per month of the BSC blended comparator.
Blended comparator consisting of equal proportions of four chemotherapy regimens	The ERG notes in Section 5 that are marked differences between the costs assumed for rituximab and non-rituximab based regimens considered in the BSC blended comparator. It is unclear whether the assumption that all four regimens are equally used in clinical practice is plausible. The ERG tests two extreme scenarios where the blended comparator is assumed to consist of: iii. 50:50 of the two rituximab containing regimens iv. 50:50 of the two non-rituximab containing regimens
Training costs for one healthcare professional	The ERG notes that the model appears unlikely to reflect the level of training required by the RMP that is likely to be imposed by the regulatory authorities within the marketing authorisation. The resource use associated with this item of cost is highly uncertain and will depend on the requisites of the RMP. The ERG performs two scenarios where the company's assumption that only two days of a healthcare professional (consultant) time will be required, by increasing the number of healthcare professionals to: i. 5 health care professionals ii. 10 health care professionals
Key: BSC, best supportive care; CRS, cytokine release syndrome; HRG, healthcare resource group; ICU, intensive care unit; RMP, risk management plan.	

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

You are asked to check the ERG report from Centre for Reviews and Dissemination and Centre for Health Economics – York [ID1115] to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Thursday 10 May 2018** using the below proforma 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.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 ERG's base case OS extrapolation method

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Figure 18 which illustrates the ERG's base case OS extrapolation approach does not follow best practice in showing the fit of the modelled approach to extrapolation versus the trial data observed to date (best practice which is implemented in the previous figure by the ERG). By failing to implement this widely recognised best practice, it is difficult to assess the visual fit of the modelled OS to the observed data (as recommended in TSD14). In this specific case this opaque approach masks the implausible fit of the ERG's extrapolation approach to the data observed to date. It prevents the reader noticing that the ERG's suggested approach is not plausible, overly conservative and biases against axi-cel. The relevant sections/pages: • On page 24 of the ERG report, it states, "*While the ERG's approach to OS extrapolation and cure assumptions provides a plausible alternative to the*	Kite/Gilead requests ERG to revise the ERG's base case approach on axi-cel OS extrapolation or add clear limitations of ERG's axi-cel OS extrapolation approach. Kite/Gilead requests ERG to add axi-cel OS KM data in Figure 18 and discuss the underestimation of ERG's OS (compared to OS KM) towards the end of the trial follow up period and comment on the clinical plausibility that there are no post-progression patients after 2 years. Kite/Gilead suggests that the ERG's OS approach can be included as a scenario analysis and should use the gamma mixture-cure model (the most plausible mixture-cure model for PFS based on the company's additional analyses to respond to ERG's clarification questions) for	Kite/Gilead does not agree that ERG's base case axi-cel OS extrapolation approach is fair or plausible. Instead when compared to the observed trial data it seems to lead to a bias against axi-cel. Kite/Gilead's key concerns of ERG's approach and the justification for these concerns are: • OS, not PFS, is the gold standard and the most objective and relevant clinical outcome for oncology. However, ERG's OS extrapolation ignored the plausibility of OS extrapolation and instead relied on a fitted PFS curve for OS extrapolation (i.e. OS follows PFS when the two converge). Kite/Gilead believes the focus should be on identifying the most plausible OS extrapolation, rather than relying on PFS extrapolation to be applied to OS extrapolation. • The axi-cel OS predicted by ERG's base case is not clinically plausible and has very poor visual fit to trial KM data (note, Figure 18 in ERG report did not overlay the OS KM data. Kite/Gilead believes ERG's base case OS extrapolation approach significantly underestimates the OS	We do not consider that this is an issue of factual accuracy. The ERG's approach to OS extrapolation is presented as a plausible alternative to the optimistic (cure fraction approach based on OS) and conservative (single parametric analysis) approaches for axi-cel considered by the company. The ERG considers the mixture-cure model used in the company base-case to be overly optimistic as a basis for the lifetime extrapolation of OS for axi-cel, given that: i. Survival data in ZUMA-1 is too immature to robustly estimate the size of the cure fraction; ii. Median follow-up is shorter than the two years that the company considers to be the time point at which cure can be observed; iii. Cure at two years is also highly uncertain, as excess mortality risk appears likely to persist for at least 5 years.

optimistic and conservative approaches considered by the company, results remain highly uncertain." • Section 5.2.2 • Figure 18	representing axi-cel PFS instead of the Gompertz single curve fit used by ERG in this scenario. This is because the mixture-cure model better represents the cure assumption that the ERG made for pre-progression patients.	for patients receiving axi-cel. • The ZUMA-1 OS and PFS KM curves indicate that there are significant gaps between the OS and PFS curves, and that the plateaus occur at different levels for OS and PFS, with OS plateau higher than PFS plateau. The ERG's base case OS and PFS extrapolation contradicts these observations. • Because the very conservative and implausible choice of axi-cel OS in ERG's base case, ERG's base case predicts there are no post-progression patients after around 2 years (25 months) years. Kite/Gilead believes this is not clinically plausible and believes, similar to recent immune-oncology treatments (e.g. nivolumab, pembrolizumab), that a proportion of patients treated with axi-cel who may have clinically progressed are long-term survivors. Therefore, Kite/Gilead believes the ERG's base case axi-cel extrapolation underestimates the QALYs of potential long-term survivors who have initial disease progression.	Given the immaturity of evidence and lack of robustness in the estimated cure fraction for OS (varying between 1% and 53% of patients), the ERG considers that more conventional extrapolation approaches appear equally justifiable as the mixture-cure approach employed by the company. While the ERG acknowledges that the use of a single parametric curve for the entire model horizon provides implausible lifetime projections (i.e. resulting in the OS curve for axi-cel crossing the OS curve for BSC), the ERG considers that some convergence in the OS curves is plausible for the reasons stated above. Faced with what the ERG considered to be the most optimistic and pessimistic assumptions presented by the company, the ERG presented an alternative 'hybrid' approach (employing a more conventional single parametric function for OS and constraining this by the cure fraction for PFS and general population mortality). The rationale and justification for this were clearly stated in the ERG report. The ERG does not consider their approach to be overly conservative, implausible or unfair. Indeed, the ERG notes that the lack of

			robustness in the estimated cure fraction for OS suggests that more conservative approaches than that considered by the ERG also retain some plausibility. The ERG report clearly stated that their preferred approach and assumptions were also affected by uncertainty given the lack of mature data.

Issue 2 ERG's interpretation of "cure" assumption at 2 years

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In various places in the report (see below the list), the ERG suggested that the company model assumes patients (or pre-progression patients) are cured after 2 years. This is not in line with the assumption and approach used in the company submitted model. Relevant sections/pages: • On page 18 of the ERG report, it states: "*This is equivalent to a separate structural 'cure' assumption applied in the model that prevents transitions from the 'Pre-progression' to the 'Post-progression' state after two years*." • On page 21 of the ERG report, the 4th	Kite/Gilead requests ERG to remove these statements or revise the text to be aligned with the assumptions used in the submitted model.	Kite/Gilead does not agree that the model assumes cure for pre-progression patients (or alive patients) after two years. It is correct that the model assumes pre-progression patients after 2 years revert to age-matched general population utility and do not incur cancer specific costs. But the model did not assume pre-progression patients (or alive patients) are cured after 2 years and did not apply age-matched general population mortality to PFS or OS after 2 years. Instead, mixture-cure models were fitted to the axi-cel OS patient level data in the base case. For mixture-	We do not consider that this is an issue of factual accuracy. We fail to understand how the statement provided by the company in the justification for amendment (i.e. "It is correct that the model assumes pre-progression patients after 2 years revert to age-matched general population utility and do not incur cancer specific costs") is not equivalent to a separate structural 'cure' assumption. The ERG further notes that this structural assumption is unrelated to the mixture-cure approach and is not explicitly

main concern identified by ERG – "The inclusion of additional structural assumptions related to cure" • On page 23 of the ERG report, it states: o ii. Median follow-up is shorter than the two years that the company considers to be the time point at which cure can be observed; o iii. Cure at two years is in itself highly uncertain, as excess mortality risk appears likely to persist for at least 5 years. • On page 73, the ERG states: "There are three key aspects to the cure assumption: (i) the estimated cure fraction; (ii) the time point at which cure is assumed to occur; and (iii) whether patients cured from lymphoma may still differ from the general population in terms of excess mortality, costs, and HRQoL."		cure models, two distinctive patients groups (cured and not cured) are modelled separately, with cured patients assumed to follow age-matched general population mortality from time zero and uncured follow various parametric survival curves (Weibull distribution for the base case) from time zero.	stated in the CS.

Issue 3 ERG's Interpretation of cure fraction for PFS mixture-cure model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 23 of the ERG report, it states: "…axi-cel OS was extrapolated with a	Kite/Gilead suggests removing this sentence.	Kite/ Gilead does not understand why "constrained by the UK general	We do not consider that this is an issue of factual accuracy.

single parametric curve constrained by the UK general population mortality to ensure consistent cure fractions for PFS and OS, …"		population mortality" can "ensure consistent cure fractions for PFS and OS". More importantly, Kite/ Gilead does not think it is correct to enforce the same cure fractions between PFS and OS. The interpretation of mixture-cure model and cure fraction are straightforward for OS. However, for PFS, there does not seem to be a consensus in the wider biostatistical literature as to whether mixture-cure model is an appropriate method to apply to PFS data and neither is there a consensus concerning how the cure fraction for PFS should be interpreted. Note, the original submitted model does not include mixture-cure models for PFS and these were added following ERG clarification questions. More detailed explanation on the PFS mixture-cure model was provided in Kite/Gilead's response to ERG clarification questions (Question B3).	See response to Issue 1.

Issue 4 ERG's choice of including known ECOG 0-1 from SCHOLAR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG's base case for BSC arm applies known ECOG 0-1 patients from SCHOLAR-1 which overestimates the OS	Kite/Gilead requests ERG to change this analysis to a scenario analysis,	Kite/Gilead acknowledges the limitation of including SCHOLAR-1 patients with unknown ECOG status	We do not consider that this is an issue of factual accuracy.

curve for the BSC arm and underestimates the SCT costs for BSC arm, so biases against axi-cel.	rather than a base case	(company base case) and understands the rationale for ERG's base case to include only known ECOG 0-1 patients. However, Kite/Gilead's base case is more plausible; ERG's base case would overestimate the OS curve for the BSC arm (and hence underestimate the relative treatment effect for axi-cel vs BSC) and underestimate the costs for BSC arm. The rationales are: • Given the single arm trial design of ZUMA-1 and differences in baseline patient characteristics (not only ECOG status) between ZUMA-1 and SCHOLAR-1, Both the company and ERG's base cases are subject to uncertainty and Kite/ Gilead does not believe the ERG's base case is more plausible than the company's base case • ECOG status is only one of many prognostic factors affecting OS for the patients. ZUMA-1 patients in general have a worse prognosis than all SCHOLAR-1 patients because ZUMA-1 patients have more previous lines of	The company base-case is based on an analysis which removes patients ([redacted]) with known ECOG 2-4 from SCHOLAR-1, without any further adjustment. Hence, the company base-case includes a significant number of patient without a known ECOG classification (43.5% of SCHOLAR population). The ERG justified restricting the comparison to patients in SCHOLAR-1 with known ECOG 0-1 status based on the differences reported in the KM data (see page 74 of the ERG report). The ERG acknowledges that the company and ERG analyses are subject to potential bias (e.g. due to differences in other possible confounding) given the non-randomised nature of the comparisons. However, the ERG does not consider that the various rationales provided by the company suggest any clear reason why the company base case is more plausible than the ERG's. The ERG notes that further

		treatments compared to SCHOLAR-1 patients. Therefore, removing ECOG 2+ patients from SCHOLAR-1 (company base case) is more plausible to obtain a SCHOLAR-1 subpopulation that is comparable to ZUMA-1 patients. • With ERG's approach to include only known ECOG 0-1 patients, the % of SCHOLAR-1 patients receiving SCT is [redacted] based on the SCHOLAR-1 patient level data. This is much higher than the 29% for SCHOLAR-1 patients where ECOG 2+ patients are removed (company base case). Therefore, the % of patients having subsequent SCT should be changed from [redacted] to [redacted] for the BSC arm for consistency under the ERG's approach. In addition, overall survival observed in patients receiving transplant is significantly longer than in those patients who did not received transplant leading to severely biased results in favour of BSC.	adjustments using the ECOG 0-1 subgroup might address some of the potential bias due to differences in other observable sources of confounding. However, the company did not provide these analyses. Instead, the company's approach appears to have been focused on maximising sample size and reducing statistically significant baseline differences across the two studies, rather than adjusting for clinically important imbalances (which may not necessarily be statistically significantly different) in covariates known to be important in affecting outcomes. The ERG was not provided with the additional data of the proportion of patients with known ECOG 0-1 who received SCT. Hence, the ERG does not consider that this is an issue of factual accuracy. However, an addendum has been submitted which includes the results of an additional scenario to address this point. The ERG notes that this results in a

			small improvement in the ICER (equal or lower than 1.6% reduction in ICER across scenarios) and hence does not consider that the original results are 'severely biased'.

Issue 5 ERG's discussion regarding delay between the decision to use axi-cel and subsequent infusion

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 21 of the ERG report, it states: "*The ERG considers that the delay between the decision to use axi-cel and subsequent axi-cel infusion (i.e. the time between the initial leukapheresis procedure and receipt of axi-cel infusion) is likely to be significantly longer than the decision to use salvage chemotherapy and the start of chemotherapy.*"	Kite/Gilead suggests removing this sentence or they should provide a reference to support this claim that the time between the decision to use axi-cel and the infusion will be significantly longer than the decision to use and start chemotherapy. Also, the word "delay" should be deleted as this suggests the period of time will always be longer than expected or planned. .	Kite/Gilead is not clear on the evidence that the ERG are using to support their concern for the use of the mITT population for axi-cel.	We do not consider that this is an issue of factual accuracy. The specific page referred to is part of the Executive Summary where it not conventional to report references. The relevant considerations (e.g. additional time to manufacturer axi-cel) which underpin this statement are stated on p28. For clarity, we have replaced the word "delay" with "period of time". For axi-cel the complete process takes 21-24 days. For comparator treatments our clinical adviser told us that the typical period of time between the decision to use salvage chemotherapy and the start of the first chemotherapy infusion is 1-2 weeks.

Issue 6 Excess mortality assumption

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 21, the ERG states: "However, the ERG identified several other studies that suggest that significant excess mortality remains up until at least five years post-diagnosis."	Kite/Gilead requests that a reference is added to support this statement or the statement should be removed.	This statement is important for the interpretation of survival after 2 years, so a reference should be given to support the ERG's opinion.	We do not consider that this is an issue of factual accuracy. The specific page referred to is part of the Executive Summary where it is not conventional to report references. The references are reported within the appropriate sections where this specific issue is discussed in detail (e.g. see page 80).

Issue 7 VBA coding and PSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 112, the ERG states: "The VBA coding was opaque and it was unclear whether or not parameter values were being sampled from the full range of distributions to which they were assigned."	Kite/Gilead requests that this statement is removed.	The submitted model has a parameter sheet which assigns different distributions to parameters used in the PSA. While the VBA coding used for the PSA may be extensive, the code was laid out as clearly as possible and was commented consistently. Therefore, the statement that the coding was "opaque" is not factually	We do not consider that this is an issue of factual accuracy. This reflects the ERG's view based on their extensive experience of reviewing VBA code across multiple submissions.

		correct.	

Issue 8 ASCT eligibility/ineligibility

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 28, the ERG states: "Stem cell transplant is not listed as a comparator in the final scope but a proportion of both ZUMA-1 (21%) and SCHOLAR-1 (18%) patients are relapsed following ASCT (Table 9, Appendix)."	This statement is misleading and Kite/Gilead requests this will be removed or amended.	The statement implies that ASCT is a comparator on the basis that a proportion of patients entering the ZUMA-1 and SCHOLAR-1 trials have relapsed following ASCT. However, as discussed in the submission, relapse following ASCT is an ineligibility criterion for subsequent ASCT and the relevant population for this submission is a population that are considered ineligible for ASCT.	This should read: "Stem cell transplant is not listed as a comparator in the final scope but a proportion of both ZUMA-1 ([redacted]) and SCHOLAR-1 ([redacted]) patients went on to receive stem cell transplant"
On page 47, the ERG states: "[redacted] of SCHOLAR-1 patients went on to receive ASCT. The ERG notes that ASCT is not in the NICE scope list of comparator treatments. Also, the draft EMA license for axi-cel relates to patients who are ineligible for ASCT. An ideal comparator treatment group should therefore include very few patients who go on to receive ASCT."	Kite/Gilead requests to clarify here that an analysis has been presented that attempts to control for the difference in subsequent ASCT between SCHOLAR-1 and ZUMA-1 in the comparative effectiveness analyses.	Without this point, it could be assumed by a naïve reader that the comparative effectiveness results are not appropriate. Whereas the advantage of using studies for which patient-level data were available was that it allowed for this type of adjustment.	We do not consider that this is an issue of factual accuracy. The company's standardised analyses are addressed in the ERG report (see section 3.2).

Issue 9 The clinical SLR and the selection of studies for SCHOLAR-1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 15, the ERG states: "However, the almost complete lack of a narrative explaining how the company went from including 22 studies in the systematic review to then effectively excluding them and instead using the ZUMA-1 and SCHOLAR-1 patient-level datasets is a limitation of this aspect of the submission. SCHOLAR-1 was not identified as an included study in the systematic review, nor was it mentioned as a potentially useful excluded study."	Kite/Gilead requests the statement is edited to remove the phrase "the almost complete lack of narrative" as it makes it an opinion driven statement that does not fully reflect the submission.	The statement in the summary is misleading and does not fully reflect the submission, or what is presented elsewhere within the ERG report. At the beginning of Section B.2.9 of the submission it states: "Due to the large amounts of heterogeneity between the studies identified in the SLR and the ZUMA-1 study, which included much more heavily pre-treated patients compared to the majority of the SLR studies which were mostly patients after first-line treatment, direct comparison between these studies was not considered appropriate. Instead, the SCHOLAR-1 study was conducted using data from four sources for which patient-level data were available: MD Anderson Cancer Centre (MDACC) database; Mayo Clinic and University of Iowa (MC/IA) Specialised Program of Research Excellence (SPORE) database; the National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) randomised Phase 3 study LY.12; and the French Lymphoma Academic Research Organisation (LYSARC) randomised phase 3 Collaborative	We do not consider that this is an issue of factual accuracy.

		Trial in Relapsed Aggressive Lymphoma (CORAL) study. This would allow patients to be included that more closely matched the patient population of ZUMA-1 and would allow for adjustment to be made to account for any differences between patients and therefore allow for a more appropriate comparison."	
On page 37, the ERG states: "the almost complete lack of a narrative regarding how the company went from including 22 studies in the review to then effectively excluding them and instead using the SCHOLAR-1 IPD dataset is a limitation of this aspect of the submission."	As directly above.	As directly above.	We do not consider that this is an issue of factual accuracy.
On page 38, the ERG states: "The ERG acknowledges the many potential advantages of utilising patient-level data to compare single-arm datasets. Nevertheless, the description in the CS of how this approach was developed over time, and in particular how it related to the systematic review, was very limited and could have been much clearer."	Kite/Gilead requests that the latter concluding statement is edited as it misrepresents the approach for SCHOLAR-1 and could mislead a naïve reader.	As discussed in the CS and presented within Section 3.1.3 (page 36) of the ERG report, the driving factor behind the choice of data for SCHOLAR-1, was the availability of patient-level data, which the ERG acknowledges has many potential advantages	We do not consider that this is an issue of factual accuracy.

Issue 10 Heterogeneity in SCHOLAR-1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 16, the ERG states: "However, the test used is known to be poor at detecting true heterogeneity, especially when the number of included studies is low."	Kite/Gilead requests that a reference is added to support this statement or the statement should be removed.	This statement is important for the interpretation of the SCHOLAR-1 data, so a reference should be given to support the ERG's opinion.	We do not consider that this is an issue of factual accuracy. The specific page referred to is part of the Summary (Section 1) where it is not conventional to report references. The reference is reported in section 3.2.2 of the ERG report where this specific issue is discussed in detail (see page 47-48).

Issue 11 Equality issues

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 33, the ERG states: "The CS reports a greater proportion of males are diagnosed with DLBCL, who then experience poorer outcomes. However, the ERG notes that, contrastingly, more females are diagnosed with PMBCL (p18). The CS reports women improving more from similar treatment, but presents analyses demonstrating consistent results by age and	Kite/Gilead requests to make clear that PMBCL is a much smaller population than DLBCL and that like DLBCL, outcomes in males are poorer than females. PMBCL only constitutes 6-10% of all DLBCL (6,332 total incidence of DLBCL mentioned in the NICE scope for this appraisal would correspond to only 380 to 633 patients with PMBCL).[1] Male sex is a significant indicator of poor prognosis in PMBCL.[1] The point that is being made in the CS is that with current standard of care there are gender	The ERG statement seems to misinterpret what has been stated in the CS.	The text should read: "The CS reports a greater proportion of males are diagnosed with DLBCL, who then experience poorer outcomes. However, the ERG notes that, contrastingly, more females are diagnosed with PMBCL representing 5% of NHL diagnoses each year (p18). The CS reports gender differences favouring women with current SoC (p27), but the

gender (p27). Gender also does not form the foundation of the company's submitted analysis, nor does the CAR-T mechanism suggest a gender specific action."	differences in treatment outcomes and improvements over time. Men have poorer outcomes than females so have a greater need for effective therapies in later lines in DLBCL and PMBCL. In contrast, with axi-cel there are no differences between males and females, which would remove this bias for those patients able to receive axi-cel.		CAR-T mechanism does not suggest a gender-specific action. Nonetheless, gender does not form the foundation of the company's submitted analysis."

Issue 12 Potential selective outcome bias in the clinical SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 35, the ERG states: "The final entry listed in the Outcomes section of Table 5 was 'any other relevant outcome of interest'; there was no exclusion based on outcomes. Although this criterion had the potential to make the review prone to selective outcome reporting, it should not be problematic provided a clear focus was made on the outcomes listed in the NICE scope."	Kite/Gilead requests to remove the beginning of the final sentence ("Although this criterion had the potential to make the review prone to selective outcome reporting") as it is incorrect.	By not including a restriction on outcomes, the SLR is actually removing the risk of selective outcome reporting by identifying all potentially relevant studies regardless of what outcomes were reported. Therefore, the statement is factually incorrect.	We do not consider that this is an issue of factual accuracy. Allowing studies with 'any other relevant outcome of interest' to be included means it is possible that cherry picking of these other outcomes to focus on favourable results may occur. Also, other outcomes with unfavourable results may not be reported.

Issue 13 Inclusion of studies in the SCHOLAR-1 analysis

Description of problem	Description of proposed amendment	Justification for amendment	
On page 48, the ERG states: "The ERG notes that the smallest study (MAYO) appears to be somewhat of an outlier when comparing the	Kite/Gilead requests that this statement is removed.	The selective data from the study that the ERG has chosen to present do not provide robust evidence that	We do not consider that this is an issue of factual accuracy. The study results presented

2-year survival results (10% versus 17%, 22% and 23%) and median survival results (5.0 months versus 6.5, 6.6 and 6.6 months). The MAYO study had a higher proportion of ECOG 2-4 patients (24%) compared with the other studies (15%, 11%, 10%). The ERG considers that this raises questions about the clinical meaning of the pooled SCHOLAR-1 results."		the study is an outlier.	serve to highlight potential issues in interpreting the pooled results.

Issue 14 Methods for the standardised analysis of SCHOLAR-1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 51, the ERG states: "The two covariates described were ECOG performance status and last refractory subgroup (Table 10 CS appendices). The results, which are presented on p63-65 of the CS, also mention standardisation by refractory subgroup and subsequent ASCT, which was not explained in the methods section (nor in Table 10 of the CS appendices)."	Kite/Gilead requests that the statement "which was not explained in the methods section" is removed.	The statement from the ERG misrepresents the information provided in the CS and could result in the analyses being misinterpreted. On page 25 of the CS appendices, it states that: "Two covariates were used to define the strata. These covariates were refractory subgroup, based on Last Refractory Categorisation, and ECOG category." The methods for the standardisation were also presented within this section of the CS appendices, with standardisation for ASCT following the same methods (for patients who did, or did not, receive subsequent	We do not consider that this is an issue of factual accuracy. Subsequent ASCT is not mentioned in the CS appendix section on standardisation.

		ASCT).	

Issue 15 End of life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 130, the ERG discusses the mean survival estimates from the model in relation to end of life criteria: "While the SCHOLAR-1 data suggests that the first criterion is met, the ERG notes a marked difference between the median and the mean estimates for survival predicted over the entire lifetime horizon of the model. The modelled (discounted) mean overall survival for BSC was [redacted] years in the company base-case and model and [redacted] years in the ERG's alternative base-case. While the extrapolations of OS are subject to uncertainty, the lifetime survival estimates for BSC are based on more mature evidence from the SCHOLAR-1 data."	Kite/Gilead requests to remove the paragraph discussing the choice of means versus medians and how it affects whether the first criterion is judged to be met.	The first criterion for considering an intervention a 'life-extending treatment at the end of life' is that, "the treatment is indicated for patients with a *short* life expectancy, *normally* less than 24 months" [emphasis added]. Given the extremely short life expectancy of the majority of patients on standard of care a discussion of means versus medians prioritises numerical precision over a grounded analysis of the severity of the condition The use of median rather than mean survival is clinically more appropriate here due to the large proportion of patient dying at 6 months. The majority of patients are therefore facing the end of life when receiving current standard of care – only a very small proportion experience favourable long term survival. The addition of the discussion on mean survival here may inappropriately bias the interpretation by misrepresenting the nature of the prognosis that the majority of patients currently face.	We do not consider that this is an issue of factual accuracy. The End of Life criteria is a deliberative matter for the committee. The ERG note that these deliberations are routinely based on considerations relating to the median and mean estimates.

Issue 16 Conditioning therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 28, the ERG states: "Pre-treatment conditioning chemotherapy of cyclophosphamide 500mg/m2 IV and fludarabine 30mg/m2 IV are delivered on the 5th, 4th and 3rd day prior to axi-cel. The CS reports this to be delivered in an outpatient setting, however, the clinical advisor to the ERG suggested that although this is possible it would be more likely to be delivered at the centre administering axi-cel with proximity to intensive care."	Kite/Gilead would suggest deleting the following statement "with proximity to intensive care".	Patients are not required to be in proximity to intensive care to receive chemotherapy.	We have amended the text to clarify. The final sentence should read: "The CS reports this to be delivered in an outpatient setting, however, the clinical advisor to the ERG suggested that although this is possible it would be more likely to be delivered at the centre administering axi-cel (that also has proximity to intensive care for delivery of axi-cel)."

References

1. Maurizio Martelli, Andrés Ferreri, Alice Di Rocco, Michela Ansuinelli, Peter W.M. Johnson. Primary mediastinal B-cell lymphoma. Critical Reviews in Oncology/Hematology. 2017; 113:318–327. Available online at: https://www.sciencedirect.com/science/article/pii/S104084281630244X?via%3Dihub. Accessed 10 May 2018.

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma

Addendum to the ERG appraisal of the additional information submitted by the manufacturer at the factual accuracy check

Produced by	Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)
Date	18/05/18

This document reports the results of additional analyses whereby the ERG alternative base-case is updated to reflect additional evidence provided by the company within the factual accuracy check document.

The additional scenarios replicate the ERG alternative base-case analysis presented in page 126-128 of the ERG report and update the rate of autologous stem cell transplant (ASCT) for the best supportive care (BSC) comparator to [redacted]. The rate of ASCT applied to BSC in the ERG alternative base-case was [redacted] as reported for the subgroup of patients in SCHOLAR-1 excluding ECOG 2-4. In the absence of evidence for this parameter particular to the SCHOLAR-1 ECOG 0-1 patient subgroup, we previously assumed the same rate as for the company's base-case. The company provided the rate of ASCT for the SCHOLAR-1 ECOG 0-1 patient subgroup ([redacted]) within the factual accuracy check document, and this was applied in the scenario analysis presented in this addendum. All other assumptions considered for the ERG alternative base-case analysis are applied to the additional scenarios, as follows:

1. BSC OS is based on SCHOLAR-1 ECOG 0-1 patient subgroup survival data;
2. Axi-cel overall survival is based on a loglogistic parametric model constrained by the progression free survival curve, with general population mortality risk applied at the point of convergence;
3. Costs and health related quality of life at 52 months and onward for patients in 'Pre-progression' are assumed to be equal to the age- and gender-matched UK population;
4. The cost of an intensive care unit (ICU) stay (£1,363) is assumed to represent a per-diem estimate and is applied to the average ICU hospitalisation period (4 days);
5. The follow-up costs assumed for patients receiving SCT are discounted;
6. The proportion of BSC patients who received SCT are assumed to have all undergone ASCT.

Results are presented in Table A for the modified intention to treat (mITT) and intention to treat (ITT) populations and for the alternative discount rates (3.5% and 1.5%). Due to issues identified in the ERG report regarding the code used to program the probabilistic sensitivity analysis, all results correspond to deterministic estimates.

Table A: Cost-effectiveness results - ERG alternative base-case updated to reflect rates of ASCT on SCHOLAR-1 ECOG 0-1 patient subgroup

Population	Scenario	BSC		Axi-cel		Inc. Costs	Inc. QALYs	ICER (£/QALY)
		Total costs	Total QALYs	Total costs	Total QALYs			
mITT	Discount rate 3.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Discount rate 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ITT	Discount rate 3.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Discount rate 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical engagement document for clinical, patient and commissioning experts and Kite/Gilead comment

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma

1.1. This document has been prepared by the NICE technical team with input from the technology appraisal committee chair.

1.2. NICE would like to engage with the company, clinical, patient and commissioning experts to comment on key areas of uncertainty in this appraisal.

The responses will be used by the technical team to inform both the company and the Appraisal Committee in preparation for the appraisal committee meeting on 31 July 2018.

1.3. This document includes:

- a summary of the background and technical considerations likely to be relevant to the clinical and cost effectiveness assessment for the appraisal.
- questions on key areas of uncertainty for your feedback and comment

This document is based on the key evidence and views submitted by the company, nominated clinical and patient experts and the ERG.

1.4. Technical team summary:

There is a paucity of data on outcomes for people with relapsed or refractory disease. The clinical effectiveness evidence submitted by the company for axicabtagene ciloleucel (axi-cel) came from ZUMA-1, an ongoing Phase 1/2 multicentre, open-label, single-arm study. The median follow-up for the trial is 15.4 months. Although the trial showed axi-cel to be effective at increasing response rate, progression-free and overall survival, the immaturity of the data and the lack of data comparing it with other treatments makes the magnitude of the benefit uncertain.

The company performed an indirect treatment comparison using patient level data from ZUMA-1 and SCHOLAR-1 (a retrospective cohort study) to estimate comparative effectiveness results for axi-cel and salvage chemotherapy (the current treatment option for people with refractory or relapsed diffuse large B-cell lymphoma). In order to address the baseline imbalances between the 2 studies, the company presented results from the intention-to-treat population and 2 standardised analyses. The result showed that axi-cel significantly improves overall survival compared with salvage chemotherapy. However, the adjustments to the SCHOLAR-1 cohort made by the company to account for differences in baseline characteristics between the 2 studies may not fully account for confounding. Therefore, there is considerable uncertainty about the comparative effectiveness estimates.

In the cost-effectiveness modelling, the company used a partitioned survival approach where PFS and OS estimates were modelled independently, with the proportion of progressed patients at each cycle, calculated as the difference between the OS and PFS curves. Axi-cel PFS was extrapolated from ZUMA-1 patient level data using a conventional single parametric survival curve while OS was extrapolated using a mixture-cure model. This models survival for 2 distinct cohorts, those who are cured (cure fraction) and those who are not. The OS curve is a weighted average of the age and gender matched general all-cause mortality and the OS parametric curve fitted to the ‘not-cured’ patients. The

weights correspond to the cure fraction and the proportion of 'not-cured' patients, respectively. The company's base case assumed a 50% cure fraction. OS for salvage chemotherapy was extrapolated based on the SCHOLAR-1 last refractory cohort (patients treated with chemotherapy after refractory status), and excluded patients with known ECOG scores 2-4, while PFS for salvage chemotherapy was derived by assuming the same ratio between PFS and OS for axi-cel in ZUMA-1 could be applied to the SCHOLAR-1 data.

The company's base case assumed that patients in the progression-free state for at least 2 years were long-term survivors and reverted to general population mortality and utility and no longer incurred the costs of medical resource use. It is generally accepted that some people would revert to general population mortality, but it is uncertain when this assumption should be applied in the cost-effectiveness modelling.

Costs of treatment, adverse events (AE), stem cell transplants (SCT) (procedure and follow up) and training costs were applied in the first model cycle (1 month) for both treatment arms. Health state medical resource use including professional and social services, health care professionals, treatment follow-up and hospital services were assumed to be the same for both treatment arms but applied based on health state. The company assumed all SCT were allogenic and applied the cost of an ICU stay for patients who experienced a cytokine release syndrome (CRS) AE Grade 3 and above, and costs for all patients who received either tocilizumab or intravenous immunoglobulins (IVIG) in the trial.

The company's base case incremental cost-effectiveness ratio (ICER) was [redacted] per quality adjusted life year (QALY) gained based on the confidential list price. The ERG base-case ICER was [redacted] per QALY gained, based on the confidential list price.

The differences between the company and the ERG base cases and scenario analyses are a result of key considerations and concerns (and subsequent analyses) from the ERG's review of the company submission regarding the following:

- The adjustment made to the SCHOLAR-1 cohort used for the comparative effectiveness results in the salvage chemotherapy treatment arm.

- The company's use of the modified intention-to treat (mITT) population for axi-cel.

- The company's approach for extrapolating overall survival for axi-cel.

- The assumptions around mortality risks for long-term survivors in the pre-progression state of the model.

- Uncertainties surrounding the health related quality of life and costs of adverse events associated with axi-cel (specifically for B-cell aplasia and CRS).

- Uncertainty surrounding broader infrastructure and training requirements for providing axi-cel in the NHS and their inclusion in the cost-effectiveness modelling.

- Uncertainty surrounding the assumption that all patients who received post-treatment stem cell transplants would receive allogenic transplants, and the incorporation of these costs in the model.

Both the company's and ERG's base case ICERs are significantly higher than the range that NICE considers an acceptable use of NHS resources. The NICE technical team and appraisal committee chair consider the assumptions presented by the company to be potentially over optimistic while those presented by the ERG to be potentially conservative.

Life expectancy for people with refractory or relapsed diffuse large B-cell lymphoma is generally considered to be less than 24 months. Axi-cel is likely to extend people's lives by more than 3 months. Based on the modelling

assumptions axi-cel is likely to meet NICE's criteria to be considered a life-extending treatment at the end of life.

Axi-cel could be considered innovative as it represents a step-change in the treatment of lymphoma. However, the company has not presented any evidence to suggest that there are additional benefits that have not been captured in the QALY calculations.

The company has suggested that it would prefer axi-cel to be available for routine use in the NHS and therefore has not made a case in its submission for axi-cel to be considered for use within the Cancer Drugs Fund. The overall survival data from ZUMA-1 are immature and no further analysis are expected in the near future. Collecting data on disease progression after axi-cel would help to address the uncertainties around the survival benefit in the axi-cel treatment arm. The technical team and the committee chair consider axi-cel to be a potential candidate for entry into the CDF (assuming that it meets the criteria to have plausible potential to be cost-effective).

The current pathways of care for the treatment of diffuse large B cell lymphoma, primary mediastinal lymphoma and transformed follicular lymphoma are well defined. Axi-cel will have a significant impact on the current pathways of care for these non-Hodgkin lymphomas (NHLs), and on other specialties, whose major engagement in the treatment pathway will now be required or will need to increase as a result of the delivery requirements and side effect profile of the new technology.

1.5. Summary of questions for comment and key considerations for the appraisal; refer to pages 10 to 19 for more detail:

- **Key areas of uncertainty:**

  Clinical evidence

  - **Appropriate adjustments for comparative effectiveness results** (See Question 1)
  - **Expected relapse rate after the period of follow-up available from ZUMA-1** (See Question 2)

Cost-effectiveness modelling

- **Extrapolation of overall survival for axi-cel** (See Question 3)
- **Mortality risks for long-term survivors** (See Question 4)

Implementation

- **Storage and administration of axi-cel in the NHS** (See Question 5)
- **Training requirements for healthcare professionals involved in the administration of axi-cel** (See Question 6)
- **Prioritisation of axi-cel eligible patients during phased implementation** (See Question 7)
- **Requirements for ambulatory care close to the hospital post infusion of axi-cel** (See Question 8)
- **ICU bed availability for patients receiving axi-cel** (See Question 9)

- **End of life** – end of life criteria are likely to be met.
- **Discount rate** – the alternative discount rate of 1.5% is unlikely to be considered appropriate (see NICE's 'Guide to the methods of technology appraisal' (2013) sections 5.6.3 and 6.2.19).
- **Innovation** – (See Questions 10) clinical experts state the technology is a step change and potential game changer in an area of high unmet need and is therefore likely to be considered innovative, but no additional benefits outside QALY gains have been identified.
- **Cancer Drugs Fund** – (See Question 11) clinical trial evidence shows a significant improvement in overall survival compared with salvage chemotherapy (the current treatment options for people with refractory or relapsed diffuse large B-cell lymphoma). However, the data is immature and there is uncertainty around the appropriate adjustment to comparative cohorts and correct methods for extrapolation. Extended follow-up could provide more robust estimates on which the committee could base its decision. Recommendation for the CDF would require plausible potential of the technology to be cost-effective. All plausible estimates using current list price are higher than what NICE normally considers good use of NHS resources.
- **Other areas of uncertainty**:(See Question 12)
    - Comparators (exclusion of pixantrone and use of a blended comparator)

- Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1
- Re-treatment with axi-cel in the ZUMA-1 population
- Patients receiving post-treatment SCTs and the associated assumptions
- AEs - occurrence of CRS and associated costs
- Long term costs of hypogammaglobulinemia and IVIG treatment in the cost-effectiveness model.

Questions for your comment

Question 1: Adjustment of SCHOLAR-1 cohort for comparative effectiveness estimates	
Questions for engagement	• *Are clinical outcomes for patients with ECOG status 0-1 and those with ECOG status 2-4 likely to be different?* • *Is a population from SCHOLAR-1 which includes patients with possible ECOG status 2-4 suitable to compare to the ZUMA-1 population whose eligibility criteria included only people with ECOG score 0-1?* • *Adjusting for ECOG status will not account for all imbalances in the SCHOLAR-1 and ZUMA-1 populations. Are there any additional comments on the approach used by the company or ERG to provide comparative effectiveness estimates?*
Why this issue is important	The adjustment to the SCHOLAR-1 cohort and resulting comparative efficacy results has a large impact on the ICER. Using the ERG's preferred salvage chemotherapy cohort which excludes patients with unknown ECOG score, the ICER increased from [redacted] per QALY gained in the company's base case to [redacted] per QALY gained.
Background/ description of issue	There is a paucity of data on outcomes for people with relapsed or refractory disease. The clinical effectiveness evidence submitted for axi-cel came from ZUMA-1, an ongoing Phase 1/2 multicentre, open-label, single-arm study. Comparative effectiveness estimates obtained from single-arm studies are inherently prone to bias unless appropriate adjustments are made. **The company** used patient level data from ZUMA-1 and SCHOLAR-1 (a retrospective cohort study) to provide comparative efficacy estimates. In order to address the baseline imbalances between the 2 studies they presented results from the intention-to-treat population and 2 standardised analyses. In the first standardised analysis the company excluded patients with ECOG score greater than 1 to align with the ZUMA-1 eligibility criteria. In the second standardisation, the company also excluded patients who received stem cell transplants after conventional therapy. The results of the indirect comparison are considered confidential by the company (therefore cannot be reported here) but demonstrated significant survival benefit in each scenario from

	treatment with axi-cel compared with salvage chemotherapy. **The ERG** was concerned that missing data was a problem for all covariates but were included the company's standardised analyses. The ERG requested an alternative approach at clarification stage excluding the patients with unknown ECOG score. Treatment with axi-cel remained more effective than salvage chemotherapy but overall survival (OS) in the salvage chemotherapy cohort increased marginally. The ERG considered the results to confirm the importance of ECOG status on OS in SCHOLAR-1. The company stated that the improved survival could be a result of a high proportion of patients subsequently receiving ASCT in this cohort.

Question 2: Expected relapse rate after the period of follow-up available	
Questions for engagement	• *Is a patient considered cured if they have not experienced an event by 15 months post treatment (trial follow period)?* • *What is the expected relapse rate for patients in remission between 2-5 years after treatment?* • *Is there additional data expected from the ZUMA-1 trial which would increase the duration of the follow-up period and reduce uncertainty in the assumptions around survival for patients who received axi-cel?* • *Would additional data collection reduce uncertainty?* • *Long-term survival is apparent in both treatment arms. Does this reflect clinical practice in the UK for patients treated with salvage chemotherapy?*
Why this issue is important	There is limited follow-up on patients who have received axi-cel. Any assumptions made from the clinical data are subject to uncertainty.
Background/ description of issue	The clinical effectiveness evidence submitted for axi-cel came from ZUMA-1 and at the data cut-off for this submission, median follow-up was only 15.4 months. **The company** report Kaplan-Meier plots for progression-free survival (PFS) and OS (see appendix A) which appear to plateau around 6 months for PFS and 10 to 11 months for OS with few events occurring after these time points. The PFS was reported at 3 month intervals. The results show at 6 months PFS was 49% (95% CI, 39 to 58), at 12 months 44% (95% CI, 31 to 50) and at 15 months 41% (95% CI, 31 to 50). The OS rates were

	59% (95% CI, 49 to 68) at 12 months, and 52% (95% CI, 41 to 62) at 18 months. The company suggested that these data support the potential for cure for a district group of patients who respond to therapy and are able to maintain their response leading to long-term survival. **The ERG** noted that from month 12 onwards the KM plots become heavily influenced by censoring of data with limited numbers of patients remaining 'at risk' beyond 12 months. The ERG highlighted the need for cautious interpretation of the ZUMA-1 data and believe the uncertainty in the slope of the curve can only be resolved from longer periods of follow-up.

Question 3: Appropriate extrapolation for overall survival in axi-cel treatment arm	
Questions for engagement	• *How long are patients with progressed disease expected to survive?* • *Is it plausible that a patient could be cured in terms of survival but not from disease progression?* • *Would patients who responded to treatment be expected to experience additional mortality risks or have a different quality of life compared to the general population for the first 1-2 years after treatment?* • *The company's assumptions appear optimistic based on the evidence available. The ERG have proposed an alternative scenario which accounts for the uncertainty in the data. Is it reasonable to use the progression free survival curve to estimate the proportion of patients' cured following treatment with axi-cel?*
Why this issue is important	The majority of survival benefits of axi-cel are conferred during the extrapolation period and therefore has a large impact on the ICER. Using the ERG's extrapolation for OS, the ICER increased from [redacted] per QALY gained in the company's base case to [redacted] per QALY gained.
Background/ description of issue	Median OS was not reached in the ZUMA-1 trial so OS needs to be extrapolated over the model time horizon. The use of single parametric survival curves to model axi-cel OS would produce implausible results as they do not account for long-term survival. **The company** used a mixture cure model (MCM) with Weibull distribution to estimate a cure fraction. For mixture cure models, the 2 distinctive patient groups are modelled separately. The company's base case

	extrapolation assumed long-term remission for 50% of patients treated with axi-cel that occurs immediately after infusion, restoring patients to the age and gender-matched mortality of the general UK population. Uncured patients follow the parametric survival curve from the time of infusion. The cure fraction for the company's alternative modelling approaches of OS varied between 1% and 53% of patients. **The ERG** was concerned that the company's approach produced estimates that were overly optimistic. Existing follow-up after axi-cel is limited and the data from ZUMA-1 is considered by the ERG to be too immature to robustly estimate size of the cure fraction. The ERG proposed an alternative approach in which it used the cure fraction estimated for axi-cel PFS. The company's alternative modelling approaches for axi-cel PFS given in response to clarification gave more robust estimates of the cure fraction (43-40%). The ERG selected the best fitting single parametric OS curve for axi-cel (loglogistic) and constrained it so that patients receiving axi-cel were restored to the age and gender-matched mortality of the general UK population once the OS curve converged with the PFS MCM curve. This approach led to a cure fraction of 40% occurring around 52 months. The ERG noted that the difference in PFS and OS cure fraction estimates could be because of the number of patients who become cured following progression (as a result of subsequent therapies) or the immaturity of the data.

Question 4: long-term survivors risk of excess mortality compared to the general population	
Questions for engagement	• *Do long term survivors experience excess mortality compared to the general population?* • *How long after diagnosis/treatment would any excess mortality be expected to last for long term survivors?* • *Is there an increased long-term risk of infection and excess mortality due to prolonged B cell aplasia?* • *The company and ERG provide opposing views on the evidence available for excess mortality risks, which is the most applicable to clinical practice in the UK?*

Why this issue is important	Applying an arbitrary 0.9 multiplier for mortality to the cure fraction to the company's preferred assumptions, the ICER increases from [redacted] per QALY gained in the company's base case to [redacted] per QALY gained. Applying the ERG's preferred assumptions of cure at 52 months without any additional mortality applied to the cure fraction or changes to the extrapolation of overall survival increases the ICER to [redacted] per QALY gained.
Background/ description of issue	There is plausible potential for long term survival for people with relapsed or refractory disease. **The company** assumes pre-progression patients after 2 years revert to age-matched general population mortality. . **The ERG** believe the company's 24 month assumption is equivalent to a structural cure assumption embedded into the model to account for long term survival in people with relapsed or refractory disease. These patients experience no excess mortality compared to the general population. Clinical and patient expert statements suggest patients eligible for axi-cel have often experienced harsh side effects as a result of multiple courses of chemotherapy. The company's mortality estimate is taken from a US based study however, the ERG identified several other studies which suggest significant mortality remains for up to 5 years post diagnosis. In the ERG's preferred base case a structural cure assumption is made at 52 months aligned to the convergence of the OS and PFS curve.

Question 5: Storage and administration of CAR T therapy in the NHS	
Questions for engagement	• *What additional storage equipment and space would be required for centres to administer axi-cel?* • *Would specialist centres need to purchase additional thawing equipment to use in the administration of axi-cel?*
Why this issue is important	No costs of storage or thawing equipment are included in the cost-effectiveness model.

Background/ description of issue	The list price of axi-cel includes all shipping, engineering and generation of the CAR T-cells. The company also include costs of drug administration which cover average cost of elective inpatient excess bed days The description of the technology given by the company includes a step-by-step process for administering axi-cel to a patient. Axi-cel is cryopreserved by the company and should be stored at low temperatures to avoid thawing. Prior to infusion the product is thawed and administered to the patient. It could be possible a delay in manufacturing would mean patients receive bridging therapy prior to receipt of axi-cel. During this time specialist centres may be required to store the product until the patient was ready to have axi-cel.

Question 6: Implementation of CAR T therapy in the NHS – training requirements	
Questions for engagement	• *What roles and how many healthcare professionals are likely to be reqired to administer CAR T cell therapy in specialist centres?* • *Would specialists providing care to patients who experience AEs after infusion with axi-cel also require specific training on CAR T therapy?* • *Uncertainty around the training requirements for healthcare professionals is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?*
Why this issue is important	The effectiveness and safety of CAR T treatment is dependent on the provision of appropriate training. The ERG's exploratory scenarios marginally increase the company's ICER but is an important consideration in the implementation of CAR T and the potential budget impact assessment.
Background/ description of issue	The technology requires new service specifications and broad infrastructure requirements. **NHS England** state implementation of CAR T therapy will require substantial workforce and infrastructure changes within the NHS. **The company** assumed that training would require 16 hours of consultant time per centre infusing 20 patients every 2 years - equivalent to one specialist.

	A clinical expert stated a highly specialised and trained team would be required to deliver CAR T therapy. This would be comprised of physicians (middle grade and senior), nurses, intensivists and technicians. **The ERG** considered the cost of training included in the model to underestimate the training requirements needed to implement CAR T cell therapy in clinical practice. Alternative scenarios including the training costs of 5-10 healthcare professionals are provided.

Question 7: Implementation of CAR T therapy in the NHS – Prioritisation of eligible patients	
Questions for engagement	• *Who would determine which patients are prioritised to receive axi-cel therapy during a phased implementation?* • *What criteria would or should be used to prioritise patients for axi-cel treatment?* • *Given the novelty of the treatment and limited information around follow up, how would patients who received axi-cel be monitored and new knowledge shared between specialist centres to improve overall patient care?* • *Uncertainty around the requirements for multidisciplinary teams and phased implementation is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model and budget impact assessment?*
Why this issue is important	As a result of the novelty of the treatment, the expertise required and the logistics involved, all key stakeholders have indicated the need for a phased implementation period if recommended. NHS England, clinical experts and the ERG have noted that this could cause equality issues around eligibility of access as referral pathways and patient selection would need to be carefully considered.

Question 8: Implementation of CAR T therapy in the NHS – ambulatory care close to the hospital post infusion	
Questions for engagement	• *Where would a patients stay for aftercare if their home is not located close to the treatment centre?* • *How long would patients be expected to stay in close proximity to the treatment centre following CAR T treatment?* • *What provisions would be made for family and carers during this period?* • *Are there other conditions with similar requirements which would be used as a model for axi-cel?* • *Uncertainty around the need for ambulatory care is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?*
Why this issue is important	No costs of ambulatory care are included in the cost-effectiveness model.
Background/ description of issue	Axi-cel is given as a single infusion. There is a delay between the collection of white blood cells by leukapheresis to the administration of axi-cel. After infusion of axi-cel, people are likely to remain in hospital for a period of time (average stay from ZUMA-1 trial data is academic in confidence and therefore not reported here). During this time they are monitored and treated for AEs. **The company** stated that the safety profile of axi-cel is well described, with established protocols to manage AEs which ensures an acceptable risk-benefit ratio for the target patient population. One such protocol is the requirement of patients to remain in close proximity to the treatment centre of 1 month following infusion. **The ERG** and **NHS England** are concerned about equity issues around access to treatment based on geographical location, and who will bear the costs of ambulatory care for patients not living in close proximity to the treatment centre.

Question 9: Implementation of CAR T therapy in the NHS – ICU bed availability	
Questions for engagement	• *Would an ICU bed need to be available for a patient before they were able to start their infusion with axi-cel?* • *What proportion of patients would be admitted to ICU following infusion with axi-cel if they did not experience a CRS AE?* • *How long would a patient admitted to ICU as the result of (a) axi-cel infusion or (b) a serious CRS event be expected to stay?* • *Uncertainty around the requirements for ICU beds is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?*
Why this issue is important	Time spent in ICU following a CRS AE (Grade 3-4) increased the company's base case ICER from [redacted] per QALY gained to [redacted] per QALY gained. Additional capacity requirements would increase the ICER further and could cause opportunity loss for other patients using NHS services which would need careful consideration by the committee and implementing partners.
Background/ description of issue	Data on adverse events was obtained from ZUMA-1 phase 1 cohort. Costs associated with an AE of CRS included cytokine inhibitor drugs and intensive care hospitalisation for the proportion of patients whom required it in the trial population. **The company** calculated the cost of an ICU hospitalisation as the weighted average of HRGs for non-specific, general adult critical care in the NHS national schedule of reference costs for patients in whom it was required during ZUMA-1. **The ERG** considered it is possible that specialist centres may require an ICU bed to be available during the period a patient is considered to be at risk of CRS, regardless of whether they then actually experience a serious AE.

Question 10: Innovation	
Questions for engagement	• *Do you consider that the use of the technology will result in any substantial benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?* • *Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy. Would this have an impact on a patient's health-related quality of life?* • *Should a weight be applied to the QALYs gained in the axi-cel treatment arm to account for the large survival gains/QALYs?*
Background/ description of issue	**Clinical experts** state that the technology is a step change and potential game changer in an area of high unmet need and is therefore likely to be considered innovative. **The ERG** highlighted previous NICE committees applying discretion in determining whether it reasonable to apply a weight to the QALYs gained acknowledging the large survival benefit and represented a step-change in treatment. **The company** stated that axi-cel provides complete personalised immunotherapy. It has demonstrated a positive benefit-risk profile and offers a new and effective treatment option for patients with no curative options and short expected survival.

Question 11: Cancer Drugs Fund (CDF)	
Questions for engagement	• *Please specify whether you consider the technology to be a candidate for entry into the CDF?* • *What data may be available for collection to resolve the uncertainty in this appraisal?* • *How would additional data collection resolve the uncertainty in this appraisal?* • *What timelines would be appropriate for additional data collection?* • *Do you know of any additional evidence currently or likely to become available that may help to address the uncertainties?*

Background/ description of issue	• NICE is now able to recommend a cancer drug for use in the CDF if it has the plausible potential to be cost-effective, but the clinical evidence is not robust enough for a recommendation in routine use. The drug will then be available within the CDF while more evidence is gathered to resolve the key areas of uncertainty**.**

Question 12: Other areas of uncertainty	
Comparators (exclusion of pixantrone)	• *In clinical practice in the NHS, is pixantrone monotherapy given to patients with relapsed or refractory disease?*
Comparators (use of a blended comparator)	• *Are salvage regimes considered equally effective, with and without ritixumab?* • *Are salvage regimes distributed equally to patients with relapsed or refractory DLBCL, PLBCL and TFL in clinical practice in the NHS?*
Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1	• *What is the average time period between the clinical decision taken to administer salvage chemotherapy to a patient and the patient receiving chemotherapy?* • *Would there be a concern that patients may experience disease progression during the additional time required for manufacturing of axi-cel?*
Re-treatment with axi-cel in the ZUMA-1 population	• *Would patients who received retreatment with axi-cel be expected to have improved outcomes compared with those whose disease progressed and did not receive a second round of treatment?*
Patients receiving post-treatment SCTs and the associated assumptions	• *What proportion of patients (R/R after 2nd line or who previously failed an ASCT) receiving salvage chemotherapy would become eligible for a SCT in clinical practice?* • *Are outcomes for patients who receive a stem cell transplant likely to be significantly different from patients who receive salvage chemotherapy?* • *Would patients be likely to receive autologous or allogenic stem cell transplants after response to treatment with either salvage chemotherapy or axi-cel?*

	• *How long on average would patients receive follow-up care following a stem cell transplant?*
Long term usage and costs of IVIG treatment - real world experience	• *What proportion of patients would you expect to still be affected by B-cell aplasia after 12 months following treatment with axi-cel?* • *Would these patients require continued IVIG treatment and for how long?*

Appendix A

Figure 1. Progression-free survival in the ZUMA-1 updated analysis (n=108, median follow-up 15.4 months)

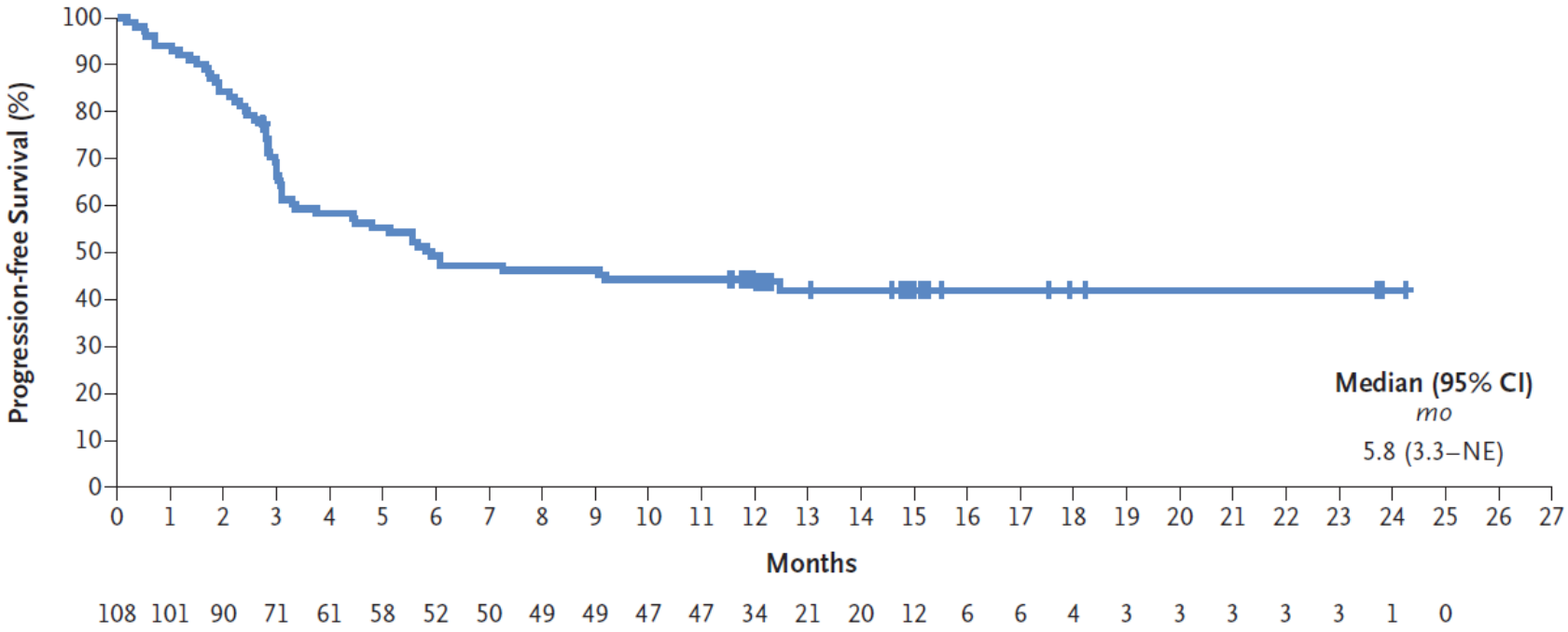
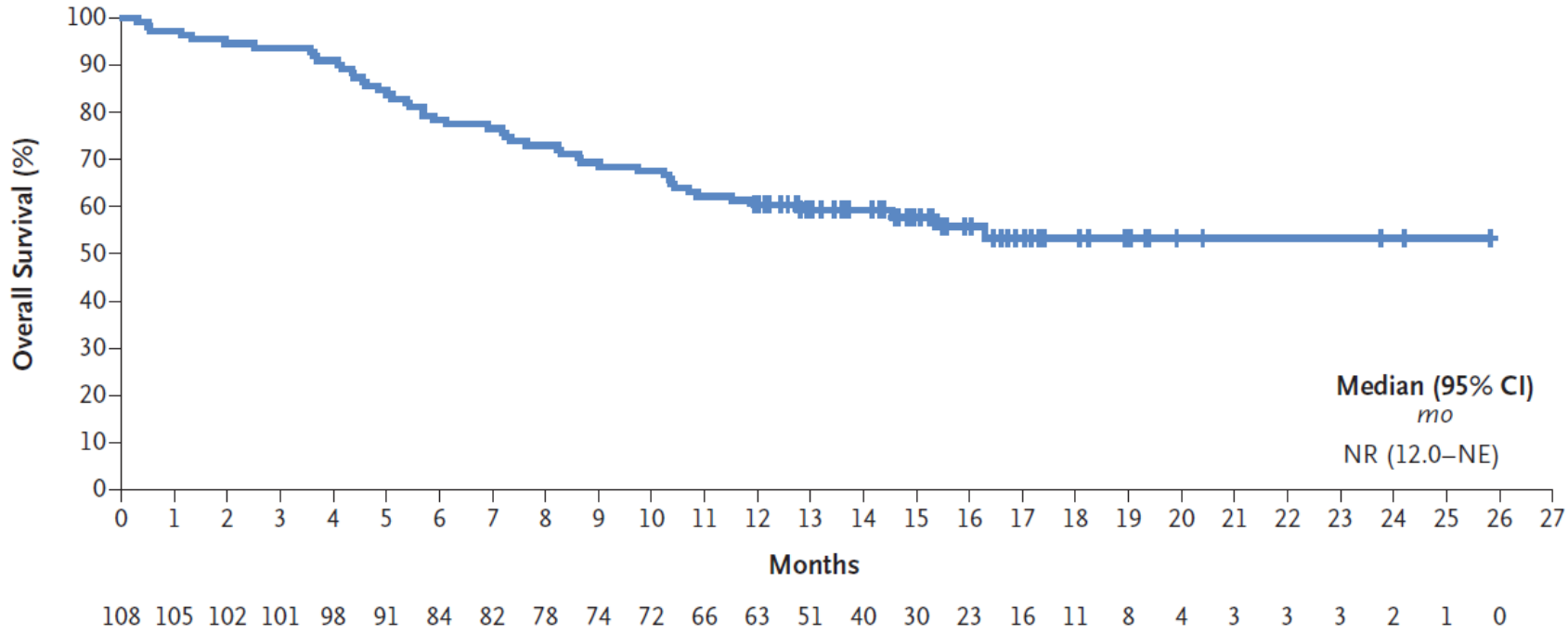


Figure 2. Overall survival in the ZUMA-1 updated analysis (n=108, median follow-up 15.4 months)



Source of Figures 1 and 2: Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *NEJM*. 2017.

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Technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Thank you for agreeing to give us your comments and feedback as part of the technical engagement step to assist us in identifying the most plausible assumptions in the clinical and cost-effectiveness for this technology.

As a technical engagement stakeholder for this appraisal step, we highly appreciate your input, comment and ongoing support for this appraisal.

To help you give your views, please use this questionnaire. You do not have to answer every question. The text boxes will expand as you type. Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

Information on completing this technical engagement response

- Prior to completing this response table please see the technical engagement document which summarises the background, and submitted evidence for this appraisal. This will provide you with context and outline the questions below in greater detail for which we require your comments and feedback.
- 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.

Please note that comments from the technical engagement will be collated and summarised as part of the committee pre-meeting briefing document, which will be made available to all stakeholders with a signed confidentiality agreement as part of the committee papers accompanying the post committee documentation (ACD or FAD) following the meeting on 31 July 2018.

Deadline for comments **5pm on 22 June 2018**

NICE National Institute for Health and Care Excellence

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)	**Director, Market Access**
Are you (please tick all that apply)	☒ a representative from the company (Kite, Gilead)? ☐ a clinical expert? ☐ a commissioning expert? ☐ a patient expert or organisation? ☐ an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Questions for engagement

Question 1: Adjustment of SCHOLAR-1 cohort for comparative effectiveness results	
Are clinical outcomes for patients with ECOG status 0-1 and those with ECOG status 2-4 likely to be different?	Yes, patient outcomes are likely to be different for patients with ECOG status 0-1 compared with those who have ECOG status 2-4. Patient's fitness status and comorbidities are important factors when considering a patient for transplant. Patients with ECOG 0-1 status are more likely to be able to undergo a transplant than patients with an ECOG of 2 or more. In the SCHOLAR-1, the plateau observed in the OS curves is

<table>
<tr><td></td><td>most likely as a result of a minority of patients that were able to undergo a SCT (in SCHOLAR-1 - median OS in patients post ASCT was 14.4 months vs 5.1 months in patient that did not undergo ASCT; 31 patients who achieved a CR underwent ASCT and their median OS was more than 6 years at the time of the analysis).

Clearly, surviving patients on this plateau will <u>not</u> be candidates for axi-cel. Axi-cel would only be considered for patients relapsing post ASCT, where transplant has failed, or to patients with chemo-resistant disease who in the absence of sufficient response to chemotherapy cannot reach transplant. Moreover, patients with ECOG status 2-4 will likely not be candidates for axi-cel given the fitness requirements for treatment.</td></tr>
<tr><td>Is a population from SCHOLAR-1 which includes patients with possible ECOG status 2-4 suitable to compare to the ZUMA-1 population whose eligibility criteria included only people with ECOG score 0-1?</td><td>In order to conduct the most appropriate and robust analysis, ECOG status 2-4 patients were excluded from analysis to provide a more appropriate control group for comparison with patients in ZUMA-1 who were all ECOG status 0-1. As discussed above, patient outcomes between ECOG 0-1 and ECOG 2-4 are likely to be different; however, ECOG is not the only factor contributing to patient outcomes. There was an imbalance in the baseline characteristics between the ZUMA-1 and SCHOLAR (please see table below), with patients in the ZUMA-1 trial having worse prognostic factors than patients in the SCHOLAR-1, namely:

• Older age
• Higher IPI
• Advanced disease stage
• Prior lines of therapy.

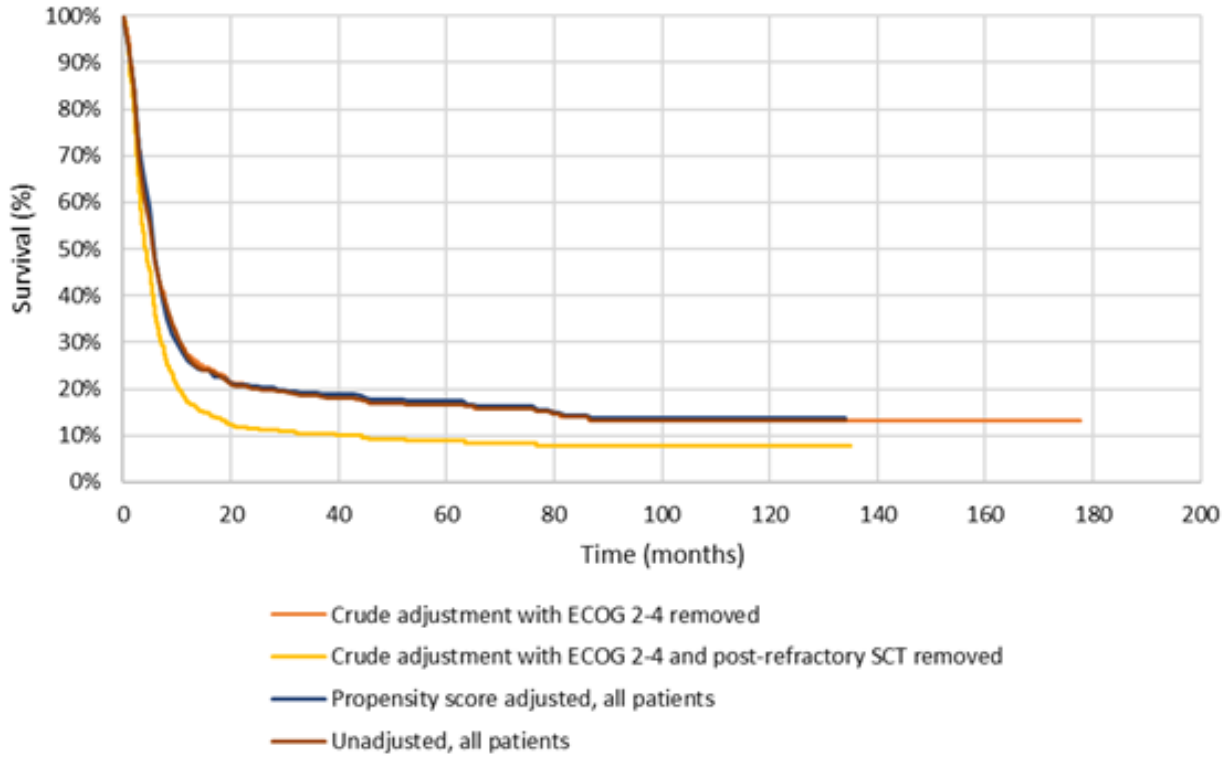
Table 1: Baseline characteristics on ZUMA-1 and SCHOLAR-1
<table>
<tr><th></th><th></th><th colspan="4">SCHOLAR-1</th></tr>
<tr><th></th><th>ZUMA-1 mITT (N = 108)</th><th>All patients (N = 593)</th><th>ECOG 0-1 (N = 188)</th><th>ECOG 2-4 (N = 36)</th><th>ECOG unknown (N = 369)</th></tr>
</table></td></tr>
</table>

Age (years)					
Median (Min, Max)	59 (23, 76)	56 (20, 83)	54 (20, 69)	56 (23, 69)	56 (20, 83)
<65 Years, n (%)	81 (75)	509 (86)	181 (96)	33 (92)	295 (80)
≥65 Years, n (%)	**27 (25)**	**84 (14)**	7 (4)	3 (8)	74 (20)
IPI Score					
0 – 1, n (%)	27 (25)	69 (12)	69 (37)	0 (0)	0 (0)
2, n (%)	33 (31)	61 (10)	54 (29)	6 (17)	1 (0)
≥3, n (%)	**48 (44)**	**80 (13)**	54 (29)	26 (72)	0 (0)
Not Assessed, n (%)	0	383 (65)	11 (6)	4 (11)	368 (100)
Disease Stage					
I-II, n (%)	18 (17)	69 (12)	62 (33)	6 (17)	1 (0)
III-IV, n (%)	**90 (83)**	**149 (25)**	119 (63)	27 (75)	3 (1)
Not Assessed, n (%)	0	375 (63)	7 (4)	3 (8)	365 (99)
Total Number of Lines of Chemotherapy & ASCT Received					
1, n (%)	2 (2)	89 (15)	44 (23)	8 (22)	37 (10)
2-3, n (%)	65 (60)	464 (78)	143 (76)	28 (78)	293 (80)
≥4, n (%)	**35 (33)**	**37 (7)**	1 (1)	0 (0)	36 (10)

Key: IPI, international prognostic index; ECOG, Eastern Cooperative Oncology Group; ASCT, autologous stem cell transplant; mITT, modified intent to treat

Taking these imbalances into consideration, the most plausible comparative effectiveness between ZUMA-1 and SCHOLAR-1 was established by excluding patients with known ECOG 2-4 to align to the ZUMA-1 inclusion criteria. In this analysis we included patients with ECOG unknown to provide the most robust dataset, maximising patient level data and sample size for analysis. We accept that a small proportion of patients in the unknown category may have ECOG 2-4, however, this is unlikely to impact on the comparative effectiveness as much as the existing imbalances already described above.

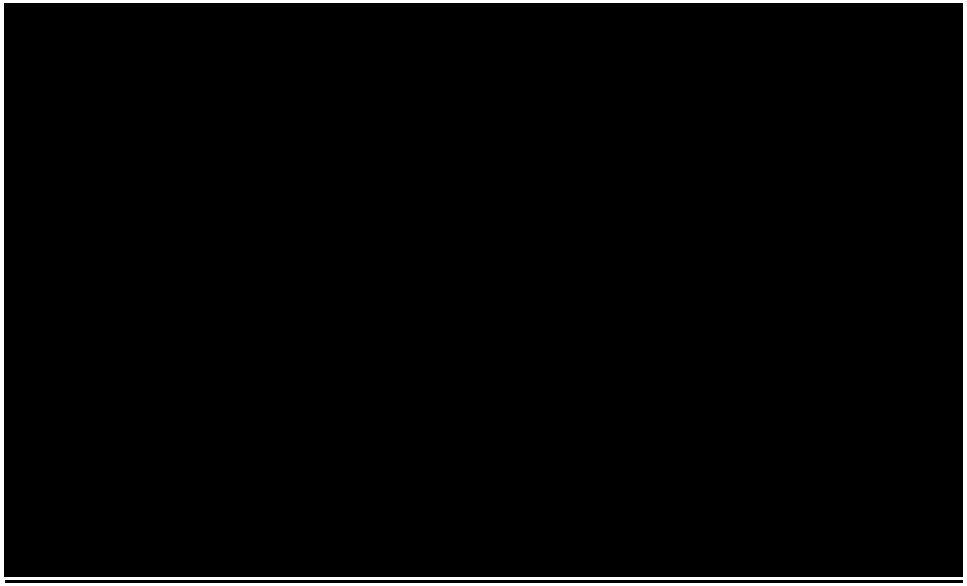
	If patients with unknown ECOG were to be removed as per the ERG base case, the proportion of patients in that group that underwent previous SCT is over-represented increasing to 41% which is higher than the overall SCHOLAR-1 SCT rate of [redacted]. This biases the overall survival outcomes in favour of BSC. As explained in the previous question, patient outcomes post SCT are significantly better than patients not able to undergo SCT and some patients achieve long-term survival post SCT. Patients that are in long-term remission post SCT are not the patients that will be treated with axi-cel. Whilst the data from SCHOLAR-1 do not align exactly with UK clinical practice (e.g. the proportion of patients receiving a SCT is much lower in clinical practice) it can be considered the most appropriate data set for comparison with ZUMA-1 and subsequently for the purposes of decision making.
Adjusting for ECOG status will not account for all imbalances in the SCHOLAR-1 and ZUMA-1 populations. Are there any additional comments on the approach used by the company or ERG to provide comparative effectiveness estimates?	As described above, imbalances other than ECOG in the baseline characteristics have been identified between ZUMA-1 and SCHOLAR-1 and which favour SCHOLAR-1. To account for these imbalances, three different scenarios were explored by the company regarding OS: 1. no adjustments were made to SCHOLAR-1 compared to ZUMA-1 2. a propensity score adjustment was performed 3. SCHOLAR-1 was adjusted by excluding ECOG 2-4 and post-refractory SCT patients. The impact of excluding ECOG 2-4 and post refractory SCT patients is shown below in Figure 1. This was explored because of the difference in the proportions of patients receiving post refractory SCT in the ZUMA-1 and SCHOLAR-1 studies: [redacted] and [redacted], respectively. Figure 1 shows how survival is improved in SCHOLAR-1 patients receiving post-refractory SCT (company base case) compared to not receiving post-refractory SCT. Therefore, the company base case (including SCHOLAR-1 patients who receive post-refractory SCT) is considered potentially conservative regarding comparative effectiveness for axi-cel versus BSC – i.e. the results have the potential for bias in favour of the comparative BSC arm. **Figure 1: Overall survival of SCHOLAR-1 patients, base case and different scenarios tested**



The propensity score matching method attempts to adjust for differences between characteristics between ZUMA-1 and SCHOLAR-1 populations at baseline. These were: age, disease stage, diagnosis (i.e. DLBCL versus PMBCL and TFL), and relapse post-ASCT status. It was found that the propensity score adjustment made very little difference to the company base case (see Figure 1). The scenario without any adjustment for imbalances between ZUMA-1 and SCHOLAR-1 also produced an OS similar to the company base case. These findings support the company's base case approach of adjusting SCHOLAR-1 by removing known ECOG 2-4 patients and retaining patients with unknown ECOG.

Question 2: Expected relapse rate after the period of follow-up available from ZUMA-1	
Is it appropriate to assume a patient is considered if they have not experienced an event by 15 months post treatment (trial follow-up period)?	In the ZUMA-1 trial, there was a steep drop in the PFS curve early on with over half of progressions occurring by month 3, followed by a plateau at around month 6 onwards. A plateau in the OS curve was observed from around 12 /13 months. Given the aggressive nature of the disease, it is generally accepted that most relapses tend to occur earlier rather than later with current treatments, and patients are discharged after 24 months if they are in remission. Additional data analysis of the ZUMA-1 presented at ASCO 2018[1] show that response to axi-cel at 3 months (CR or PR) may be prognostic for long-term remission, i.e. if patients show a complete response at 3 months they are likely to remain a responder. Median PFS is not yet reached in that group and is approximately 70% at 15 months. CAR-T cells expand upon infusion and can persist at detectable levels for years continuing to have potential long term efficacy. Their long term persistence may be able to maintain immune surveillance and control of the tumour[2]. Given that R-chemotherapy is a relatively short duration intervention that can drive a complete response and long term remission/cure it may be plausible that CAR-Ts' long-term persistence could induce similar if not more durable responses. In addition, some patients (18 out of 44 patients) treated with axi-cel that were in PR were able to deepen their response to CRs over time[1]. Given all of the above, it is reasonable to assume that if a patient has not relapsed by 15 months, they are at least as likely to have long -term remission as those who receive chemotherapy in the same situation.
What is the expected relapse rate for patients in remission between 2-5 years after treatment?	According to the BCSH guidelines, the relapse rate with current treatments after 24 months is less than 10%. Patients that are in remission at 24 months are discharged in most centres and assumed to have a similar mortality risk to the age-adjusted population. Whilst care in extrapolating this is required, the relapse rates observed with CAR-Ts in the long term follow-up from the NCI study[2] of seven patients show that four patients have an ongoing CR after 24 months (38, 44, 51, 56 months) and have not relapsed. Although the numbers are small, these indicate a

	low relapse rate in patients that were able to achieve a CR. Furthermore, it should be noted that the proportion of patients remaining in CR (four out of seven) is similar to that observed at the 15.4 months follow-up in the ZUMA-1 trial.
Is there additional data expected from the ZUMA-1 trial which would increase the duration of the follow-up period and reduce uncertainty in the assumptions around survival for patients who received axi-cel?	Yes, 24 months follow-up data is expected to be presented at ASH in Dec 2018. This will include additional data on PFS and OS.
Would additional data collection reduce uncertainty?	Yes. The additional data from the ZUMA-1 trial that will be presented at ASH in December 2018 has the potential to reduce uncertainty in the long-term projection of survival and progression of patients. This would help to further increase confidence in that the plateau in the data can be expected to continue, suggesting long-term remission in a proportion of axi-cel patients. Additional data would also help to have more robust estimates of survival and subsequent SCT for patients who have disease progression after initial axi-cel treatment.
Long-term survival is apparent in both treatment arms. Does this reflect clinical practice in the UK for patients treated with salvage chemotherapy?	As outlined above, patients that are able to undergo SCT have the best outcomes with the possibility of long-term survival as indicated in fig 1 above. The probability of getting a patient to SCT decreases as you progress through lines of therapy and only a minority of patients will be able to undergo SCT in any line of salvage. Axi-cel would be given to patients that have been previously treated with at least 2 lines of therapy and have already had the opportunity to have an ASCT if eligible.
Question 3: **Appropriate extrapolation for overall survival in axi-cel treatment arm**	
How long are patients with progressed disease expected to survive?	There are 56 patients in ZUMA-1 who had disease progression. The post-progression survival KMs for all patients in ZUMA-1 with disease progression (n=56) is shown in **Figure 2**. The median post-progression survival is around 5 months and around 20% of patients are alive at 12 months from disease progression. The post progression survival from ZUMA-1 shows that ERG's base case survival extraction for axi-cel (where post progressions survival is zero after OS and PFS converge) is not plausible.

	Figure 2: Survival of patients with progressed disease in ZUMA-1 
Is it plausible that a patient could be cured in terms of survival but not from disease progression?	There are a number of patients who have progressed but are alive at 12 months. It is plausible that a minority of patients that have progressed may have some clinical benefit from the persistence of CAR-T and have prolonged survival. Further data from the 2 year data cut that will be presented as ASH in December 2018 should confirm the extent of this benefit.
Would patients who responded to treatment be expected to experience additional mortality risks or have a different quality of life compared to the general population for the first 1-2 years after	The patients experienced a decrease in utility scores from screening to week 4 which is in line with the associated CAR-T toxicity observed in the first few weeks – CRS and neurotoxicity with a median onset of 2 and 5 days respectively. QoL scores increased above baseline at months 3 and

treatment?	6. Any increased mortality associated with CAR-T is most likely to occur in the first few days post-infusion due to the well characterised transient risks associated with CRS and neurotoxicity. However, based on the current knowledge of this toxicity there are clear protocols in place to mitigate this and prevent any life-threatening/fatal events. An age matched general population cohort will not be selected on the basis of ECOG status or general fitness to receive CAR-T therapy. So, given the age of patients with DLBCL, an age matched general population would be expected to have considerable prevalence of diabetes, ischaemic heart disease, chronic renal disease, respiratory disease etc. which would impact on their mortality. As the CAR-T treated population is fitter and without these comorbidities they would have a lower risk.
The company's assumptions appear optimistic based on the evidence available. The ERG have proposed an alternative scenario which accounts for the uncertainty in the data. Is it reasonable to use the progression free survival curve to estimate the proportion of patients' cured following treatment with axi-cel?	Kite/Gilead does not agree that ERG's base case axi-cel OS extrapolation approach (essentially using the PFS curve to model OS and assume zero survival after progression after around 2 years) is fair or plausible. Instead, compared to the observed trial data from ZUMA-1, it seems to lead to a bias against axi-cel. Kite/Gilead's key concerns of ERG's approach and the justification for these concerns are: • OS, not PFS, is the gold standard and the most objective and relevant clinical outcome for oncology. However, ERG's OS extrapolation ignored the plausibility of OS extrapolation and instead relied on a fitted PFS curve for OS extrapolation (i.e. OS follows PFS when the two converge). Kite/Gilead believes the focus should be on identifying the most plausible OS extrapolation, rather than relying on the PFS extrapolation being applied to the OS extrapolation. • The ERG predicted OS base case for axi-cel is not clinically plausible and has very poor visual fit to the trial KM data (note, Figure 18 in ERG report did not overlay the OS KM data). Kite/Gilead believes ERG's base case OS extrapolation approach significantly underestimates the OS for patients receiving axi-cel. • The ZUMA-1 OS and PFS KM curves indicate that there are significant gaps between the OS and PFS curves, and that the plateaus occur at different levels for OS and PFS, with the OS plateau being higher than PFS plateau. The ERG's base case OS and PFS extrapolation

	contradicts these observations. • Because the very conservative and implausible choice of axi-cel OS in ERG's base case, ERG's base case predicts there are no patients with post-progressive disease alive after around 2 years (25 months) from the commencement of treatment. Kite/Gilead believes this is not clinically plausible. Patients were progressing up to 12 months from the commencement of the trial and figure 3 illustrates that of patients who progress, 23% survive for an additional 12 months following disease progression. It is therefore reasonable to believe a non-negligible number of patients with progressive disease will remain alive after 24 months. Additionally, Kite/Gilead believes, similar to recent immune-oncology treatments (e.g. nivolumab, pembrolizumab), that a proportion of patients treated with axi-cel who may have clinically progressed are long-term survivors. Therefore, Kite/Gilead believes the ERG's base case axi-cel extrapolation underestimates the QALYs of potential long-term survivors who have initial disease progression.
Question 4: long-term survivors risk of excess mortality compared to the general population	
Do long term survivors experience excess mortality compared to the general population?	Given the fitness status requirements for patients to be eligible for CAR-T treatment – e.g. good pulmonary, liver, heart and renal function, it is plausible that long term survivors will have similar or even lower mortality risk compared to the general population Long-term survivors have a potential risk of developing chemo-related toxicities (e.g. cardiotoxicity with anthracyclines) or secondary malignancies, independent of CAR-T treatment. This risk is not clearly defined and there are conflicting reports in the literature. The ESMO guidelines, having reviewed all available evidence, have concluded that patients with EFS at 24 months have a mortality risk of the age-adjusted population. Furthermore, with long term follow-up in 7 patients[2] no long-term chronic toxicity (except for B cell depletion) or increased mortality risk was attributable to axi-cel.

Is there an increased long-term risk of infection and excess mortality due to prolonged B cell aplasia?	B-cell aplasia is a common phenomenon in the rituximab era and clinicians are very experienced in managing it. B-cell aplasia was present in 60% of 80 evaluable patients at baseline. At month 3 post axi-cel treatment, over 75% of 84 evaluable patients had B-cell aplasia. Of these, 11% experienced grade 1 or 2 hypogammaglobulinaemia and 7 patients received immunoglobulins as replacement therapy. In long term follow-up[2], patients had a low incidence of severe infections despite prolonged periods of B-cell depletion and no increased mortality risk was reported due to B-cell aplasia. Importantly, in 3 of the 4 patients in CR, B-cell counts recovered.
How long after diagnosis/treatment would any excess mortality be expected to last for long term survivors?	As discussed above no long-term mortality risks have been identified associated with CAR-Ts at this point in time.
The company and ERG provide opposing views on the evidence available for excess mortality risks, which is the most applicable to clinical practice in the UK?	
Question 5: Storage and administration of CAR-T therapy in the NHS	
What additional storage equipment and space would be required for centres to administer axi-cel?	No additional storage or space would be required as centres are already equipped with what is required for SCT. Patient numbers per unit per month are not expected to be substantial at around three to five patients per unit per month by the fourth year of introduction; we do not believe this would present a resource constraint for transplant units that would justify additional capital investment.
Would specialist centres need to purchase additional thawing equipment to use in the administration of axi-cel?	No additional thawing equipment will be needed beyond what is already used for SCT.

Question 6: Implementation of CAR-T therapy in the NHS – training requirements	
What roles and how many healthcare professionals are likely to be required to administer CAR T cell therapy in specialist centres?	Haematology consultant (transplant and lymphoma), CNS, lead nurse on ward, pharmacists, transplant co-ordinator, stem cell lab staff
Would specialists providing care to patients who experience AEs after infusion with axi-cel also require specific training on CAR T therapy?	Yes, training on CAR-T therapy and AE management is a critical element of this process. AE treatment algorithms have been developed to assist with patient management and will be delivered to the hospital staff involved in CAR-T therapy. This will include Risk Management Plan training delivered by Gilead/Kite Medical Affairs team and training materials will be provided accordingly.
Uncertainty around the training requirements for healthcare professionals is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	Training costs have been included in the company cost-effectiveness model (cost per centre - £1,664; cost per patient - £83). Varying these costs has a minimal impact on the cost-effectiveness outcomes.
Question 7: Implementation of CAR-T therapy in the NHS – Prioritisation of eligible patients	
Who would determine which patients are prioritised to receive axi-cel therapy during a phased implementation?	We anticipate that NHS England will address this via a national / regional MDT and patients will be prioritised for CAR-T based on clinical need. We anticipate that this will be addressed in the NHS England service specification.
What criteria would or should be used to prioritise patients for axi-cel treatment?	We anticipate that this will be addressed in the NHS England service specification in line with the SPC.

Given the novelty of the treatment and limited information around follow up, how would patients who received axi-cel be monitored and new knowledge shared between specialist centres to improve overall patient care?	Gilead/Kite is planning a training programme facilitated by US experts that have experience with the administration of axi-cel prior to sites initiating their first patient. Ongoing medial education events will be provided by Gilead/Kite locally, nationally and internationally. This will include a preceptorship offering to treatment-naive sites prior to first CAR-T administration.
Uncertainty around the requirements for multidisciplinary teams and phased implementation is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model and budget impact assessment?	Details around the NSH England service specification is not captured in the cost-effectiveness model. We would not anticipate this to be a key driver of cost-effectiveness.
Question 8: Implementation of CAR-T therapy in the NHS – ambulatory care close to the hospital post infusion	
Where would a patients stay for aftercare if their home is not located close to the treatment centre?	An NHS model for Allo SCT transplant already exists and required patients to remain in close proximity to a transplant centre for up to 3 months. We anticipate a similar model for CAR-T implementation to be adopted.
How long would patients be expected to stay in close proximity to the treatment centre following CAR-T treatment?	Hospital admissions would be at the discretion of the treating physician but patients would be expected to remain within close proximity to the hospital for 1 month following the administration of axi-cel.
What provisions would be made for family and carers during this period?	An NHS model is already in place (e.g. as in UCLH, MRI) for Allo SCT, addressing the needs of both patients and family/caretakers. Family members can stay at the hospital-associated hotel for as long as required.

Are there other conditions with similar requirements which would be used as a model for axi-cel?	Allo SCT is very similar to CAR-T cell therapy in terms of requirements and after-care. The same model used for Allo SCT can be applied - e.g. from apheresis to patient monitoring. This model is already in place and validated.
Uncertainty around the need for ambulatory care is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	Ambulatory care has been included in the cost-effectiveness model. This is not a key driver of cost-effectiveness.
Question 9: Implementation of CAR-T therapy in the NHS – ICU bed availability	
Would an ICU bed need to be available for a patient before they were able to start their infusion with axi-cel?	We do not believe an ICU bed would need to be available for a patient before they were able to start their infusion with axi-cel. The same model used for Allo SCT can be implemented. The current set up for Allo SCT is that patients are transferred to ITU as and when required and therefore ITU beds are not reserved in advance. The same scenario can be used for CAR-T cell therapy. No ITU bed would need to be reserved.
What proportion of patients would be admitted to ICU following infusion with axi-cel if they did not experience a CRS AE?	Based on the data from ZUMA-1, [redacted] patients out of [redacted] or [redacted] were admitted to ICU, most of these were associated with CRS. Therefore, few admissions not related to CRS would be expected.

How long would a patient admitted to ICU as the result of (a) axi-cel infusion or (b) a serious CRS event be expected to stay?	Patients that are receiving axi-cel would only require admittance to ICU if they experienced a grade 3 or 4 adverse reaction (e.g. CRS). A serious CRS would only be expected to stay within an ICU for a few days.
Uncertainty around the requirements for ICU beds is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	We did not observe a significant requirement for ICU capacity in the ZUMA-1 trial with only [redacted] patients being admitted to ICU. It is important to manage these patients at a high level for the first few weeks after treatment, as with allogenic transplant. Resource use and unit costs of ICU beds for patients treated with axi-cel for the management of CRS adverse events are already included in the model. The resource use and costs of ICU is not a key driver for the cost-effectiveness results.
Question 10: Innovation	
Do you consider that the use of the technology will result in any substantial benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes we believe there are substantial benefits that are unlikely to be included in the QALY calculation: - The introduction of CAR-T treatments to healthcare systems globally represents a new era of oncology therapies similar to that seen for other immunotherapies including PD-1 inhibitors. The creation of these new pathways of care represents a notable step change the importance of which cannot be captures or appreciated using the QALY calculation. Moreover the continued studies of the use of CAR-T technology in combination with other immunotherapies may provide improved outcomes for patients and lead to even greater cure rates and overall survival gains -

	https://www.clinicaltrials.gov/ct2/show/NCT02926833?term=axicabtagene&rank=5 - **Patient experience of treatment** – as demonstrated in the ZUMA-1 data, axi-cell offers patients a potentially curative treatment option where other treatment options have been exhausted. The potential for receiving this curative treatment option may have substantial benefits in terms of a patients' mental health and wellbeing in addition to the indirect benefits it may offer friends, family and carers (e.g. prior to ASCT patients may be hospitalised and kept in isolation for 4-6 weeks and unable to see their family). These are important factors to consider which cannot be captured in the QALY calculation. - **Single treatment vs multiple chemotherapy cycles** - traditional chemotherapy involves regular, long-term clinical visits and treatment/monitoring of associated adverse effects. Axi-cell offers a less toxic and potentially curative treatment option compared to these regimens. In addition, patients who have not responded adequately to previous lines of chemotherapy may receive a heterogeneous mixture of remaining treatment options with a slim chance of optimal clinical response.
Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy. Would this have an impact on a patient's health-related quality of life?	The company believes there are potential HRQoL benefits of patients only requiring a single treatment of a drug (i.e. axi-cel) compared to requiring recurrent cycles of traditional chemotherapy involving regular, long-term clinical visits and treatment/monitoring of associated adverse effects. The company model base case is conservative in this regard because no HRQoL benefit has been accounted for in the model. The company model base case is also conservative because it does not accrue any costs or

	disutilities due to adverse events for the BSC arm, some of which could potentially be related to current cycles of traditional chemotherapy infusion.
Should a weight be applied to the QALYs gained in the axi-cel treatment arm to account for the large survival gaines/QALYs?	The company believes the large survival/QALYs gained with axi-cel treatment compared to current standard of care, the long-term benefit (lifetime) for patients, and the innovative nature of axi-cel should be reflected by the modelling QALYs gained. The company argued for a 1.5% discount rate to be applied and presented this as a scenario analysis in the original submission. The company believe a 1.5% discount rate would be suitable for the model base case (or considered to be contributing to the model base case). The company base case ICER is [redacted] (a 22% reduction from base case ICER) when a discount rate of 1.5% is applied in the initial company submission.
Question 11: Cancer Drugs Fund (CDF)	
Please specify whether you consider the technology to be a candidate for entry into the CDF?	Kite/Gilead believe this is a potential area of discussion following the NICE Technology Appraisal Committee meeting in July.
What data may be available for collection to resolve the uncertainty in this appraisal?	
How would additional data collection resolve the uncertainty in this appraisal?	
What timelines would be appropriate for additional data collection?	
Do you know of any additional evidence currently or likely to become available that may help to address he uncertainties?	
Question 12: Other areas of uncertainty	

Comparators (exclusion of pixantrone) *In clinical practice in the NHS, is pixantrone monotherapy given to patients with relapsed or refractory disease?*	Although NICE approved, pixantrone is not mentioned in the BCSH guidelines and the ESMO guidelines state that patients should be enrolled to CTs over pixantrone. Clinical advice at an advisory board confirmed that pixantrone is not used in UK clinical practice.
Comparators (use of a blended comparator) *Are salvage regimens considered equally effective, with and without rituximab?* *Are salvage regimes distributed equally to patients with relapsed or refractory DLBCL, PMBCL and TFL in clinical practice in the NHS?*	Rituximab-containing chemotherapy is the standard of care salvage treatment, independent of whether or not the patient received rituximab in first line. The efficacy of different salvage regimens is broadly similar regardless of whether they are used with rituximab or without rituximab.

Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1 *What is the average time period between the clinical decision taken to administer salvage chemotherapy to a patient and the patient receiving chemotherapy?*	Once a salvage regimen has been selected, it is expected that start date would be within a week in most centres depending on variable individual hospital factors.
Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1. Would there be a concern that patients may experience disease progression during the additional time required for manufacturing of axi-cel?	Yes, given the time required to manufacture axi-cell there is a potential risk of patients experiencing disease progression. Although there is no data to support bridging chemotherapy before axi-cel in ZUMA-1 (as it could be a confounding factor) the use of bridging chemotherapy is not contraindicated in the SPC. The use of bridging chemotherapy in the clinical setting will be the physician's decision. Steroids could be used in clinical practice for bridging but care will be required in terms of timing immediately in advance of axi-cell administration so as not to impact on axi-cell efficacy.
Re-treatment with axi-cel in the ZUMA-1 population *Would patients who received retreatment with axi-cel be expected to have improved outcomes compared with those whose disease progressed and did not receive a second round of treatment?*	In the ZUMA-1 trial, although axi-cel was given as a one-off infusion, some patients were retreated in line with the trial protocol (10/108 subjects were retreated based on the August 2017 data cut; nine patients from Phase 2 and one patient from Phase 1 trial). Based on best overall responses per investigator, among the nine retreated patients from the Phase 2 trial, [redacted] and [redacted] patients had CR and PR, respectively; [redacted] patient had stable disease and [redacted] patients had progressed disease. Therefore, it appears that retreated patients in ZUMA-1 have similar outcomes compared with the rest of patients in ZUMA-1.

Patients receiving post-treatment SCTs and the associated assumptions *What proportion of patients (R/R after 2nd line or who previously failed an ASCT) receiving salvage chemotherapy would become eligible for a SCT in clinical practice?*	In current clinical practice, the outcomes of this patient population is very poor and only a minority of patients are able to undergo Allo SCT.
Patients receiving post-treatment SCTs and the associated assumptions. Are outcomes for patients who receive a stem cell transplant likely to be significantly different from patients who receive salvage chemotherapy?	A small proportion of patients that have been able to undergo SCT may be able to have long term survival as demonstrated in Figure 1 above. However, very limited date is available for patients undergoing Allo SCT post axi-cel.
Patients receiving post-treatment SCTs and the associated assumptions. Would patients be likely to receive autologous or allogenic stem cell transplants after response to treatment with either salvage chemotherapy or axi-cel?	Patients that were included in the ZUMA 1 had, either already received an ASCT and relapsed, or were ineligible for an ASCT, therefore ASCT post axi-cel treatment is not applicable. There are very limited data for transplant post axi-cel (based on [redacted] patients receiving SCT). Furthermore, the data from ASCO 2018 suggests that many patients in PR are able to achieve a deepening of response (from PR to CR over time) or maintain a prolonged CR. It is possible that giving further high dose chemotherapy to CAR-T treated patients who are in CR/PR may destroy the CAR-T cells and therefore have a negative impact on patient outcome, whilst increasing toxicity.
Patients receiving post-treatment SCTs and the associated assumptions. How long on average would patients receive follow-up care following a stem cell transplant?	For ASCT, it is common to see patients on a very regular basis for 3 months after the initial 4-6 weeks of admission, if no complications occur. Thereafter the patient is referred back to the care of the referring lymphoma team for further follow-up (this varies between centres in the UK – from 2 years to indefinite). For Allo SCT, in the first 3 months after transplant, patients are reviewed twice weekly, followed by weekly and monthly visits for the first year but the follow-up may continue indefinitely in most centres due to chronic toxicity (GvHD).
Long term costs of IVIG treatment - real world experience *What proportion of patients would still be affected by*	In the NCI study with long-term follow-up[2] severe infections were rare in patients that had prolonged B cell aplasia and incomplete immunoglobulin recovery.

B-cell aplasia after 12 months following treatment with axi-cel?	
Long term costs of IVIG treatment - real world experience. Would these patients require continued IVIG treatment and for how long?	Based on the current ZUMA-1 data and the NCI study, IVIG was rarely used and not expected to be required over a prolonged period of time. In the ZUMA-1 trial, a total of 8.3% patients received IVIG.

Thank you for your time.

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REFERENCES

[1] Locke et al 2018. Axicabtagene Ciloleucel (Axi‑Cel) in Patients With Refractory Large B Cell Lymphoma: Durability of Response in ZUM-1. EHA 2018; Poster PF259

[2] Kochenderfer et al. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. Molecular Therapy Vol. 25 No 10 October 2017

NICE National Institute for Health and Care Excellence

Technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Thank you for agreeing to give us your comments and feedback as part of the technical engagement step to assist us in identifying the most plausible assumptions in the clinical and cost-effectiveness for this technology.

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Deadline for comments **5pm on 22 June 2018**

NICE National Institute for Health and Care Excellence

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)	Bloodwise
Are you (please tick all that apply)	☐ a representative from the company (Kite, Gilead)? ☐ a clinical expert? ☐ a commissioning expert? ☒ a patient expert or organisation? ☐ an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	None

Questions for engagement

Question 1: Adjustment of SCHOLAR-1 cohort for comparative effectiveness results	
Are clinical outcomes for patients with ECOG status 0-1 and those with ECOG status 2-4 likely to be different?	
Is a population from SCHOLAR-1 which includes patients with possible ECOG status 2-4 suitable to compare to the ZUMA-1 population whose eligibility criteria included only people with ECOG score 0-1?	
Adjusting for ECOG status will not account for all imbalances in the SCHOLAR-1 and ZUMA-1	

populations. Are there any additional comments on the approach used by the company or ERG to provide comparative effectiveness estimates?	
Question 2: Expected relapse rate after the period of follow-up available from ZUMA-1	
Is it appropriate to assume a patient is considered if they have not experienced an event by 15 months post treatment (trial follow-up period)?	
What is the expected relapse rate for patients in remission between 2-5 years after treatment?	
Is there additional data expected from the ZUMA-1 trial which would increase the duration of the follow-up period and reduce uncertainty in the assumptions around survival for patients who received axi-cel?	
Would additional data collection reduce uncertainty?	
Long-term survival is apparent in both treatment arms. Does this reflect clinical practice in the UK for patients treated with salvage chemotherapy?	
Question 3: Appropriate extrapolation for overall survival in axi-cel treatment arm	
How long are patients with progressed disease expected to survive?	
Is it plausible that a patient could be cured in terms of survival but not from disease progression?	
Would patients who responded to treatment be expected to experience additional mortality risks or have a different quality of life compared to the general population for the first 1-2 years after treatment?	

The company's assumptions appear optimistic based on the evidence available. The ERG have proposed an alternative scenario which accounts for the uncertainty in the data. Is it reasonable to use the progression free survival curve to estimate the proportion of patients' cured following treatment with axi-cel?	
Question 4: long-term survivors risk of excess mortality compared to the general population	
Do long term survivors experience excess mortality compared to the general population?	
Is there an increased long-term risk of infection and excess mortality due to prolonged B cell aplasia?	
How long after diagnosis/treatment would any excess mortality be expected to last for long term survivors?	
The company and ERG provide opposing views on the evidence available for excess mortality risks, which is the most applicable to clinical practice in the UK?	
Question 5: Storage and administration of CAR-T therapy in the NHS	
What additional storage equipment and space would be required for centres to administer axi-cel?	It is our understanding that additional storage and thawing equipment (in addition to those already used for stem cell transplants) will be required. We hope that the details of these additional requirements will be included in NHS England's new service specification.
Would specialist centres need to purchase additional thawing equipment to use in the administration of axi-cel?	

Question 6: Implementation of CAR-T therapy in the NHS – training requirements	
What roles and how many healthcare professionals are likely to be required to administer CAR T cell therapy in specialist centres?	
Would specialists providing care to patients who experience AEs after infusion with axi-cel also require specific training on CAR T therapy?	The clinicians we have spoken to who have worked on CAR-T academic clinical trials at UCLH confirm that specialists administering the therapy and dealing with the care of patients who experience adverse events following with axi-cel will require specific training or that additional medical staff will be required.
Uncertainty around the training requirements for healthcare professionals is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	
Question 7: Implementation of CAR-T therapy in the NHS – Prioritisation of eligible patients	
Who would determine which patients are prioritised to receive axi-cel therapy during a phased implementation?	
What criteria would or should be used to prioritise patients for axi-cel treatment?	
Given the novelty of the treatment and limited information around follow up, how would patients who received axi-cel be monitored and new knowledge shared between specialist centres to improve overall patient care?	

Uncertainty around the requirements for multidisciplinary teams and phased implementation is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model and budget impact assessment?	
Question 8: Implementation of CAR-T therapy in the NHS – ambulatory care close to the hospital post infusion	
Where would a patients stay for aftercare if their home is not located close to the treatment centre?	The patients we interviewed when preparing our initial submission stayed in the ambulatory care facility available at UCLH. They were expected to stay in close proximity to the hospital for at least one month after the infusion of the engineered CAR-T cells for monitoring as they were for advised that it was likely they would develop adverse reactions to the treatment and require specialist care.
How long would patients be expected to stay in close proximity to the treatment centre following CAR-T treatment?	See above.
What provisions would be made for family and carers during this period?	A family member was also able to stay in this facility with the patients and during any periods when they were readmitted to hospital
Are there other conditions with similar requirements which would be used as a model for axi-cel?	The most similar model for care as far as we are aware is the care required before and after a stem cell transplant.
Uncertainty around the need for ambulatory care is likely to be addressed in the new service specification by NHS England. How should this	

information be incorporated into the current cost-effectiveness model?	
Question 9: Implementation of CAR-T therapy in the NHS – ICU bed availability	
Would an ICU bed need to be available for a patient before they were able to start their infusion with axi-cel?	We were advised by clinicians that there is a reasonably high chance that adverse events will occur after infusion with the engineered CAR-T cells including neutropenic sepsis which could necessitate admission to ICU so we recommend that beds are available before the infusion.
What proportion of patients would be admitted to ICU following infusion with axi-cel if they did not experience a CRS AE?	
How long would a patient admitted to ICU as the result of (a) axi-cel infusion or (b) a serious CRS event be expected to stay?	
Uncertainty around the requirements for ICU beds is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	
Question 10: Innovation	
Do you consider that the use of the technology will result in any substantial benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is difficult to comment on this in any detail as we have not seen the company's submission. However, there is no doubt that the treatment is hugely innovative and represents the start of a new era for treatment of blood cancer so this should be taken into account in the committee's decision making process. It also offers patients a last chance at survival where all other treatments have failed which should take it outside the usual remit.

Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy. Would this have an impact on a patient's health-related quality of life?	The patients who informed our submission described how although the treatment itself is intensive and disruptive as it required admission and staying in close proximity to the hospital for several weeks, this was less onerous than many weekly appointments for chemotherapy. As stated in our submission, any inconvenience or adverse reactions were overshadowed by the prospect that the treatment might work where traditional treatment including chemotherapy had failed.
Should a weight be applied to the QALYs gained in the axi-cel treatment arm to account for the large survival gaines/QALYs?	Yes for the reasons outlined above.
Question 11: Cancer Drugs Fund (CDF)	
Please specify whether you consider the technology to be a candidate for entry into the CDF?	
What data may be available for collection to resolve the uncertainty in this appraisal?	
How would additional data collection resolve the uncertainty in this appraisal?	
What timelines would be appropriate for additional data collection?	
Do you know of any additional evidence currently or likely to become available that may help to address he uncertainties?	
Question 12: Other areas of uncertainty	
Comparators (exclusion of pixantrone) *In clinical practice in the NHS, is pixantrone monotherapy given to patients with relapsed or refractory disease?*	

Comparators (use of a blended comparator) *Are salvage regimens considered equally effective, with and without rituximab?* *Are salvage regimes distributed equally to patients with relapsed or refractory DLBCL, PMBCL and TFL in clinical practice in the NHS?*	
Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1 *What is the average time period between the clinical decision taken to administer salvage chemotherapy to a patient and the patient receiving chemotherapy?* *Would there be a concern that patients may experience disease progression during the additional time required for manufacturing of axi-cel?*	
Re-treatment with axi-cel in the ZUMA-1 population *Would patients who received retreatment with axi-cel be expected to have improved outcomes compared with those whose disease progressed and did not receive a second round of treatment?*	
Patients receiving post-treatment SCTs and the associated assumptions *What proportion of patients (R/R after 2nd line or who previously failed an ASCT) receiving salvage chemotherapy would become eligible for a SCT in clinical practice?* *Are outcomes for patients who receive a stem cell transplant likely to be significantly different from patients who receive salvage chemotherapy?*	

Would patients be likely to receive autologous or allogenic stem cell transplants after response to treatment with either salvage chemotherapy or axi-cel? *How long on average would patients receive follow-up care following a stem cell transplant?*	
Long term costs of IVIG treatment - real world experience *What proportion of patients would still be affected by B-cell aplasia after 12 months following treatment with axi-cel? Would these patients require continued IVIG treatment and for how long?*	

Thank you for your time.

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Technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

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As a technical engagement stakeholder for this appraisal step, we highly appreciate your input, comment and ongoing support for this appraisal.

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Deadline for comments **5pm on 22 June 2018**

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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)	**Lymphoma Action** The responses in this document are summarised from asking some of the questions to our Patient Advisory Group and selected patients with an interest in CAR T-cell technology. Our Information and Support team also reviewed this submission.
Are you (please tick all that apply)	☐ a representative from the company (Kite, Gilead)? ☐ a clinical expert? ☐ a commissioning expert? **X** a patient expert or organisation? ☐ an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None.**

Questions for engagement

Question 1: Adjustment of SCHOLAR-1 cohort for comparative effectiveness results	
Are clinical outcomes for patients with ECOG status 0-1 and those with ECOG status 2-4 likely to be different?	Nothing to add.
Is a population from SCHOLAR-1 which includes patients with possible ECOG status 2-4 suitable to compare to the ZUMA-1 population whose eligibility criteria included only people with ECOG score 0-1?	Nothing to add.

Adjusting for ECOG status will not account for all imbalances in the SCHOLAR-1 and ZUMA-1 populations. Are there any additional comments on the approach used by the company or ERG to provide comparative effectiveness estimates?	Nothing to add.
Question 2: Expected relapse rate after the period of follow-up available from ZUMA-1	
Is it appropriate to assume a patient is considered if they have not experienced an event by 15 months post treatment (trial follow-up period)?	Nothing to add.
What is the expected relapse rate for patients in remission between 2-5 years after treatment?	Nothing to add.
Is there additional data expected from the ZUMA-1 trial which would increase the duration of the follow-up period and reduce uncertainty in the assumptions around survival for patients who received axi-cel?	Nothing to add.
Would additional data collection reduce uncertainty?	Nothing to add.
Long-term survival is apparent in both treatment arms. Does this reflect clinical practice in the UK for patients treated with salvage chemotherapy?	Nothing to add.
Question 3: **Appropriate extrapolation for overall survival in axi-cel treatment arm**	
How long are patients with progressed disease expected to survive?	Nothing to add.
Is it plausible that a patient could be cured in terms of survival but not from disease progression?	Nothing to add.
Would patients who responded to treatment be expected to experience additional mortality risks or have a different quality of life compared to the	Existing treatments carry the risk of problems both in the short-term after treatment and in the longer-term. From a patient perspective, follow-up and monitoring are likely to be very important

general population for the first 1-2 years after treatment?	following treatment, in order to keep a close eye on any problems resolving or developing. Patients often report that their local team have little knowledge of the risk of problems after successful treatment so close monitoring by an expert team might offer reassurance, as well as enabling extra data on the longer term effects of the treatment to be gathered.
The company's assumptions appear optimistic based on the evidence available. The ERG have proposed an alternative scenario which accounts for the uncertainty in the data. Is it reasonable to use the progression free survival curve to estimate the proportion of patients' cured following treatment with axi-cel?	This may depend on the type of lymphoma. Certainly people with high-grade lymphomas are more likely to be cured with existing treatments as time goes on, so it seems plausible that this would be the case for axi-cel.
Question 4: long-term survivors risk of excess mortality compared to the general population	
Do long term survivors experience excess mortality compared to the general population?	Patients report that they would like to know more about the risks after successful treatment, particularly as there is a lack of support and knowledge about late effects in GPs and other healthcare professionals. Existing treatments cause potentially severe long-term effects – are a greater proportion of patients likely to suffer such effects after axi-cel? If there were no other treatment options, the general feeling is that the risk of long-term effects is worth the hope offered by the new technology. CAR T-cell technology offers a lot of hope for patients who have had little success with conventional chemotherapy treatments and who are running out of options.
Is there an increased long-term risk of infection and excess mortality due to prolonged B cell aplasia?	Nothing to add.
How long after diagnosis/treatment would any excess mortality be expected to last for long term survivors?	Close follow-up will be important both for collecting this data and giving patients the reassurance that they are being looked after by an expert team. Many patients report that their local teams have little or no knowledge of managing the effects of existing treatments.

The company and ERG provide opposing views on the evidence available for excess mortality risks, which is the most applicable to clinical practice in the UK?	Nothing to add.
Question 5: Storage and administration of CAR-T therapy in the NHS	
What additional storage equipment and space would be required for centres to administer axi-cel?	Nothing to add.
Would specialist centres need to purchase additional thawing equipment to use in the administration of axi-cel?	Nothing to add.
Question 6: Implementation of CAR-T therapy in the NHS – training requirements	
What roles and how many healthcare professionals are likely to be required to administer CAR T cell therapy in specialist centres?	Nothing to add.
Would specialists providing care to patients who experience AEs after infusion with axi-cel also require specific training on CAR T therapy?	Nothing to add.
Uncertainty around the training requirements for healthcare professionals is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	Nothing to add.
Question 7: Implementation of CAR-T therapy in the NHS – Prioritisation of eligible patients	
Who would determine which patients are prioritised to receive axi-cel therapy during a phased implementation?	Nothing to add.

What criteria would or should be used to prioritise patients for axi-cel treatment?	Patients offered various views on who should be prioritised but broadly: • Those with no other options or who do not respond to chemotherapy. • Those most likely to benefit. • Those without other issues likely to make treatment more difficult.
Given the novelty of the treatment and limited information around follow up, how would patients who received axi-cel be monitored and new knowledge shared between specialist centres to improve overall patient care?	Many patients feel that their local teams do not know enough to support them after conventional therapies, so they will need expert follow-up and support.
Uncertainty around the requirements for multidisciplinary teams and phased implementation is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model and budget impact assessment?	Nothing to add.
Question 8: Implementation of CAR-T therapy in the NHS – ambulatory care close to the hospital post infusion	
Where would a patients stay for aftercare if their home is not located close to the treatment centre?	Patients asked if it would be possible to be transferred to local hospitals for aftercare. However, the general view was also that staying away from home for this would be worth it if you were being treated at a centre of excellence. There are concerns, however, about how they could be

	supported by family and friends. There would also be cost implications of staying near the treating hospital for follow-up.
How long would patients be expected to stay in close proximity to the treatment centre following CAR-T treatment?	If patients are being treated far from home, it will become increasingly difficult for the patient over time due to distance from their support networks. In the short-term, if the treatment is only offered at a small number of centres and patients have to fund staying nearby for aftercare, this is likely to restrict who can have it.
What provisions would be made for family and carers during this period?	Nothing to add.
Are there other conditions with similar requirements which would be used as a model for axi-cel?	Nothing to add.
Uncertainty around the need for ambulatory care is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	Nothing to add.
Question 9: Implementation of CAR-T therapy in the NHS – ICU bed availability	
Would an ICU bed need to be available for a patient before they were able to start their infusion with axi-cel?	Nothing to add.
What proportion of patients would be admitted to ICU following infusion with axi-cel if they did not experience a CRS AE?	Nothing to add.
How long would a patient admitted to ICU as the result of (a) axi-cel infusion or (b) a serious CRS event be expected to stay?	Nothing to add.

Uncertainty around the requirements for ICU beds is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	Nothing to add.
Question 10: Innovation	
Do you consider that the use of the technology will result in any substantial benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	This technology appears to be a big step forward, particularly for those people who do not respond to conventional treatments, who desperately need an alternative to chemotherapy. Patients are keen to be involved in driving forward this new development.
Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy. Would this have an impact on a patient's health-related quality of life?	The psychological advantage of getting treatment over in one hit could be significant for patients. Patients have reported that cycles of treatment can be very wearing, and many feel worse with each cycle. Patients in general were very supportive of the idea of a single treatment, even bearing in mind the toxicity.
Should a weight be applied to the QALYs gained in the axi-cel treatment arm to account for the large survival gaines/QALYs?	Nothing to add.
Question 11: Cancer Drugs Fund (CDF)	
Please specify whether you consider the technology to be a candidate for entry into the CDF?	Nothing to add.
What data may be available for collection to resolve the uncertainty in this appraisal?	Nothing to add.
How would additional data collection resolve the uncertainty in this appraisal?	Nothing to add.

What timelines would be appropriate for additional data collection?	Nothing to add.
Do you know of any additional evidence currently or likely to become available that may help to address he uncertainties?	Nothing to add.
Question 12: Other areas of uncertainty	
Comparators (exclusion of pixantrone) *In clinical practice in the NHS, is pixantrone monotherapy given to patients with relapsed or refractory disease?*	Nothing to add.
Comparators (use of a blended comparator) *Are salvage regimens considered equally effective, with and without rituximab?* *Are salvage regimes distributed equally to patients with relapsed or refractory DLBCL, PMBCL and TFL in clinical practice in the NHS?*	Nothing to add.
Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1 *What is the average time period between the clinical decision taken to administer salvage chemotherapy to a patient and the patient receiving chemotherapy?* *Would there be a concern that patients may experience disease progression during the additional time required for manufacturing of axi-cel?*	Nothing to add.
Re-treatment with axi-cel in the ZUMA-1 population *Would patients who received retreatment with axi-cel be expected to have improved outcomes compared*	Nothing to add.

with those whose disease progressed and did not receive a second round of treatment?	
Patients receiving post-treatment SCTs and the associated assumptions *What proportion of patients (R/R after 2nd line or who previously failed an ASCT) receiving salvage chemotherapy would become eligible for a SCT in clinical practice?* *Are outcomes for patients who receive a stem cell transplant likely to be significantly different from patients who receive salvage chemotherapy?* *Would patients be likely to receive autologous or allogenic stem cell transplants after response to treatment with either salvage chemotherapy or axi-cel?* *How long on average would patients receive follow-up care following a stem cell transplant?*	Nothing to add.
Long term costs of IVIG treatment - real world experience *What proportion of patients would still be affected by B-cell aplasia after 12 months following treatment with axi-cel? Would these patients require continued IVIG treatment and for how long?*	Nothing to add.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed response form

NICE National Institute for Health and Care Excellence

Technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Thank you for agreeing to give us your comments and feedback as part of the technical engagement step to assist us in identifying the most plausible assumptions in the clinical and cost-effectiveness for this technology.

As a technical engagement stakeholder for this appraisal step, we highly appreciate your input, comment and ongoing support for this appraisal.

To help you give your views, please use this questionnaire. You do not have to answer every question. The text boxes will expand as you type. Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

Information on completing this technical engagement response

- Prior to completing this response table please see the technical engagement document which summarises the background, and submitted evidence for this appraisal. This will provide you with context and outline the questions below in greater detail for which we require your comments and feedback.
- 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.

Please note that comments from the technical engagement will be collated and summarised as part of the committee pre-meeting briefing document, which will be made available to all stakeholders with a signed confidentiality agreement as part of the committee papers accompanying the post committee documentation (ACD or FAD) following the meeting on 31 July 2018.

Deadline for comments **5pm on 22 June 2018**

NICE National Institute for Health and Care Excellence

About you

Your name	**Professor Peter Clark**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NHS England**
Are you (please tick all that apply)	☐ a representative from the company (Kite, Gilead)? ☐ a clinical expert? ☐ a commissioning expert? ☐ a patient expert or organisation? ☒ an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Questions for engagement

Question 1: Adjustment of SCHOLAR-1 cohort for comparative effectiveness results	
Are clinical outcomes for patients with ECOG status 0-1 and those with ECOG status 2-4 likely to be different?	NHS England notes that all the patients in the ZUMA-1 trial were of ECOG performance status (PS) 0 or 1. The patient population was thus a fit one. This is important for safety reasons given the very considerable toxicity of CAR T cell therapy. This is why NHS England would only wish to commission axi-cel treatment in patients of ECOG PS 0 or 1: this is the sole evidence base for both efficacy and toxicity. The toxicity issue would be the main driver of concern in treating patients of PS 2 for example. Chemo-immunotherapy remains the cornerstone of 1st line treatment for patients with DLBCL. If patients are to receive optimal therapy, they have to be medically fit to receive combination

	chemotherapy (cyclophosphamide, vincristine, doxorubicin and prednisolone) given in conjunction with rituximab. Such patients have a 70-80% chance of remaining free of disease progression. Less fit patients do much less well. Patients who relapse after 1st line therapy do so within the first 2 years after completing treatment and, if fit for optimal (but toxic) chemo-immunotherapy, have a low chance of remaining free of disease progression if just treated with conventional doses of chemotherapy. Only the responders who are sufficiently fit would be considered for stem cell transplantation (SCT) as part of 2nd line salvage chemotherapy. Thus, fitness determines the ability to withstand the rigours of treatment with chemotherapy and to obtain the best outcomes. Performance status is an important determinant of prognosis at any line of chemotherapy for large B cell lymphoma. Patients of PS 0-1 will always do better than patients of PS 2-4, partly because of their ability to tolerate treatment but partly too because worse PS is usually associated with greater tumour load.
Is a population from SCHOLAR-1 which includes patients with possible ECOG status 2-4 suitable to compare to the ZUMA-1 population whose eligibility criteria included only people with ECOG score 0-1?	The indirect comparison of ZUMA-1 with SCHOLAR-1 has serious disadvantages given the heterogeneity of the 4 data sources that informed the outputs of SCHOLAR-1: a mixture of retrospective and prospective databases, of audits and clinical trials, of ECOG performance status patients 0-4, of primary refractory patients and of previously received lines of therapy. Of note is that the SCHOLAR-1 trial OS curve flattening at about 7 years at about 13-14% of patients, 28% being alive at 1 year and 20% being alive at 2years. This long term rate of OS will be mainly related to the fact that [redacted] of SCHOLAR-1 patients received subsequent SCT. This figure is higher than that recorded in NHS practice as part of 3rd line salvage chemotherapy (10-15%). The comparator for axi-cel is 3rd line chemotherapy. In addition, NHS England notes that Kite Pharma was directly involved in both the funding and the writing of the SCHOLAR-1 publication.

	NHS England therefore has great reservations as to the comparability of ZUMA-1 and SCHOLAR-1 of which the inclusion of patients with worse PS in SCHOLAR-1 is one of many factors that results in uncertainly as to the robustness of such a comparison. NHS England also observes that the long term OS rate from SCHOLAR-1 used in the economic model is 13-14% .NHS England regards this figure as being high and presumably relates to the high rate of SCTs assumed in the economic model. If there is a 10-15% rate of SCTs in this group of patients in England as part of 3rd line chemotherapy, there is likely to be about a 6-8% (or less) long term survival rate for patients embarking on 3rd line therapy. A large proportion of these 3rd line SCTs will be allogeneic. In addition, no progression-free survival (PFS) data was reported in SCHOLAR-1. To overcome this, PFS was estimated for the comparator population in the Gilead economic model by assuming that the same ratio between PFS and OS at each time point in the axi-cel arm can be applied to the comparator arm. Since these two modalities of treatment are completely different, there must be significant uncertainty as to the validity of this assumption.
Adjusting for ECOG status will not account for all imbalances in the SCHOLAR-1 and ZUMA-1 populations. Are there any additional comments on the approach used by the company or ERG to provide comparative effectiveness estimates?	Please see above re the uncertainty in the robustness of the indirect treatment comparison of ZUMA-1 and SCHOLAR-1. There are other key issues relating to cost effectiveness which NHS England wishes to raise and these are listed below. <u>Population to be treated</u> The key interpretation of the likely marketing authorisation when directed to clinical practice is whether 'relapsed and refractory' applies to the '2' lines of therapy. NHS England's interpretation is that patients whether relapsed after or refractory to 1st line treatment must have failed standard 2nd line therapy i.e. if a SCT was planned in the current 2nd line treatment pathway and patients respond sufficiently, then those patients should proceed to SCT as currently commissioned and not to CAR T cell therapy.

	There is thus an issue as to how the MA should be interpreted in relation to the population of patients in ZUMA-1 versus those contained in the marketing authorisation. ZUMA-1 recruited 3 groups of patients. The first was a group which consisted of patients' refractory to 1st line therapy: those that had progressive disease to 1st line treatment or who had stable disease after 1st line treatment and progressed within 6 months of completing 1st line treatment (2 patients treated). The second group was patients refractory to 2nd or later lines of therapy: those that had progressive disease to 2nd line treatment or had stable disease and relapsed within 6 months of completing 2nd line therapy (78 patients treated). A third group was those patients that had autologous SCT and had relapsed within 12 months of receiving the SCT; a biopsy had to prove such a disease relapse and if the patients were treated with further chemotherapy, the patients must either have not responded or had relapsed following such chemotherapy (21 patients treated). NHS England believes that the 2nd and 3rd groups fall within the expected marketing authorisation for axi-cel but not the first group. <u>Uncertainty as to outcomes</u> The current median duration of follow up in the axi-cel trial is 15.4 months. The efficacy results even for patients with relapsed/refractory DLBCL who have failed 2+ lines of therapy are immature. NHS England notes that progression free survival (PFS) is plateau**ing** in ZUMA-1 but relapses have still occurred at 12 months. PFS rates at 6 months were 49%, at 12 months were 44% and at 15 months were 41%. NHS England notes that there are very few patients at risk after 14 months and so regards these PFS results as very encouraging but not mature. Overall survival (OS) is also plateau**ing** but NHS England notes that deaths have occurred at 12-16 months and for this reason the 18 month OS figure of 52% is lower than the figure of 59% at 12 months which in turn is lower than 78% at 6 months. There are very few patients at risk after 16 months. In addition, NHS England notes that in its economic model Gilead assumes that axi-cel overall survival has plateaued at 50% and then falls in line with the mortality decline for the general population. NHS England regards these 2 factors as being optimistic as the OS rate in ZUMA-1 may fall given the immaturity of follow up and the fact that these patients are heavily treated with

	chemotherapy which is known to add a survival disadvantage in the long term. Furthermore, a long term OS plateau at the latest percentage figure of patients remaining progression-free (42%) seen so far in the Zuma-1 trial might be a more realistic (but still optimistic) number to use rather than 50%. Degree of patient selection It would be important for NICE and NHS England to see the ZUMA-1 trial screening log: the number of patients who were initially considered for the ZUMA-1 trial. In addition, the treating centres will have screening logs of patients potentially eligible for axi-cel therapy before patient selection begins. These logs would offer a clearer picture of the degree of selection that was necessary in trial centres between the number of patients referred, the number actively screened and then the number of patients actually selected for axi-cel treatment. Costs of leukapheresis NHS England notes that 10% of patients entered into the study were leukapheresed but did not receive axi-cel: 4 of the 81 DLBCL patients and 6 of the 30 PMBCL/TFL patients. The main cause of this was progressive disease and its consequences in the time in between leukapheresis and arrival of the axi-cel for infusion. NHS England would wish to see confirmation that there is inclusion of leukapheresis costs for all the patients in whom Gilead manufactures axi-cel infusions, not just the patients who actually receive the axi-cel infusions. Generalisability NHS England considers that the highly selected ZUMA-1 trial population is generalisable to the highly selected population of patients in the NHS which would be treated with axi-cel. The only difference in patient characteristics would be the number of previous lines of therapy. In future NHS practice this will be 2 lines of previous therapy for the great majority of patients and not the ZUMA-1 figures of 69% having had ≥ 3 lines of therapy and 40% having had ≥ 4 lines of treatment. Nevertheless, as 42% of ZUMA-1 patients were of ECOG performance status 0 and 58% of performance status 1, ZUMA-1 attracted very fit patients despite being heavily pre-treated.

	The population can thus be regarded as having outcomes which are generalisable to NHS practice. Utilities NHS England notes the utility data by response status and the small numbers in these analyses (0.74 for complete response, 0.79 for partial response, 0.64 for stable disease and 0.65 for progressive disease). It is counter intuitive for the partial response utility to be higher than that for a complete response. Given that progressive disease after CAR T cell therapy is a disaster for patients, it is surprising that the progressive disease utility is not lower than 0.65. NHS England also notes that the results by health state also do not show much differential: 0.72 for remaining free of progression and 0.65 for progressed disease. Costs of inpatient and intensive care unit stay NHS England notes that the mean length of inpatient stay in the ZUMA-1 study was 17.6 days and that the company's model costs this according to NHS weighted inpatient haematological costs. What is unclear is how many intensive care unit days are incorporated and at what cost, especially considering that the type of intensive care unit has to be one which is capable of 24 hour EEG monitoring and interpretation. The considerable amount of expert neurology input does not appear to have been costed and nor has the multidisciplinary team costs given the need for respiratory, renal, hepatic and microbiological input. Costs of administration of chemotherapy The company assumes that the comparator chemotherapy is given as an inpatient and thus this attracts high costs as the costing comparison uses the weighted haematology inpatient costs. 3 of the 4 regimens used in the economic analysis can be given as day cases and thus the costs of the comparator chemotherapy have been significantly inflated in the company's model. SCT rate in comparator arm

	The company appears to have applied a rate of [redacted] SCT to the comparator arm which appears to be a very significant overestimation of the likely SCT rate in such a population in England (10-15% with a long term survival rate of 6-8%). As this [redacted] rate of SCT and the 13-14% long term rate of overall survival in SCHOLAR-1 seem high, the economic model in this regard appears to have inflated both the survival and costs of the comparator population for axi-cel. Other issues NHS England plans to ensure that patients remain within a 1 hour travel time for the first 4 weeks after CAR T cell treatment. Some patients may be able to stay with relatives/friends but many will require either hostel or hotel accommodation. These costs of patients having to remain close to treating centres need to be included in the economic analysis. NHS England recognises that assessing the hospital costs of introduction of CAR T cell therapy in this indication is difficult. For example, currently there are a range of local currencies and prices for allogeneic transplant in England. A sensitivity analysis is recommended which uses the costs of procedures which bear some similarity to the infrastructure required for CAR T cell therapy. Clinical advice to NHS England therefore would suggest that using the inpatient and follow up costs of an allogeneic SCT for an unrelated donor (plus the separate and extra costs of ITU stay for axi-cel) would offer a useful analysis to compare with the company and ERG's base case assumptions of the hospital costs of CAR T cell therapy. This is calculated to be in the region of [redacted]. NHS England intends to use this approach as a baseline for reimbursement for CAR T activity. However it is also intended to require commissioned providers to collect and report costing data in order that a more granular assessment of the additional costs associated with the delivery of CAR T therapy can be made by year 2 of implementation.
Question 2: Expected relapse rate after the period of follow-up available from ZUMA-1	

Is it appropriate to assume a patient is considered if they have not experienced an event by 15 months post treatment (trial follow-up period)?	The current median duration of follow up in the axi-cel trial is 15.4 months. The efficacy results even for patients with relapsed/refractory DLBCL who have failed 2+ lines of therapy are immature. NHS England notes that progression free survival (PFS) is plateauing in ZUMA-1 but relapses have still occurred at 12 months. PFS rates at 6 months were 49%, at 12 months were 44% and at 15 months were 41%. NHS England notes that there are very few patients at risk after 14 months and so regards these PFS results as very encouraging but not mature. Overall survival (OS) is also plateauing but NHS England notes that deaths have occurred at 12-16 months and for this reason the 18 month OS figure of 52% is lower than the figure of 59% at 12 months which in turn is lower than 78% at 6 months. There are very few patients at risk after 16 months.
What is the expected relapse rate for patients in remission between 2-5 years after treatment?	This depends on which line of therapy is being considered. For this appraisal and thus for 3rd line therapy, the expected relapse rate for patients still in remission after 2 years is likely to be very low. Of some caution however, albeit in the very heterogeneous population of SCHOLAR-1, later deaths were seen but it is not known how many of these were related to lymphoma relapse.
Is there additional data expected from the ZUMA-1 trial which would increase the duration of the follow-up period and reduce uncertainty in the assumptions around survival for patients who received axi-cel?	A further data analysis with a median duration of follow-up in excess of 2 years would be appropriate, as would an even better analysis with a minimum duration of follow-up of 2 years for all patients.
Would additional data collection reduce uncertainty?	NHS England regards axi-cel as a good candidate for the Cancer Drugs Fund as the PFS and OS results are still not mature. Relapses are still being observed at 12 months and few patients are at risk beyond 14 months. A minimum of an extra 12 months of follow-up of ZUMA-1 patients would significantly reduce this uncertainty and thus make a potential NICE recommendation for routine commissioning decision one that ensures value for money for a very high cost technology.

Long-term survival is apparent in both treatment arms. Does this reflect clinical practice in the UK for patients treated with salvage chemotherapy?	Long term survival in the comparator arm will largely be as a consequence of SCT. NHS England believes that the rate of SCT is 10-15% for 3rd line treatment of large B cell lymphoma and thus the long term survival rate is likely to be 6-8% or less.
Question 3: **Appropriate extrapolation for overall survival in axi-cel treatment arm**	
How long are patients with progressed disease expected to survive?	Survival is likely to be measured in single numbers of months once patients fail axi-cel.
Is it plausible that a patient could be cured in terms of survival but not from disease progression?	Patients can only be cured if they remain free of disease progression.
Would patients who responded to treatment be expected to experience additional mortality risks or have a different quality of life compared to the general population for the first 1-2 years after treatment?	Patients having axi-cel have already had 2 lines of conventionally dosed combination chemotherapy and a significant proportion will have had a high dose chemotherapy and autologous SCT. Patients cured by axi-cel therapy will still be at risk of the long term complications of chemotherapy (e.g. risk of 2nd malignancy, myelodysplasia, cardiovascular toxicity etc.) and thus will carry an excess risk of mortality as a consequence. There will therefore be some drop in HRQOL as a consequence of previous chemotherapy as well as adding both the known risks of axi-cel in the longer term (eg hypogammaglobulinaemia and infection) and the as yet unknown long term risks. Additional treatments such as immunoglobulin may be required which, in addition to providing clinical benefit, also carry with their use potential side effects. It should be noted immunoglobulin is subject to a demand management plan due to global supply issues.
The company's assumptions appear optimistic based on the evidence available. The ERG have proposed an alternative scenario which accounts for the uncertainty in the data. Is it reasonable to use the progression free survival curve to estimate the proportion of patients' cured following treatment with axi-cel?	See above comments. Without being able to see the ERG's report, this question is difficult to answer. Nevertheless, as has been stated above, using the estimate PFS rate is reasonable to estimate the percentage of patients cured which is why it is curious that the company has used a figure of 50% when the currently known rate from the ZUMA-1 trial is 42%. As has been stated above, there is still great uncertainty as to whether this 42% figure represents the level at which the PFS has plateaued and will drop no further.

Question 4: long-term survivors risk of excess mortality compared to the general population	
Do long term survivors experience excess mortality compared to the general population?	Yes. See above
Is there an increased long-term risk of infection and excess mortality due to prolonged B cell aplasia?	There is known axicabtagene ciloleucel toxicity in this regard. Acutely, there were significant side-effects with infection in [redacted] of patients (bacterial, viral and fungal) and hypogammaglobulinaemia. In this population of adult patients, the long term need for intravenous immunoglobulin (IVIG) after CAR T cell therapy is likely to be modest but is difficult to enumerate at present.
How long after diagnosis/treatment would any excess mortality be expected to last for long term survivors?	See above: the answer is for many years given the risk of second malignancy and other toxicities eg cardiovascular side-effects.
The company and ERG provide opposing views on the evidence available for excess mortality risks, which is the most applicable to clinical practice in the UK?	These have been raised in recent TAs (eg brentuximab, nivolumab and pembrolizumab in Hodgkin lymphoma).
Question 5: **Storage and administration of CAR-T therapy in the NHS**	
What additional storage equipment and space would be required for centres to administer axi-cel?	CAR T cell centres will have cell therapy laboratory and pharmacy expertise in the handling, storage and thawing of advanced therapy medicinal products. In addition, centres will have considerable expertise in leukapheresis. A first wave of providers is being inspected by JACIE over the summer and the inspection will assess providers with regard to storage and space. It is as yet unclear whether extra dedicated equipment will be required for storage, temperature monitoring, thawing, or personal protection, or whether additional space will be required. Therefore, at this time NHS England is unable to comment with certainty as to whether there will be a specific need for extra equipment or space as described.
Would specialist centres need to purchase additional thawing equipment to use in the administration of axi-cel?	See above.

	There are other issues which NHS England wishes to raise as regards the resources required for the implementation of CAR T cell therapy. Ambulatory care CAR T cell teams similar to those in allogeneic transplant will have to be created, as well as wrapping-around all the specific people and expertise required to safely care for patients with the toxicities as set out below. Of note, this model of care not only improves patient experience but addresses demand and capacity issues which will be further intensified by axi-cel. NHS England notes that treatment with axi-cel is associated with many side-effects, some of them being life threatening and particularly so in the first month of treatment. It observes that serious toxicity diminishes as experience with CAR T cell therapy increases but nevertheless recognises that it has to wrap all the appropriate 24-hour expertise around each patient in order to maximise safety and optimise outcomes for patients and the NHS. In the ZUMA-1 trial, 95% of patients experienced a grade ≥3 adverse event, [redacted] a grade ≥3 serious adverse event and [redacted] of patients died of a treatment-related cause. The two most dangerous side-effects of axi-cel are of cytokine release syndrome (CRS) and neurotoxicity. Feedback to NHS England from the clinical trial centres in England who are currently involved in CAR T cell therapy consistently report how diverse the manifestations of toxicities can be and how vigilant and alert patients and staff must be to apparently minor symptoms which can then escalate quickly if not heeded and acted upon. 94% of patients recorded some degree of CRS but it is in 13% that grade 3 or worse CRS was seen. CRS occurs soon after treatment with axi-cel. Mild/moderate CRS requires considerable observation and supportive care but more severe CRS needs full intensive care plus the administration of tocilizumab and steroids. CRS toxicities resolved in all but [redacted]. The need for baseline and ongoing training for all staff from the haematological ward to the intensive care unit is very great as the manifestations of CRS are so diverse and unexpected. Tocilizumab must be included in the model as NHS England does not currently have a policy position that would permit the use of this drug in this indication. The cost is

	assumed to be [redacted] per dose. The other major side effect is neurotoxicity which can occur early or late. 64% of patients suffer neurological events, the majority of which are mild but 28% experience grade ≥3 toxicity (encephalopathy, confusion, aphasia, and somnolence). The clinical manifestations are diverse with expert neurological input required to closely monitor progression of symptoms or signs. Grade ≥3 neurotoxicity takes a median of 17 days to resolve. Intensive care must have the facility for 24 hour electroencephalography. Other significant side-effects are infection in [redacted] of patients (bacterial, viral and fungal) and hypogammaglobulinaemia. In this population of adult patients, the long term need for intravenous immunoglobulin after CAR T cell therapy is likely to be modest.
Question 6: **Implementation of CAR-T therapy in the NHS – training requirements**	
What roles and how many healthcare professionals are likely to be required to administer CAR T cell therapy in specialist centres?	Ambulatory care CAR T cell teams of specialist nurses and doctors will be required as well as a wide range of acute medical expertise including up to level 3 ITUs with 24 hour availability of monitoring and interpretation of electroencephalography. Regular training will be necessary for them all as well as staff on haematology wards. Patients can be expected to be inpatients for 3-7 days during their conditioning chemotherapy prior to CAR T cell infusion. They will be inpatients for a minimum of 7 days after CAR T cell infusion during which they will have twice daily assessments of cytokine release syndrome and 3 times daily testing for neurotoxicity. Patients will have to remain within a 1 hour travelling time of the CAR T cell centre for 4 weeks after infusion of axi-cel. CAR T cell centres will have to offer rapid admission pathways of care which offer immediate access to assessment by experienced and trained staff in managing the diverse complications of CAR T cell therapy. NHS England plans to institute a national large B cell lymphoma MDT for patients with relapsed/refractory disease who have failed 2 lines of therapy and in whom CAR T cell therapy is considered as a potential option. This national MDT will produce criteria for patient selection and

	prioritisation, take referrals from the CAR T cell centres, identify eligible patients for CAR T cell therapy, liaise closely with the first wave CAR T cell centres, direct which patients are to be treated with CAR T cell therapy and the associated timing, receive regular audits of outcomes from the regional CAR T cell centres and collate these audits into regular national assessments as to the efficacy and toxicity of CAR T cell therapy as well ensuring equity of access. The first wave CAR T cell centres will have large B cell lymphoma CAR T cell MDTs which will be primarily concerned with taking referrals from specialist lymphoma MDTs in their respective regions, making individual patient assessments prior to treatment, referring to the national lymphoma CAR T cell MDT, the initiation of therapy, the management of toxicity and the provision of regular audits of outcomes. There will be a regular mechanism through which treating centres can collectively discuss issues and experience such that there is as much sharing of expertise as possible. All CAR T cell centres will be JACIE-accredited both in terms of Immune Effector Cell standards and for the delivery of allogeneic haematopoietic stem cell transplantation. On-site critical care is required. Capability to deliver the critical care needs of all CAR T patients at all times including those with the most serious side effects (e.g. level 3) is required. Risk management plans and documented evidence of experience in managing the types of toxicities associated with CAR T will be required e.g. sustained and frequent experience in the management of multi-organ failure. CAR T cell centres will need immediate and 24/7 access to a wide range of support specialists in intensive, renal, respiratory, cardiovascular and neurological medicine. The ITU must have the availability of immediate and 24 hour electroencephalography monitoring as well as the expertise necessary for its interpretation.
Would specialists providing care to patients who experience AEs after infusion with axi-cel also require specific training on CAR T therapy?	Yes, as above.
Uncertainty around the training requirements for healthcare professionals is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	NHS England is producing a service specification for axi-cel. This is not yet complete and will be subject to consultation. Therefore assumptions included may be subject to change following review of feedback. An estimate of the staff numbers involved in the direct care of CAR T cell patients will be necessary: in the clinic (where much selection of patients will take place), in the leukapheresis

	unit, in the haematology ward, in the ITU and with all the specialist nurses and doctors required to offer the wide range of disciplines called upon to treat CAR T cell toxicity. A regular update programme is necessary as well as CPD events at sharing expertise between centres and nationally.
Question 7: **Implementation of CAR-T therapy in the NHS – Prioritisation of eligible patients**	
Who would determine which patients are prioritised to receive axi-cel therapy during a phased implementation?	NHS England plans to institute a national large B cell lymphoma MDT for patients with relapsed/refractory disease who have failed 2 lines of therapy and in whom CAR T cell therapy is considered as a potential option. This national MDT will produce criteria for patient selection and prioritisation, take referrals from the CAR T cell centres, identify eligible patients for CAR T cell therapy, liaise closely with the first wave CAR T cell centres, direct which patients are to be treated with CAR T cell therapy and the associated timing, receive regular audits of outcomes from the regional CAR T cell centres and collate these audits into regular national assessments as to the efficacy and toxicity of CAR T cell therapy as well ensuring equity of access. The role of the national MDT in prioritisation of patients may not be required once services commissioned to deliver CAR T cell therapy reach optimal capacity. The first wave CAR T cell centres will have large B cell lymphoma CAR T cell MDTs which will be primarily concerned with taking referrals from specialist lymphoma MDTs in their respective regions, making individual patient assessments prior to treatment, referring to the national lymphoma CAR T cell MDT, the initiation of therapy, the management of toxicity and the provision of regular audits of outcomes. There will be a regular mechanism through which treating centres can collectively discuss issues and experience such that there is as much sharing of expertise as possible. Based on assumptions about balancing expertise, geographical access and likely demand, as well as awaiting the outcome of JACIE accreditation and company on-boarding, NHS England's base case assumption is that 4 CAR T cell therapy centres would start with each treating at a rate of 25 patients per year **by the end of the 1st year of implementation**. A 2nd wave of another 4 CAR T cell treatment centres could follow in the second year. Given that it will take time for each CAR T centre to increase its capacity from an initial cautious rate and depending on the timing of any NICE recommendation, 20-40 patients could be treated in 2018/19, about 100-140 patients treated in 2019/20, and approximately 200 patients/year thereafter. In the event that a greater

	number of providers is able to demonstrate readiness and meet company requirements, it is possible that implementation could be faster than the assumed base case and this would align to NHS England's aspiration to begin to make the treatment, if approved, available as soon as possible.
What criteria would or should be used to prioritise patients for axi-cel treatment?	These criteria for prioritisation of candidates for CAR T cell therapy will be set by the national CAR T cell lymphoma MDT in the period during which demand exceeds capacity. NHS England would wish to set treatment criteria for axicabtagene ciloleucel as treatment for relapsed/refractory large B cell lymphoma after 2 or more lines of systemic therapy, which reflects the known marketing authorisation, the relevant treatment pathways in England, the evidence base submitted to NICE and considerations made by the NICE technology appraisal committee. These provisional criteria are set out below: 1. I confirm that this application is made by and that treatment with axicabtagene ciloleucel will be initiated by a consultant haematologist specifically trained and accredited in the use of systemic anti-cancer therapy with day to day expertise in the use of allogeneic bone marrow transplantation and who is a member of the Trust's large B cell lymphoma CAR T cell multidisciplinary team 1. I confirm the patient has a confirmed histological diagnosis of diffuse large B cell lymphoma or primary mediastinal B cell lymphoma or transformed follicular lymphoma to large cell lymphoma and in relation to transformed follicular lymphoma, these 2 lines of treatment must refer to treatment of the large B cell component of the disease (tick boxes as to which of these 3 types of lymphoma)

	2. I confirm that the patient has received at least 2 prior lines of treatment 3. I confirm that the patient has had a standard 2nd line treatment regimen such as DHAP±R, GDP±R, ICE±R or IVE±R (tick boxes to which) 4. I confirm that the patient has failed to respond to 2nd line treatment or has a biopsy-proven relapse within 12 months of receiving autologous stem cell transplantation 5. I confirm that the patient is of ECOG performance status 0 or 1 6. I confirm that the patient does not have any significant comorbidity which contraindicates CAR T cell therapy with axicabtagene ciloleucel 7. I confirm that the patient has had no previous therapy with any genetically modified autologous T cell immunotherapy 8. I confirm that approval for the use of axicabtagene ciloleucel has been formally given by the national adult large B cell lymphoma CAR T cell multidisciplinary team meeting 9. I confirm that following national approval for use of axicabtagene ciloleucel there has been local CAR T cell multidisciplinary team agreement that this patient has the necessary fitness for treatment and fulfils all treatment criteria listed here 10. I confirm that axicabtagene ciloleucel will be otherwise used as set out in its Summary of Product Characteristics
Given the novelty of the treatment and limited information around follow up, how would patients who received axi-cel be monitored and new knowledge shared between specialist centres to improve overall patient care?	Patients will be monitored by the treating CAR T cell team. This is important for continuity of care and long term monitoring of outcomes including toxicity. Follow-up monitoring is anticipated to be outpatient based and focused on scans, blood tests and where required treatment with drugs such as IVIG.
Uncertainty around the requirements for multidisciplinary teams and phased implementation is likely to be addressed in the new service specification by NHS England. How should this	See above NHS England recognises that assessing the hospital costs of introduction of CAR T cell therapy in this indication is difficult. For example, currently there are a range of local currencies and prices for allogeneic transplant in England. A sensitivity analysis is recommended which uses the costs

information be incorporated into the current cost-effectiveness model and budget impact assessment?	of procedures which bear some similarity to the infrastructure required for CAR T cell therapy. Clinical advice to NHS England therefore would suggest that using the inpatient and follow up costs of an allogeneic SCT for an unrelated donor (plus the separate and extra costs of ITU stay for axi-cel) would offer a useful analysis to compare with the company and ERG's base case assumptions of the hospital costs of CAR T cell therapy. This is calculated to be in the region of [redacted]. NHS England intends to use this approach as a baseline for reimbursement for CAR T activity. However it is also intended to require commissioned providers to collect and report costing data in order that a more granular assessment of the additional costs associated with the delivery of CAR T therapy can be made by year 2 of implementation. The 2 new types of MDTs required to ensure the quality and safety of the CAR T cell service will also have to be added into the costs of CAR T cell treatment. NHS England recognises that the first CAR T cell manufacturer to come to NICE would appear to have to bear all of the costs of infrastructure development and this is potentially unfair when the second manufacturer of CAR T cell therapy is being appraised only 1 month later.
Question 8: **Implementation of CAR-T therapy in the NHS – ambulatory care close to the hospital post infusion**	
Where would a patients stay for aftercare if their home is not located close to the treatment centre?	Some patients may be able to stay with relatives/friends but many will require either hostel or hotel accommodation. The costs of patients having to remain close to treating centres need to be included in the economic analysis as well as at least 1 accompanying person. A cost of £150 per day for a hospital hostel would be reasonable
How long would patients be expected to stay in close proximity to the treatment centre following CAR-T treatment?	NHS England plans to ensure that patients remain within a 1 hour travel time for the first 4 weeks after CAR T cell treatment.
What provisions would be made for family and carers during this period?	See above
Are there other conditions with similar requirements which would be used as a model for axi-cel?	Patients undergoing SCTs, particularly allogeneic SCTs.

Uncertainty around the need for ambulatory care is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	See above. NHS England recognises that assessing the hospital costs of introduction of CAR T cell therapy in this indication is difficult. For example, currently there are a range of local currencies and prices for allogeneic transplant in England. A sensitivity analysis is recommended which uses the costs of procedures which bear some similarity to the infrastructure required for CAR T cell therapy. Clinical advice to NHS England therefore would suggest that using the inpatient and follow up costs of an allogeneic SCT for an unrelated donor (plus the separate and extra costs of ITU stay for axi-cel) would offer a useful analysis to compare with the company and ERG's base case assumptions of the hospital costs of CAR T cell therapy. This is calculated to be in the region of [redacted] NHS England intends to use this approach as a baseline for reimbursement for CAR T activity. However it is also intended to require commissioned providers to collect and report costing data in order that a more granular assessment of the additional costs associated with the delivery of CAR T therapy can be made by year 2 of implementation.
Question 9: **Implementation of CAR-T therapy in the NHS – ICU bed availability**	
Would an ICU bed need to be available for a patient before they were able to start their infusion with axi-cel?	All CAR T cell centres will be JACIE-accredited both in terms of Immune Effector Cell standards and for the delivery of allogeneic stem cell transplantation. On-site critical care is required. Capability to deliver the critical care needs of all CAR T patients at all times including those with the most serious side effects (e.g. level 3) is required. Risk management plans and documented evidence of experience in managing the types of toxicities associated with CAR T will be required e.g. sustained and frequent experience in the management of multi-organ failure. CAR T cell centres will need immediate and 24/7 access to a wide range of support specialists in intensive, renal, respiratory, cardiovascular and neurological medicine. The ITU must have the availability of immediate and 24 hour electroencephalography monitoring as well as the expertise necessary for its interpretation. Patients will often be inpatients for 3-7 days during their conditioning chemotherapy prior to CAR T cell infusion. They will be inpatients for a minimum of 7 days after CAR T cell infusion during which they will have twice daily assessments of cytokine release syndrome and 3 times daily

	testing for neurotoxicity. Patients will have to remain within a 1 hour travelling time of the CAR T cell centre for 4 weeks after infusion of axi-cel. CAR T cell centres will have to offer rapid admission pathways of care which offer immediate access to assessment by experienced and trained staff in managing the diverse complications of CAR T cell therapy There will be very considerable liaison between CAR T cell teams and ITUs as to the timing of treatment. It must be remembered that chemotherapy starts 5 days before CAR T cell infusion and so this planning in advance is very important. NHS Trusts will not be able to give an absolute guarantee of ITU bed availability for any future CAR T cell severe toxicity but recognise the need for CAR T cell patients to only be managed at designated CAR T cell centres whereas this rule will not apply to many other would be ITU patients.
What proportion of patients would be admitted to ICU following infusion with axi-cel if they did not experience a CRS AE?	It is not just CRS which needs intensive care as neurotoxicity can also result in such a need. These two types of toxicity frequently co-exist in any case.
How long would a patient admitted to ICU as the result of (a) axi-cel infusion or (b) a serious CRS event be expected to stay?	A median of 7-8 days for the proportion of patients that require ITU care.
Uncertainty around the requirements for ICU beds is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	The mean ITU bed stay per patient expressed in number of days and including the cost of level 2 and 3 ITU should be incorporated into the cost effectiveness model.
Question 10: **Innovation**	
Do you consider that the use of the technology will result in any substantial benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Cure and thus long term survival is the main goal and achievement of CAR T cell therapy and thus will be incorporated into the survival analysis. See above for comment re utilities.

Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy. Would this have an impact on a patient's health-related quality of life?	It is the whole patient experience that matters, especially the management of toxicity. The mode of administration of the medicine is a minor part of the clinical care patients will experience. Some will tolerate CAR T cell therapy very well with minor problems. Many will experience severe toxicity and a small number of patients will die from side-effects.
Should a weight be applied to the QALYs gained in the axi-cel treatment arm to account for the large survival gains/QALYs?	NHS England sees no reason why such weighting should be applied as the economic model should be capturing the benefits.
Question 11: Cancer Drugs Fund (CDF)	
Please specify whether you consider the technology to be a candidate for entry into the CDF?	NHS England regards axi-cel as a good candidate for the Cancer Drugs Fund as the PFS and OS results are still not mature. Relapses are still being observed at 12 months and few patients are at risk beyond 14 months. A minimum of an extra 12 months of follow-up of ZUMA-1 patients would significantly reduce this uncertainty and thus make a potential NICE recommendation for routine commissioning decision one that ensures value for money for a very expensive technology.
What data may be available for collection to resolve the uncertainty in this appraisal?	Maturation of ZUMA-1 trial results is the key issue concerning re-appraisal
How would additional data collection resolve the uncertainty in this appraisal?	See above
What timelines would be appropriate for additional data collection?	A minimum of an extra 12 months of follow-up of ZUMA-1 patients would significantly reduce this uncertainty and thus make a potential NICE recommendation for routine commissioning decision one that ensures value for money for a very expensive technology.
Do you know of any additional evidence currently or likely to become available that may help to address he uncertainties?	As above
Question 12: Other areas of uncertainty	

Comparators (exclusion of pixantrone) *In clinical practice in the NHS, is pixantrone monotherapy given to patients with relapsed or refractory disease?*	Pixantrone is not a comparator as it is rarely used in NHS clinical practice on account of its poor efficacy.
Comparators (use of a blended comparator) *Are salvage regimens considered equally effective, with and without rituximab?* *Are salvage regimes distributed equally to patients with relapsed or refractory DLBCL, PMBCL and TFL in clinical practice in the NHS?*	Standard second line therapy would include regimes known as DHAP (cisplatin, cytarabine and dexamethasone ± rituximab), ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin ± rituximab), GDP (gemcitabine, cisplatin and dexamethasone ± rituximab), ICE (ifosfamide, cisplatin/carboplatin, etoposide ± rituximab) and IVE (ifosfamide, epirubicin, etoposide ± rituximab).Responding and fit patients would then proceed to SCT. The comparator for axi-cel would therefore be what would be used in fit patients that have failed DHAP/ESHAP/GDP/ICE/IVE ± rituximab or responded to such 2nd line standard therapy and then relapsed after subsequent SCT. Such 3rd line therapies would be one of the second line regimens as described above or gemcitabine plus methyl prednisolone ± cisplatin, the combination of gemcitabine, cyclophosphamide, vincristine and prednisolone and (less so) the combination of rituximab, vinblastine and prednisolone. There is no 3rd line standard therapy as one is clearly not superior to the others. Other options would be clinical trials of novel therapies and symptomatic therapy. Since only patients of ECOG performance status (0 or 1) would be considered for CAR T cell therapy, such fit patients in the NHS would normally be offered further chemotherapy with the possible outcome of a stem cell transplant (although SCT is uncommon in this group of patients – 10% or less of 3rd line treatment patients in the NHS).
Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1 *What is the average time period between the clinical decision taken to administer salvage chemotherapy to a patient and the patient receiving chemotherapy? Would there be a concern that patients may experience disease progression during the additional time required for manufacturing of axi-cel?*	This question cannot be answered without NICE defining what 'mITT' means. Salvage chemotherapy proceeds within a matter of a few days to a week or so i.e. it proceeds quickly. Salvage treatment needs to start quickly as often the disease is progressing quickly. As the ZUMA-1 trial shows, about 10% of patients selected for axi-cel therapy can progress

	sufficiently in the 3-4 weeks or so that it takes from leukapheresis to axi-cel infusion. This percentage should remain small in view of the patient selection required to get to leukapheresis.
Re-treatment with axi-cel in the ZUMA-1 population *Would patients who received retreatment with axi-cel be expected to have improved outcomes compared with those whose disease progressed and did not receive a second round of treatment?*	NHS England considers this question out of scope given that there is no evidence on which to base a proposal for re-treatment with axi-cel. Axi-cel is a high cost treatment and with tight funding restrictions, the NHS must obtain value for money and spread this expensive but promising technology across maximal numbers of the eligible patient population.
Patients receiving post-treatment SCTs and the associated assumptions *What proportion of patients (R/R after 2nd line or who previously failed an ASCT) receiving salvage chemotherapy would become eligible for a SCT in clinical practice?* *Are outcomes for patients who receive a stem cell transplant likely to be significantly different from patients who receive salvage chemotherapy?* *Would patients be likely to receive autologous or allogenic stem cell transplants after response to treatment with either salvage chemotherapy or axi-cel?* *How long on average would patients receive follow-up care following a stem cell transplant?*	Approximately 10-15% of rel/ref large B cell lymphoma patients who proceed to 3rd line chemotherapy will subsequently have a SCT, a mixture of allogeneic and autologous SCT. A SCT in this population offers the only chance of long term survival as responses to salvage chemotherapy alone are short-lived. SCT after a relapse following axi-cel is unlikely and therefore NHS England has not factored this into its assumptions. Follow-up is likely to be life-long for an allogeneic SCT. Follow-up could end at 5 years following an autologous SCT.
Long term costs of IVIG treatment - real world experience *What proportion of patients would still be affected by B-cell aplasia after 12 months following treatment*	Data are limited but it may be appropriate to assume [redacted] of patients may be affected by B-cell aplasia after treatment and assumed 100% of these would require life-long IVIG. The costs we have used are commercially confidential - [redacted]

with axi-cel? Would these patients require continued IVIG treatment and for how long?	For further detail and other clinical issues relevant to the technical engagement please see appendix 1.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed response form

Appendix 1:

NHS England submission for NICE appraisal of axicabtagene ciloleucel for the treatment of patients with relapsed/refractory diffuse large B cell lymphoma, primary mediastinal B cell lymphoma and transformed follicular lymphoma

Likely EMA marketing authorisation (not yet finalised but Gilead consider FDA wording is expected)
Axicabtagene-ciloleucel (axi-cel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Current care pathway for relapsed/refractory diffuse large B cell lymphoma (DLBCL)
Chemo-immunotherapy remains the cornerstone of 1st line treatment for patients with DLBCL. If patients are to receive optimal therapy, they have to be medically fit to receive combination chemotherapy (cyclophosphamide, vincristine, doxorubicin and prednisolone) given in conjunction with rituximab. Such patients have a 70-80% chance of remaining free of disease progression.

Patients who relapse do so within the first 2 years after completing treatment and, if fit for optimal (but toxic) chemo-immunotherapy, have a low chance of remaining free of disease progression if just treated with conventional doses of chemotherapy. Patients who respond to 2nd line chemotherapy and who are sufficiently medically fit enough will usually be offered high dose chemotherapy and haematopoietic stem cell transplantation (SCT), usually autologous SCT. Such consolidation of a response to 2nd line chemotherapy with SCT is considered to be part of 2nd line chemotherapy. If not salvaged by 2nd line chemotherapy with or without SCT, life expectancy for most patients is short and usually measured in terms of single numbers of months. A minority of patients have further responses to chemotherapy and a small percentage are able to proceed to high dose chemotherapy and allogeneic haematopoietic SCT.

Salvage chemotherapy in DLBCL with new agents (eg B cell pathway inhibitors, checkpoint inhibitors, inotuzumab etc) have been disappointing and hence for relapsed/refractory DLBCL after 2 lines of chemotherapy, CAR T cell therapy is the only novel and truly efficacious treatment to potentially make a big difference to outcomes in DLBCL.

Small numbers of children and teenagers are also diagnosed with DLBCL and a few of these will have relapsed/refractory disease after 2nd line therapy. These patients would benefit from CAR T cell treatment even though their ages are very likely to be outside the marketing authorisation of axicabtagene ciloleucel. Clarification needed on manufacture outside of licence.

Current care pathway for primary mediastinal B cell lymphoma (PMBCL)

There are about 60-80 patients diagnosed each year in England with PMBCL and approximately 80% will achieve freedom from disease progression with standard chemo-immunotherapy.

If patients relapse after 1st line treatment for PMBCL, successful salvage with standard 2nd line cytotoxic chemotherapy is rarely successful. Current clinical trials using checkpoint inhibitors and brentuximab offer theoretical promise in terms of potentially bridging patients to SCT but CAR T cell therapy currently offers the only novel and efficacious treatment for relapsed/refractory PMBCL.

Very small but important numbers of children and teenagers with relapsed/refractory PMBCL would have disease that is likely to benefit from CAR T cell therapy.

Current care pathway for transformed follicular lymphoma (TFL)

Follicular lymphoma has traditionally been considered to have about a 10% 10 year risk of transformation to an adverse histology, usually to DLBCL. In follicular lymphoma patients previously treated with doxorubicin-containing chemo-immunotherapy who then transform and have thus acquired adverse mutations and markers of resistance, the outlook is poor with a median survival in most series of about 1 year. As a consequence, high dose chemotherapy and SCT is incorporated into the treatment strategy of such patients if they are medically fit for high dose treatment and SCT.

Recent data suggests that the outlook for patients with TFL may be improving as a consequence of the incorporation of rituximab into treatment regimens and thus the need for such intensive (high dose chemotherapy and SCT) therapy is being questioned. CAR T cell treatment would be indicated in some patients with TFL (especially those with p53 deleted TFL) and in those that have been optimally pre-treated and who remain medically very fit.

Potential patient numbers for whom axicabtagene ciloleucel would be indicated

As yet the wording of the EMA marketing authorisation of axicabtagene ciloleucel is not known and hence the following estimates may change once this marketing authorisation has been established. The key issue is that in NHS England's view patients have to have either refractory or relapsed large B cell lymphoma **after** having received **2** lines of therapy.

Diffuse large B cell lymphoma (DLBCL)

The relevant issues in determining the potential number of patients eligible to receive axicabtagene ciloleucel are:

- There are 5130 new patients diagnosed with DLBCL in the UK each year (data from the NICE IOG 2018 guideline which was derived from the Haematological Malignancy Research Network [HMRN]). This means **4361** new patients with DLBCL in England each year

- It is important to note that the median age of patients with DLBCL at diagnosis is 70 years
- In the New England Journal of Medicine report of axicabtagene ciloleucel treatment in DLBCL (NEJM 2017; 377: 2531-2544), the median age of the 111 patients in the study was 58 years with an age range of 23-76 years and 24% were 65 years old or older. This bias towards selecting younger patients for CAR T cell therapies in this study reflects the need for patients to be very fit for a potentially highly toxic treatment and that older patients are excluded on account of increasingly significant comorbidities
- 20% of patients with DLBCL at diagnosis do not receive any active treatment. This figure comes from the HMRN for 2007 and is incorporated in a health economic model developed by the HMRN in conjunction with York University (Eur J Health Economics 2017; 18: 255-267). This 20% figure remains valid in view of the opposing trends that are evident: increasing diagnoses of DLBCL made since 2007, particularly so in the elderly (ie less likely to receive active treatment) and the ability of greater numbers of patients to undergo chemotherapy in 2018 that is better tolerated/supported than in 2007
- 5% of the total patients diagnosed will receive radiotherapy only
- 75% of the total patients diagnosed with DLBCL will receive chemotherapy, this equating to 3270 patients
- Not all of these 3270 patients will receive optimal 1st line chemotherapy but 2nd line chemotherapy is only likely to proceed in relapsed patients treated with optimal 1st line chemotherapy
- The HMRN/York economic model indicated that in 2007, **11.2%** of all DLBCL patients proceeded to have 2nd line chemotherapy, **3.2%** with subsequent SCT and **8%** without SCT. Most but not all of this **8%** in 2007 will have had aggressive 2nd line chemotherapy. Changes in practice since 2007 mean that more patients remain disease-free with 1st line chemotherapy and also that 2nd line salvage therapy is better tolerated and supported. Thus it is reasonable to assume similar percentages in 2018 to those in 2007 ie **3.2%** of all DLBCL patients still have 2nd line chemotherapy plus SCT (**142 patients** and mainly autologous SCT) and **8%** of all patients have 2nd line chemotherapy without SCT (**349 patients**)
- Of the 142 patients that have 2nd line chemotherapy and SCT (mainly autologous), approximately one quarter will remain disease-free. This therefore means that about 100 patients will relapse, often with very aggressive disease. Nevertheless, as these patients started 2nd line treatment as a fit group of patients, it is reasonable to assume that about **30-40** patients will subsequently be eligible for axicabtagene ciloleucel
- Of the 349 patients that have and nearly all fail 2nd line chemotherapy, a large proportion will be unfit for CAR T cell therapy either as a consequence of disease progression or because they lack the fitness required for CAR T cell treatment (see the selection criteria employed for the axicabtagene ciloleucel trial). It is important to note that DLBCL that has progressed after 2 lines of therapy is often rapidly growing and thus can cause a steep and rapid decline in a patient's performance status and therefore contra-indicate CAR T cell therapy. This therefore makes the likely eligible number of fit patients with relapsed DLBCL who have not had SCT to be about a third of those that had such 2nd line chemotherapy – **110-120** patients
- In the axicabtagene ciloleucel study, 21% of patients had previously had SCT. Thus the proportional estimate of patients eligible for CAR T cell treatment post SCT in England (about 30-40 of such patients) is in broad accordance with the 110-120 patients estimated to have not had SCT

- In total, NHS England estimates that approximately **140-160** patients with relapsed/refractory DLBCL will be eligible for axicabtagene ciloleucel
- The numbers of children and teenagers with relapsed/refractory DLBCL will almost all be post SCT and the number estimated to be eligible for off label CAR T cell therapy is 5-10.

Transformed follicular lymphoma (TFL)
Estimating the number of patients with TFL is difficult as there is little data as to how many of such patients there are in England and as has been mentioned above, the number of such patients seems likely to be declining.

The mix of patients in the axicabtagene ciloleucel NEJM study was approximately one quarter comprised of TFL and PMBCL together (the split is one third PMBCL and two thirds TFL) and three quarters DLBCL. It is reasonable to assume about **40** patients with TFL being eligible for axicatagene ciloleucel as the ZUMA-1 trial results will encourage recruitment of TFL patients to consideration for CAR T cell treatment.

Primary mediastinal B cell lymphoma (PMBCL)
This type of lymphoma is rare (60-80 patients/year) and 80% are cured with 1st line treatment. Of the 12-16 patients who have relapsed/refractory disease, a few will have 2nd line chemotherapy and proceed to SCT. Most patients are difficult to salvage yet are fit at the time of 2nd relapse and thus about **10** patients can be expected to be eligible for axicabtagene ciloleucel

There will be 1-3 children/teenagers with PMBCL who would be eligible for off label CAR T cell therapy.

In total, NHS England estimates that there will be about **190-210 adult patients per year** eligible for treatment with axicabtagene ciloleucel within its expected licensed indication. There would be 6-12 children or teenagers who have diseases with similar biologies to adults and who would also benefit from CAR T cell treatment.

There would be 6-12 children or teenagers who have diseases with similar biologies to adults and who would also benefit from CAR T cell treatment. Small numbers of children and teenagers are also diagnosed with DLBCL and a few of these will have relapsed/refractory disease after 2nd line therapy. These patients would benefit from CAR T cell treatment even though their ages are very likely to be outside the marketing authorisation of axicabtagene ciloleucel. Very small but important numbers of children and teenagers with relapsed/refractory PMBCL would have disease that is likely to benefit from CAR T cell therapy. There will be 1-3 children/teenagers with PMBCL who would be eligible for off label CAR T cell therapy

Further NHS England comments on axicabtagene ciloleucel for the NICE technology appraisal

The marketing authorisation
The key interpretation of the likely marketing authorisation when directed to clinical practice is whether 'relapsed and refractory' applies to the '2' lines of therapy. NHS England's interpretation is that patients whether relapsed after or refractory to 1st line treatment must have failed standard 2nd line therapy ie if a SCT was planned in the current treatment pathway and patients respond sufficiently, then those patients should proceed to SCT as currently commissioned and not to CAR T cell therapy.

The comparator
Standard second line therapy would include regimes known as DHAP (cisplatin, cytarabine and dexamethasone ± rituximab), ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin ± rituximab), GDP (gemcitabine, cisplatin and dexamethasone ± rituximab), ICE (ifosfamide, cisplatin/carboplatin, etoposide ± rituximab) and IVE (ifosfamide, epirubicin, etoposide ± rituximab).Responding and fit patients would then proceed to SCT.

The comparator for axi-cel would therefore be what would be used in fit patients that have failed DHAP/ESHAP/GDP/ICE/IVE ± rituximab or responded to such 2nd line standard therapy and then relapsed after subsequent SCT. Such 3rd line therapies would be one of the second line regimens as described above or gemcitabine plus methyl prednisolone ± cisplatin, the combination of gemcitabine, cyclophosphamide, vincristine and prednisolone and (less so) the combination of rituximab, vinblastine and prednisolone. There is no 3rd line standard therapy as one is clearly not superior to the others. Other options would be clinical trials of novel therapies and symptomatic therapy. Since only patients of ECOG performance status (0 or 1) would be considered for CAR T cell therapy, such fit patients in the NHS would normally be offered further chemotherapy with the possible outcome of a stem cell transplant (10-15% or less of 3rd line treatment patients in the NHS). Pixantrone is not a comparator as it is rarely used in NHS clinical practice on account of its poor efficacy.

ZUMA-1 trial patients
ZUMA-1 recruited 3 groups of patients. The first was a group which consisted of patients refractory to 1st line therapy: those that had progressive disease to 1st line treatment or who had stable disease after 1st line treatment and progressed within 6 months of completing 1st line treatment (2 patients treated). The second group was patients refractory to 2nd or later lines of therapy: those that had progressive disease to 2nd line treatment or had stable disease and relapsed within 6 months of completing 2nd line therapy (78 patients treated). A third group was those patients that had autologous SCT and had relapsed within 12 months of receiving the SCT; a biopsy had to prove such a disease relapse and if the patients were treated with further chemotherapy, the patients must either have not responded or had relapsed following such chemotherapy (21 patients treated). NHS England believes that the 2nd and 3rd groups fall within the expected marketing authorisation for axi-cel but not the first group.

NHS England notes that all the patients in the ZUMA-1 trial were of ECOG performance status 0 or 1. The patient population was thus a fit one. This is important for safety reasons given the very considerable toxicity of CAR T cell therapy.

The case mix in the 111 patients enrolled consisted of 81 patients with DLBCL and 30 patients with either PMBCL or TFL. This is approximately the case mix that NHS England expects that would be treated with axi-cel in clinical practice.

It would be important for NICE and NHS England to see the ZUMA-1 trial screening log: the number of patients who were initially considered for the ZUMA-1 trial. This will offer a clearer picture of the degree of selection that was necessary in trial centres between the number of patients screened versus the number of patients actually selected for axi-cel treatment.

NHS England notes that 10% of patients entered into the study were leukapheresed but did not receive axi-cel: 4 of the 81 DLBCL patients and 6 of the 30 PMBCL/TFL patients. The main cause of this was progressive disease and its consequences in the time in between leukapheresis and arrival of the axi-cel for infusion

NHS England considers that the highly selected ZUMA-1 trial population is generalizable to the highly selected population of patients in the NHS which would be treated with axi-cel. The only difference in patient characteristics would be the number of previous lines of therapy. In future NHS practice this will be 2 lines of previous therapy for the great majority of patients and not the ZUMA-1 figures of 69% having had ≥ 3 lines of therapy and [redacted] having had ≥ 4 lines of treatment. Nevertheless, as 42% of ZUMA-1 patients were of ECOG performance status 0 and 58% of performance status 1, ZUMA-1 attracted very fit patients despite being heavily pre-treated. The population can thus be regarded as having outcomes which are generalizable to NHS practice.

ZUMA-1 trial outcomes

The current median duration of follow up in the axi-cel trial is 15.4 months. The efficacy results even for patients with relapsed/refractory DLBCL who have failed 2+ lines of therapy are immature.

NHS England notes that progression free survival (PFS) is plateau**ing** in ZUMA-1 but relapses have still occurred at 12 months. PFS rates at 6 months were 49%, at 12 months were 44% and at 15 months were 41%. NHS England notes that there are very few patients at risk after 14 months and so regards these PFS results as very encouraging but not mature.

Overall survival (OS) is also plateau**ing** but NHS England notes that deaths have occurred at 12-16 months and for this reason the 18 month OS figure of 52% is lower than the figure of 59% at 12 months which in turn is lower than 78% at 6 months. There are very few patients at risk after 16 months.

ZUMA-1 trial utilities

NHS England notes the utility data by response status and the small numbers in these analyses (0.74 for complete response, 0.79 for partial response, 0.64 for stable disease and 0.65 for progressive disease). It is counter intuitive for the partial response utility to be higher than that for a complete response. Given that progressive disease after CAR T cell therapy is a disaster for patients, it is surprising that the progressive disease utility is not lower than 0.65. NHS England also notes that the results by health state also do not show much differential: 0.72 for remaining free of progression and 0.65 for progressed disease.

Axicabtagene ciloleucel toxicity

NHS England notes that treatment with axi-cel is associated with many side-effects, some of them being life threatening and particularly so in the first month of treatment. It observes that serious toxicity diminishes as experience with CAR T cell therapy increases but nevertheless recognises that it has to wrap all the appropriate 24 hour expertise around each patient in order to maximise safety and optimise outcomes for patients and the NHS. In the ZUMA-1 trial, 95% of patients experienced a grade ≥3 adverse event, [redacted] a grade ≥3 serious adverse event and [redacted] of patients died of a treatment-related cause.

The two most dangerous side-effects of axi-cel are of cytokine release syndrome (CRS) and neurotoxicity. Feedback to NHS England from the clinical trial centres in England who are currently involved in CAR T cell therapy consistently report how diverse the manifestations of toxicities can be and how alert patients and staff must be to apparently minor symptoms which can then escalate quickly if not heeded and acted upon.

94% of patients recorded some degree of CRS but it is in 13% that grade 3 or worse CRS was seen. CRS occurs soon after treatment with axi-cel. Mild/moderate CRS requires considerable observation and supportive care but more severe CRS needs full intensive care plus the administration of tocilizumab and steroids. CRS toxicities resolved in all [redacted]. The need for training for all staff from the haematological ward to the intensive care unit is very great as the manifestations of CRS are so diverse and unexpected.

The other major side effect is neurotoxicity which can occur early or late. 64% of patients suffer neurological events, the majority of which are mild but 28% experience grade ≥3 toxicity (encephalopathy, confusion, aphasia, somnolence). The clinical manifestations are diverse with expert neurological input required to closely monitor progression of symptoms or signs. Grade ≥3 neurotoxicity takes a median of 17 days to resolve. Intensive care units must have the facility for 24 hour electroencephalography.

Other significant side-effects are infection in [redacted] of patients (bacterial, viral and fungal) and hypogammaglobulinaemia. In this population of adult patients, the long term need for intravenous immunoglobulin after CAR T cell therapy is likely to be modest.

Indirect comparison of ZUMA-1 with SCHOLAR-1

The indirect comparison of ZUMA-1 with SCHOLAR-1 has serious disadvantages given the heterogeneity of the 4 data sources that informed the outputs of SCHOLAR-1: a mixture of retrospective and prospective databases, of audits and clinical trials, of ECOG performance status patients 0-4, of primary refractory patients and of previously received lines of therapy. Of note is that the SCHOLAR-1 trial OS curve flattening at about 7 years at about 13-14% of patients. This will be mainly related to the fact that [redacted] of SCHOLAR-1 patients received subsequent SCT. This [redacted] figure is higher than that recorded in NHS practice as part of 3rd line salvage chemotherapy (approximately 10-15% SCT rate). In addition, NHS England notes that Kite Pharma was directly involved in the funding of the study and in the writing of the SCHOLAR-1 publication. NHS England therefore has great reservations as to the comparability of ZUMA-1 and SCHOLAR-1.

Economic modelling

NHS England notes that in its economic model Gilead assumes that axi-cel overall survival has plateaued at 50% and then falls in line with the mortality decline for the general population. NHS England regards these 2 factors as being optimistic as the OS rate in ZUMA-1 may fall given the immaturity of follow up and the fact that these patients are heavily treated with chemotherapy which is known to add a survival disadvantage in the long term. In addition, a long term OS plateau at the latest percentage figure of patients remaining progression-free (42%) seen so far in the Zuma-1 trial might be a more realistic (but still optimistic) number to use rather than 50%.

NHS England observes that the long term OS rate in SCHOLAR-1 in the economic model is 13-14% .NHS England regards this figure as being high and presumably relates to the high number of SCTs assumed in the economic model. If there is a 10-15% rate of SCT in this group of patients in England as part of 3rd line chemotherapy (most of which will be allogeneic SCTs), there is likely to be about a 6-8% (or less) long term survival rate for patients embarking on 3rd line therapy.

No PFS data was reported in SCHOLAR-1. To overcome this, PFS was estimated for the comparator population in the economic model by assuming that the same ratio between PFS and OS at each time point in the axi-cel arm can be applied to the comparator arm. Since these two modalities of treatment are completely different, there must be significant uncertainty as to the validity of this assumption.

NHS England notes that the mean length of inpatient stay in the ZUMA-1 study was 17.6 days and that the company's model costs this according to NHS weighted inpatient haematological costs. What is unclear is how many intensive care unit days are incorporated and at what cost, especially considering that the type of intensive care unit has to be one which is capable of 24 hour EEG monitoring and interpretation. The considerable amount of expert neurology input does not appear to have been costed and nor has the multidisciplinary team costs given the need for respiratory, renal, hepatic and microbiological input.

Gilead assumes that the comparator chemotherapy is given as an inpatient and thus this attracts high costs as the costing comparison uses the weighted haematology inpatient costs. 3 of the 4 regimens used in the economic analysis can be given as day cases and thus the costs of the comparator chemotherapy have been significantly inflated in the company's model.

The company appears to have applied a rate of [redacted] SCT to the comparator arm which appears to be a very significant overestimation of the likely SCT rate in such a population in England (10-15% SCT rate with a long term survival rate of 6-8%). As this [redacted] rate of SCT and the 13-14% long term rate of overall survival seem high, the economic model in this regard appears to have inflated both the survival and costs of the comparator population for axi-cel.

NHS England would wish to see confirmation that there is inclusion of leukapheresis costs for all the patients in whom Gilead manufactures axi-cell infusions, not just the patients who actually receive the axi-cell infusions.

NHS England plans to ensure that patients remain within a 1 hour travel time for the first 4 weeks after CAR T cell treatment. Some patients may be able to stay with relatives/friends but many will require either hostel or hotel accommodation. These costs of patients having to remain close to treating centres need to be included in the economic analysis.

NHS England recognises that assessing the hospital costs of introduction of CAR T cell therapy in this indication is difficult. A sensitivity analysis is recommended which uses the costs of procedures which bear some similarity to the infrastructure required for CAR T cell therapy. Clinical advice to NHS England therefore would suggest that using the inpatient and follow up costs of an allogeneic SCT for an unrelated donor (plus the separate and extra costs of ITU stay for axi-cel) would offer a useful analysis to compare with the company and ERG's base case assumptions of the hospital costs of CAR T cell therapy.

The company estimates about 1000 patients being eligible for axi-cel but in its budget impact test submission reduces this number to 312 patients. NHS England regards this number as being too high partly because it is unclear from the company submission as to how 1st line refractory patients are being counted and partly because the company has underestimated the attrition to patient numbers which occurs when patients fail chemotherapy for an increasingly aggressive disease.

NHS England delivering CAR T cell therapy in practice

Based on assumptions about balancing expertise, geographical access and likely demand, as well as awaiting the outcome of JACIE accreditation and company on-boarding, NHS England's base case assumption is that 4 CAR T cell therapy centres would start with each treating at a rate of 25 patients per year by the end of the 1st year of implementation. A 2nd wave of another 4 CAR T cell treatment centres could follow in the second year. Given that it will take time for each CAR T centre to increase its capacity from an initial cautious rate and depending on the timing of any NICE recommendation, 20-40 patients could be treated in 2018/19, about 100-140 patients treated in 2019/20, and approximately 200 patients/year thereafter. In the event that a greater number of providers is able to demonstrate readiness and meet company requirements, it is possible that implementation could be faster than the assumed base case and this would align to NHS England's aspiration to begin to make the treatment, if approved, available as soon as possible.

All CAR T cell centres will be JACIE-accredited both in terms of Immune Effector Cell standards and for the delivery of allogeneic haematopoietic stem cell transplantation. On-site critical care is required. Capability to deliver the critical care needs of all CAR T patients at all times including those with the most serious side effects (e.g. level 3) is required. Risk management plans and documented evidence of experience in managing the types of toxicities associated with CAR T will be required e.g. sustained and frequent experience in the management of multi-organ failure. CAR T cell centres will need immediate and 24/7 access to a wide range of support specialists in intensive, renal, respiratory, cardiovascular and neurological medicine. The ITU must have the availability of immediate and 24 hour electroencephalography monitoring as well as the expertise necessary for its interpretation.
Patients will often be inpatients for 3-7 days during their conditioning chemotherapy prior to CAR T cell infusion. They will be inpatients for a minimum of 7 days after CAR T cell infusion during which they will have twice daily assessments of cytokine release syndrome and 3 times daily testing for neurotoxicity. Patients will have to remain within a 1 hour travelling time of the CAR T cell centre for 4 weeks after infusion of axi-cel. CAR T cell centres will have to offer rapid admission pathways of care which offer immediate access to assessment by experienced and trained staff in managing the diverse complications of CAR T cell therapy. The provision of ambulatory care pathways in accordance with NICE Guideline (NG47) Haematological Cancers: Improving Outcomes (https://www.nice.org.uk/guidance/NG47/chapter/Recommendations#ambulatory-care) will enable centres administering CAR T cells to satisfy these objectives safely whilst accommodating patient experience.

CAR T cell centres will have cell therapy laboratory and pharmacy expertise in the handling, storage and thawing of advanced therapy medicinal products. In addition, centres will have considerable expertise in leukapheresis.

NHS England plans to institute a national large B cell lymphoma MDT for patients with relapsed/refractory disease who have failed 2 lines of therapy and in whom CAR T cell therapy is considered as a potential option. This national MDT will produce criteria for patient selection and prioritisation, take referrals from the CAR T cell centres, identify eligible patients for CAR T cell therapy, liaise closely with the first wave CAR T cell centres, direct which patients are to be treated with CAR T cell therapy and the associated timing, receive regular audits of outcomes from the regional CAR T cell centres and collate these audits into regular national assessments as to the efficacy and toxicity of CAR T cell therapy as well ensuring equity of access. Equity of geographical access from local MDTs will be assured through an equal allocation of centres per NHS England region and representation on the national MDT.

The first wave regional CAR T cell centres will have large B cell lymphoma CAR T cell MDTs which will be primarily concerned with taking referrals from specialist lymphoma MDTs in their respective regions, making individual patient assessments prior to treatment, referring to the national lymphoma CAR T cell MDT, the initiation of therapy, the management of toxicity and the provision of regular audits of outcomes. There will be a regular mechanism through which treating centres can collectively discuss issues and experience such that there is as much sharing of expertise as possible.

Innovation

NHS England regards axicabtagene ciloleucel as highly innovative in terms of its mode of action: genetic engineering to T cells to recruit an immune response which results in a 'living' treatment against large cell lymphoma. But however clever or neat a technology may be, it is what a treatment does to meaningful outcomes for patients which results in NHS England concluding whether a new treatment is a game changer or not. CAR T cell therapy fulfils this definition of a potential game changer if it is confirmed that there are very or no few relapses in the period of 12-24 months after treatment and if there is no substantial long term toxicity.

Cancer Drugs Fund
NHS England regards axi-cel as a good candidate for the Cancer Drugs Fund as the PFS and OS results are still not mature. Relapses are still being observed at 12 months and few patients are at risk beyond 14 months. A minimum of an extra 12 months of follow-up of ZUMA-1 patients would significantly reduce this uncertainty and thus make a potential NICE recommendation for routine commissioning decision one that ensures value for money for a very expensive technology.

NHS England commissioning treatment criteria
NHS England would wish to set treatment criteria for axi-cel therapy which reflects the known marketing authorisation, the relevant treatment pathways in England, the evidence base submitted to NICE and considerations to be made by the NICE technology appraisal committee. In view of the toxicity of the CAR T cell treatment and the evidence base solely being in fit patients being treated with axi-cel, NHS England considers it vital for patient safety that only patients of good performance status are treated with axi-cel (ie patients must have an ECOG performance status of only 0 or 1). These provisional criteria are set out below.

Axicabtagene ciloleucel as treatment for relapsed/refractory large B cell lymphoma after 2 or more lines of systemic therapy

- I confirm that this application is made by and that treatment with axicabtagene ciloleucel will be initiated by a consultant haematologist specifically trained and accredited in the use of systemic anti-cancer therapy with day to day expertise in the use of allogeneic bone marrow transplantation **and** who is a member of the Trust's large B cell lymphoma CAR T cell multidisciplinary team
- I confirm the patient has a confirmed histological diagnosis of diffuse large B cell lymphoma or primary mediastinal B cell lymphoma or transformed follicular lymphoma to large cell lymphoma (tick boxes as to which)
- I confirm that the patient has received at least 2 prior lines of treatment and in relation to transformed follicular lymphoma, these 2 lines of treatment must refer to treatment of the large B cell component of the disease
- I confirm that the patient has had a standard 2nd line treatment regimen such as DHAP±R, GDP±R, ICE±R or IVE±R (tick boxes to which)
- I confirm that the patient has failed to respond to 2nd line treatment or has a biopsy-proven relapse within 12 months of receiving autologous stem cell transplantation
- I confirm that the patient is of ECOG performance status 0 or 1

- I confirm that the patient does not have any significant comorbidity which contraindicates CAR T cell therapy with axicabtagene ciloleucel
- I confirm that the patient has had no previous therapy with any genetically modified autologous T cell immunotherapy
- I confirm that approval for the use of axicabtagene ciloleucel has been formally given by the national adult large B cell lymphoma CAR T cell multidisciplinary team meeting
- I confirm that following national approval for use of axicabtagene ciloleucel there has been local CAR T cell multidisciplinary team agreement that this patient has the necessary fitness for treatment and fulfils all treatment criteria listed here
- I confirm that axicabtagene ciloleucel will be otherwise used as set out in its Summary of Product Characteristics

Prof Peter Clark, NHS England Chemotherapy Clinical Reference Group chair and clinical lead for the Cancer Drugs Fund - June 2018

NICE National Institute for Health and Care Excellence

Technical engagement response form

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Thank you for agreeing to give us your comments and feedback as part of the technical engagement step to assist us in identifying the most plausible assumptions in the clinical and cost-effectiveness for this technology.

As a technical engagement stakeholder for this appraisal step, we highly appreciate your input, comment and ongoing support for this appraisal.

To help you give your views, please use this questionnaire. You do not have to answer every question. The text boxes will expand as you type. Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

Information on completing this technical engagement response

- Prior to completing this response table please see the technical engagement document which summarises the background, and submitted evidence for this appraisal. This will provide you with context and outline the questions below in greater detail for which we require your comments and feedback.
- 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.

Please note that comments from the technical engagement will be collated and summarised as part of the committee pre-meeting briefing document, which will be made available to all stakeholders with a signed confidentiality agreement as part of the committee papers accompanying the post committee documentation (ACD or FAD) following the meeting on 31 July 2018.

Deadline for comments **5pm on 22 June 2018**

NICE National Institute for Health and Care Excellence

About you

Your name	**Dr Andrew McMillan**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**BSH / RCPath**
Are you (please tick all that apply)	☐ a representative from the company (Kite, Gilead)? ☐ **x** a clinical expert? ☐ a commissioning expert? ☐ a patient expert or organisation? ☐ an NHS England representative?
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	

Questions for engagement

Question 1: Adjustment of SCHOLAR-1 cohort for comparative effectiveness results	
Are clinical outcomes for patients with ECOG status 0-1 and those with ECOG status 2-4 likely to be different?	**Yes, CAR T cell therapy is extremely intensive with up to 20% incidence of Intensive care admission so this would risk much worse outcomes in patientients with inferior PS**
Is a population from SCHOLAR-1 which includes patients with possible ECOG status 2-4 suitable to compare to the ZUMA-1 population whose eligibility criteria included only people with ECOG score 0-1?	No , it is very difficult to compare these two groups of patients , it is clear that the ZUMA 1 population is very highly selected, whereas the Scholar 1 population is a mix of clinical trial data and observational cohorts. I also have concerns with the prominence given to the Scholar 1 dataset as in the paper it is acknowledged that the data was analysed by KITE PHARMA and the some of the Authors have COI with KITE. This is a potential source of bias which should be made transparent with any use of the data . The ORCHARRD trial data would be an alternative source

	of data (nb I am a Co Author on this paper) (J Clin Oncol. 2017 Feb 10;35(5):544-551. doi: 10.1200/JCO.2016.69.0198. Epub 2016 Dec 28. **Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study.** van Imhoff GW[1], McMillan A[1], Matasar MJ[1], Radford J[1], Ardeshna KM[1], Kuliczkowski K[1], Kim W[1], Hong X[1], Goerloev JS[1], Davies A[1], Barrigón MDC[1], Ogura M[1], Leppä S[1], Fennessy M[1], Liao Q[1], van der Holt B[1], Lisby S[1], Hagenbeek A[1].)
Adjusting for ECOG status will not account for all imbalances in the SCHOLAR-1 and ZUMA-1 populations. Are there any additional comments on the approach used by the company or ERG to provide comparative effectiveness estimates?	**I have not seen this analysis yet.**
Question 2: Expected relapse rate after the period of follow-up available from ZUMA-1	
Is it appropriate to assume a patient is considered if they have not experienced an event by 15 months post treatment (trial follow-up period)?	**I assume the word 'cure' is missing ? if so, while this is currently a reasonable assumption for Chemotherapy and Transplant patients, in my view, this is premature for CAR T treated patients. There are well described potential causes of late relapse , most notably, disappearance of the CAR T clone. The results are certainly encouraging but there is still uncertainty which , again in my view, argues for consideration of CDF status as being more appropriate.**
What is the expected relapse rate for patients in remission between 2-5 years after treatment?	**Due to current limited follow up this data is not available and I would prefer not to guess a figure**
Is there additional data expected from the ZUMA-1 trial which would increase the duration of the follow-	**In time, but my impression of the data currently in the Kaplan Meier curves is that follow up is insufficient**

up period and reduce uncertainty in the assumptions around survival for patients who received axi-cel?	
Would additional data collection reduce uncertainty?	**Yes**
Long-term survival is apparent in both treatment arms. Does this reflect clinical practice in the UK for patients treated with salvage chemotherapy?	**Yes, however success rates after second line failure are low. I would estimate only 10-20% of third line therapy achieves a response suggesting a transplant rate of around 10-20% of patients receiving third line therapy.**
Question 3: Appropriate extrapolation for overall survival in axi-cel treatment arm	
How long are patients with progressed disease expected to survive?	**For most patients I would suggest less than 3 months**
Is it plausible that a patient could be cured in terms of survival but not from disease progression?	**Very unlikely at present, but this would be possible if effective other novel therapies emerge.**
Would patients who responded to treatment be expected to experience additional mortality risks or have a different quality of life compared to the general population for the first 1-2 years after treatment?	**Yes, there will be persisting immunosuppression particularly hypogammaglobulinaemia, this could cause an increased risk of infection related mortality.**
The company's assumptions appear optimistic based on the evidence available. The ERG have proposed an alternative scenario which accounts for the uncertainty in the data. Is it reasonable to use the progression free survival curve to estimate the proportion of patients' cured following treatment with axi-cel?	**Yes , in principal, but (as above) I would have reservations about extrapolation beyond the current median follow up.**

Question 4: long-term survivors risk of excess mortality compared to the general population	
Do long term survivors experience excess mortality compared to the general population?	**If this is with respect to current therapy – yes- post allogeneic transplant there remains a risk of death from infection and graft versus host disease.**
Is there an increased long-term risk of infection and excess mortality due to prolonged B cell aplasia?	**Yes**
How long after diagnosis/treatment would any excess mortality be expected to last for long term survivors?	**No limit**
The company and ERG provide opposing views on the evidence available for excess mortality risks, which is the most applicable to clinical practice in the UK?	**I have not seen this data**
Question 5: Storage and administration of CAR-T therapy in the NHS	
What additional storage equipment and space would be required for centres to administer axi-cel?	Yes, though this could be offset by a reduced demand for Stem cell Transplantation.
Would specialist centres need to purchase additional thawing equipment to use in the administration of axi-cel?	Probably not if carried out in existing larger allogeneic centers
Question 6: Implementation of CAR-T therapy in the NHS – training requirements	
What roles and how many healthcare professionals are likely to be required to administer CAR T cell therapy in specialist centres?	This will be best answered by reference to the NHS England work program. It is highly complex and I would not wish to estimate it.
Would specialists providing care to patients who experience AEs after infusion with axi-cel also require specific training on CAR T therapy?	YES

Uncertainty around the training requirements for healthcare professionals is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	It should be
Question 7: Implementation of CAR-T therapy in the NHS – Prioritisation of eligible patients	
Who would determine which patients are prioritised to receive axi-cel therapy during a phased implementation?	I believe there is a suggestion of a National MDT modelled on the Paediatric group. This would seem an excellent suggestion as caution with respect to geographic bias will be needed especially with the initial small number of centres.
What criteria would or should be used to prioritise patients for axi-cel treatment?	Chance of benefitting and fitness to tolerate the therapy
Given the novelty of the treatment and limited information around follow up, how would patients who received axi-cel be monitored and new knowledge shared between specialist centres to improve overall patient care?	Follow up and any adverse events could be discussed at the proposed National MDT
Uncertainty around the requirements for multidisciplinary teams and phased implementation is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model and budget impact assessment?	It should be.It should be
Question 8: Implementation of CAR-T therapy in the NHS – ambulatory care close to the hospital post infusion	

Where would a patients stay for aftercare if their home is not located close to the treatment centre?	Potentially but clear readmission pathways would need to be defined.
How long would patients be expected to stay in close proximity to the treatment centre following CAR-T treatment?	3 months though this would be expected to reduce as experience increases
What provisions would be made for family and carers during this period?	This would be needed but is not well provided for in most centres
Are there other conditions with similar requirements which would be used as a model for axi-cel?	The Closest would be Allogeneic BMT
Uncertainty around the need for ambulatory care is likely to be addressed in the new service specification by NHS England. How should this information be incorporated into the current cost-effectiveness model?	It should be
Question 9: Implementation of CAR-T therapy in the NHS – ICU bed availability	
Would an ICU bed need to be available for a patient before they were able to start their infusion with axi-cel?	Ideally , but immediate capability to accept the patient would be needed
What proportion of patients would be admitted to ICU following infusion with axi-cel if they did not experience a CRS AE?	I would estimate <5% if no CRS depending on the incidence of neurological sequelae
How long would a patient admitted to ICU as the result of (a) axi-cel infusion or (b) a serious CRS event be expected to stay?	See existing trial data
Uncertainty around the requirements for ICU beds is likely to be addressed in the new service specification by NHS England. How should this	

information be incorporated into the current cost-effectiveness model?	
Question 10: Innovation	
Do you consider that the use of the technology will result in any substantial benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no
Axi-cel is given as a single infusion and single treatment rather than the recurrent cycles of traditional chemotherapy. Would this have an impact on a patient's health-related quality of life?	Potentially but outweighed by high risk of severe complications
Should a weight be applied to the QALYs gained in the axi-cel treatment arm to account for the large survival gaines/QALYs?	
Question 11: Cancer Drugs Fund (CDF)	
Please specify whether you consider the technology to be a candidate for entry into the CDF?	Definitely , the levels of uncertainty at present must be seen in combination with the lillihood of further treatment advances from clinical trials
What data may be available for collection to resolve the uncertainty in this appraisal?	Early toxicity and long term follow up
How would additional data collection resolve the uncertainty in this appraisal?	Would help to define the 'cured fraction '
What timelines would be appropriate for additional data collection?	18-24 months
Do you know of any additional evidence currently or likely to become available that may help to address he uncertainties?	Yes, there are multiple ongoing CAR T trials with a range of novel constructs.

Question 12: Other areas of uncertainty	
Comparators (exclusion of pixantrone) *In clinical practice in the NHS, is pixantrone monotherapy given to patients with relapsed or refractory disease?*	Pixantrone uptake in NHS practice has been very low, I believe there is a reappraisal due from the requested follow up trial.
Comparators (use of a blended comparator) *Are salvage regimens considered equally effective, with and without rituximab?* *Are salvage regimes distributed equally to patients with relapsed or refractory DLBCL, PMBCL and TFL in clinical practice in the NHS?*	No, patients with longer periods off therapy with rituximab should be retreated as they have a better response rate than without
Use of mITT versus the intention-to-treat (ITT) population from ZUMA-1 *What is the average time period between the clinical decision taken to administer salvage chemotherapy to a patient and the patient receiving chemotherapy?* *Would there be a concern that patients may experience disease progression during the additional time required for manufacturing of axi-cel?*	Normally for chemo this would be 1-2 weeks , this time will be markedly lengthened for CAR T
Re-treatment with axi-cel in the ZUMA-1 population *Would patients who received retreatment with axi-cel be expected to have improved outcomes compared with those whose disease progressed and did not receive a second round of treatment?*	Should be
Patients receiving post-treatment SCTs and the associated assumptions *What proportion of patients (R/R after 2nd line or who previously failed an ASCT) receiving salvage*	I would estimate 10-15 %

chemotherapy would become eligible for a SCT in clinical practice? *Are outcomes for patients who receive a stem cell transplant likely to be significantly different from patients who receive salvage chemotherapy?* *Would patients be likely to receive autologous or allogenic stem cell transplants after response to treatment with either salvage chemotherapy or axi-cel?* *How long on average would patients receive follow-up care following a stem cell transplant?*	Yes they would be better due to selection bias Long term with intensive early follow up and later Nurse lead clinics.
Long term costs of IVIG treatment - real world experience *What proportion of patients would still be affected by B-cell aplasia after 12 months following treatment with axi-cel? Would these patients require continued IVIG treatment and for how long?*	At least 80% Yes, duration unknown

Thank you for your time.

Please log in to your NICE Docs account to upload your completed response form

Single technology appraisal

Response to technical engagement comments

Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma [ID1115]

Dear Kite - a Gilead company

The technical team at NICE have reviewed the responses received as part of the technical engagement from the company, clinical, patient and commissioning experts on 22nd June 2018. These will be included in the committee papers and have been attached to this response request for your awareness and consideration.

Following the responses submitted as part of the technical engagement we would like further clarification, input and analysis from the company on the clinical and cost effectiveness data highlighted as priority areas of uncertainty. This will help the Appraisal Committee to make its decision at the appraisal committee meeting on 31 July 2018.

A meeting to discuss and resolve any queries and to hear Kite/Gilead's initial proposed response has been arranged for the 10 July 2018. Please provide any questions by email to the NICE team **by 10am on Monday 9 July.**

We will ask you to provide your final response by **5pm** on **13th July 2018.**
Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Lorna Dunning, Technical Lead (lorna.dunning@nice.org.uk). Any procedural questions should be addressed to Stephanie Callaghan, Project Manager (Stephanie.callaghan@nice.org.uk).

Yours sincerely
Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE requests for clarification and updated analysis resulting from the technical consultation

1. **Adjustment of SCHOLAR-1 cohort for comparative effectiveness estimates**
   In response to the technical engagement, consultees had reservations as to the comparability of ZUMA-1 and SCHOLAR-1 studies. They noted the high heterogeneity in the study populations, the high number of patients who received stem cell transplants (SCTs) in SCHOLAR-1 and the inclusion of patients with possible ECOG score 2-4 in the comparative effective results. Please clarify if any alternative data is available to support or validate the clinical data and survival outcomes from the SCHOLAR-1 study. Please provide clinical results and an additional scenario analysis for the cost-effectiveness modelling using the last refractory SCHOLAR-1 cohort but excluding patients who received SCT for the comparator arm.

2. **Expected relapse rate after the period of follow-up**
   All consultees agreed the results from ZUMA-1 are very encouraging, but were concerned about the limited follow up data available. Clinical and commissioning experts noted their reservations for extrapolating beyond the follow-up period, and applying statistics from conventional chemotherapy to a novel treatment with a different mode of action. It was noted that additional data collection would significantly reduce the uncertainty around long term survival. NICE have noted results from the next data cut of ZUMA-1 will be presented in December 2018. What are the expected timelines for extended follow-up data to be available to Kite/Gilead from ZUMA-1?

3. **Appropriate extrapolation for overall survival in axi-cel treatment arm**
   Median OS was not reached in the ZUMA-1 trial so OS needs to be extrapolated over the model time horizon. The company's mixture cure model extrapolating OS from the ZUMA-1 trial was presented to consultees as part of the technical engagement, along with the ERG alternative 'hybrid' approach. Clinical, patient and commissioning were asked about the plausibility of both scenarios. Experts agreed survival for patients with progressed disease is likely to be limited to a few months. They noted it would therefore be reasonable to use the cure fraction estimated from progression free survival (PFS) for the extrapolation of survival in the axi-cel arm. Kite/Gilead have suggested it is plausible a minority of patients who received axi-cel but have progressed may have some clinical benefit from the persistence of CAR-T and have prolonged survival. However, the ERG highlight the immaturity of the data and the retreatment of patients with axi-cel as a potential confounder for survival in patients with progressed disease.

   Given the comments from the technical engagement around the company's extrapolation of overall survival in the axi-cel arm please consider providing an alternative scenario for modelling survival in patients treated with axi-cel.

4. **Long-term survivors risk of excess mortality compared to the general population**

Consultees noted it may be appropriate to use general population mortality for long term survivors. However, clinical and commissioning experts agreed excess mortality related to toxicities of previous chemotherapy treatment and cardiovascular and immunosuppression side effects would be expected to persist for several years. Please provide sensitivity analyses where patients in the pre-progression state revert to age-matched general population mortality after 3-5 years.

5. **Storage and administration of CAR-T therapy in the NHS**
   There is uncertainty around the requirement for storage for CAR-T therapy. Consultees agreed that equipment required for the administration of axi-cel is currently available at recognized centres, but the capacity of these centres to accommodate CAR-T without new equipment is unclear. Please provide sensitivity analyses to include costs of additional storage and thawing equipment assuming that current clinical equipment is not available because it is used at full capacity for SCT patients.

6. **Implementation of CAR-T therapy in the NHS – training requirements**
   Consultees all agreed administration of axi-cel will require a large multidisciplinary team to administer the therapy and support patients who experience adverse events. The company state training costs have been included in the cost-effectiveness model, but other consultees and the ERG believe this could be a substantial underestimate.
   Please provide sensitivity analyses including the training of additional health care professionals (5-10 per centre) who will make up the MDT.

7. **Implementation of CAR-T therapy in the NHS – ambulatory care close to the hospital post infusion**
   After infusion with axi-cel people are likely to remain in hospital for a period of time during which they are monitored and treated for AEs. After patients are discharged they are required to remain in close proximity to the treatment centre for 1 month following infusion. All consultees suggested the pre-existing NHS model of allogenic stem cell transplant would be an appropriate example on which to base the costs of axi-cel ambulatory care. Clinical and commissioning experts note that the provision of hospital hotel facilities for a proportion of patients should be included in the costing of axi-cel. Please provide sensitivity analyses including the cost of ambulatory care (suggested cost of £150 per day for a hospital hotel for 1 patient and family member who are required to remain in close proximity for 1 month following infusion).

8. **Implementation of CAR-T therapy in the NHS – ICU bed availability**
   The cost of intensive care hospitalisation is included in the economic model. However, the period of time spent on average by a patient admitted to ICU is unclear between the clinical study report and the original evidence submission by Kite/Gilead. Please confirm the length of time used to model ICU stay in the cost-effectiveness model and provide updated results if any discrepancies are found.

9. **Innovation**
   All consultees agreed axi-cel is a step change in treatment for patients with DLBCL offering a potential cure to patients who have very limited curative treatment options

available to them currently. However, long term survival is the overall goal of treatment. No evidence has been presented for substantial benefits not captured in the QALYs. We have noted that axi-cel is provided as a single infusion compared to multiple cycles of conventional chemotherapy and committee will discuss the use of the alternative discount rate and its view on the acceptability of axi-cel as a cost-effective use of NHS resources during the first committee meeting.

10. **Long term usage and costs of IVIG treatment - real world experience**
    Given the uncertainty surrounding the potential duration of IVIG treatment, please present additional scenario analyses assuming patients require IVIG treatment for 0 months, 3 years, 5 years and a lifetime.

11. **Cost of chemotherapy administration**
    Consultees note that the company assumes the comparator chemotherapy is given as an inpatient, but 3 of the 4 regimes used in the company model can be given as day cases. Please provide a scenario analyses where patients are given conventional chemotherapy as outpatients. The unit cost should be derived from NHS reference costs (currency codes SB14Z and SB15Z).

12. **Cancer Drugs Fund**
    The technical team and the committee chair consider axi-cel to be a potential candidate for use in the CDF if the committee considers axi-cel has the plausible potential for cost-effectiveness. In response to the technical engagement consultees all agreed the results from ZUMA-1 are very encouraging, but were concerned about the limited follow up data available. It was suggested collecting data on overall survival and disease progression after axi-cel treatment would help to address the uncertainties around the survival benefit in the axi-cel treatment arm. Clinical and commissioning experts suggested a period of 12 months incorporating a minimum follow up of 24 months for all patients should be explored. Please provide an update on the company's position on the cancer drugs fund.

Technical Engagement Questions: Company responses

1. ***Adjustment of SCHOLAR-1 cohort for comparative effectiveness estimates***
   In response to the technical engagement, consultees had reservations as to the comparability of ZUMA-1 and SCHOLAR-1 studies. They noted the high heterogeneity in the study populations, the high number of patients who received stem cell transplants (SCTs) in SCHOLAR-1 and the inclusion of patients with possible ECOG score 2-4 in the comparative effective results. Please clarify if any alternative data is available to support or validate the clinical data and survival outcomes from the SCHOLAR-1 study. Please provide clinical results and an additional scenario analysis for the cost-effectiveness modelling using the last refractory SCHOLAR-1 cohort but excluding patients who received SCT for the comparator arm.

No suitable alternative data have been identified to support or validate the survival outcomes from the SCHOLAR-1 study. Specifically, the ORCHARRD study is not deemed relevant for comparison/validation for the following reasons:

- ORCHARRD study includes earlier line patients (R/R after 1st line R-CHOP) who were treated with the intention of ASCT (37% in the R-DHAP arm); this is not comparable to a population who would be eligible for axicabtagene ciloleucel
- Only the R-DHAP arm (not the O-DHAP arm) in the ORCHARRD study would be of interest
- In SCHOLAR-1, <30% of patients were R/R after 1st line with ~50% having received 2-3 prior therapies (potentially including ASCT) and 0.2% having received 4+ prior therapies, therefore the majority of SCHOLAR-1 patients are not at an earlier line of therapy and comparable to the population who would be eligible for axicabtagene ciloleucel
- The percentage going on to ASCT in the ORCHARRD study is higher than what NHS England believe is seen in clinical practice for our target population
- In contrast to SCHOLAR-1, no PLD is available for ORCHARRD to adjust the study population to be more comparable to ZUMA-1

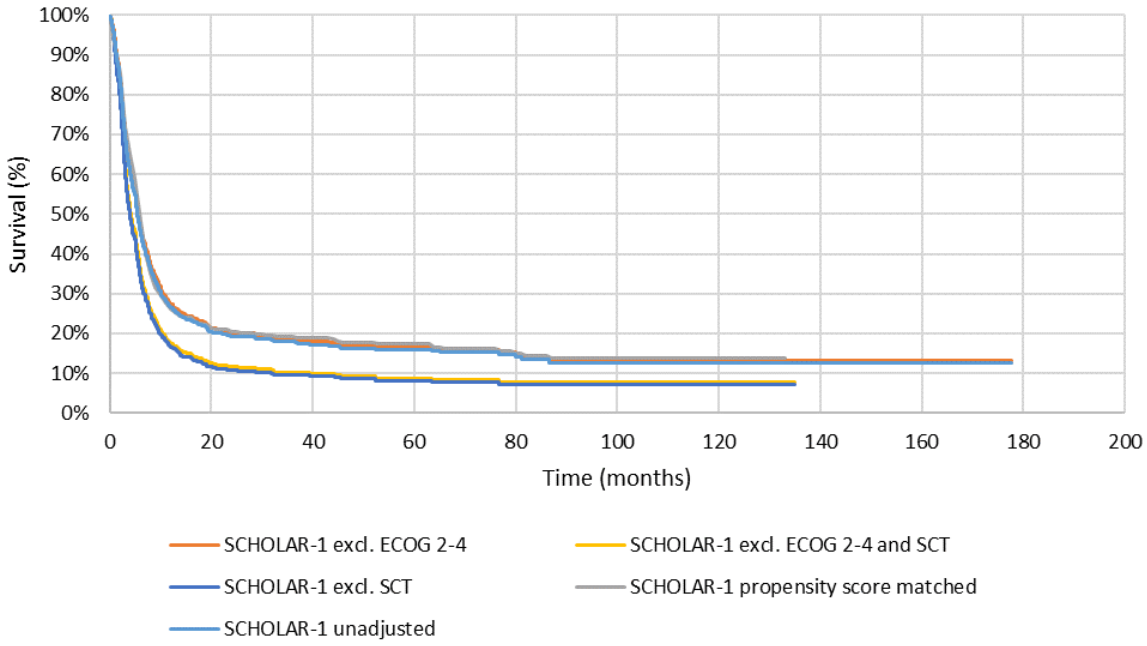
In the cost-effectiveness model, four SCHOLAR-1 scenarios have already been presented:

1. Unadjusted
2. Excluding ECOG 2-4 (base case)
3. Excluding ECOG 2-4 and SCT
4. Propensity score adjusted

An additional scenario analysis has been performed using the last refractory SCHOLAR-1 cohort but excluding patients who received SCT. This scenario is different from the existing “Excluding ECOG 2-4 and SCT” scenario as ECOG 2-4 patients are not excluded.

Figure 1 shows the OS when patients who received SCT are removed from SCHOLAR-1 compared to the other existing SCHOLAR-1 scenarios.

Figure 1: Overall survival of BSC: SCHOLAR-1 excluding SCT versus existing SCHOLAR-1 scenarios



Compared to the model base case ("Excluding ECOG 2-4"), the additional scenario results in a decrease in OS (around 10% difference at 5 years). The OS for the additional scenario appears very similar to the existing scenario where both ECOG 2-4 and SCT are removed. This implies that it is the removal of SCT patients which is main reason for the shift in OS, rather than the removal of ECOG 2-4 patients. This is expected as only around 6% (35 out of 593) patients in the SCHOLAR-1 dataset were categorised as ECOG 2-4, in contrast a much larger proportion [redacted] of SCHOLAR-1 patients who received SCT.

In this additional scenario analysis, standard parametric survival curves were fitted to the revised SCHOLAR-1 data and the Gompertz distribution was chosen as the base case based on statistical goodness of fit and visual inspection. The cost-effectiveness results of the additional scenario are presented in Table 1 which shows an ICER of [redacted]. The company base case cost-effectiveness results (as reported in the ERG report, with an ICER of [redacted]) are presented in Table 2 for comparison.

Table 1: Scenario model results: SCHOLAR-1 excluding SCT

	BSC	Axicabtagene ciloleucel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	[redacted]

Table 2: Company base case model results: SCHOLAR-1 excluding ECOG 2-4 (as reported in ERG report)

	BSC	Axicabtagene ciloleucel	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER	-	-	[redacted]

2. ***Expected relapse rate after the period of follow-up***

   All consultees agreed the results from ZUMA-1 are very encouraging, but were concerned about the limited follow up data available. Clinical and commissioning experts noted their reservations for extrapolating beyond the follow-up period, and applying statistics from conventional chemotherapy to a novel treatment with a different mode of action. It was noted that additional data collection would significantly reduce the uncertainty around long term survival. NICE have noted results from the next data cut of ZUMA-1 will be presented in December 2018. What are the expected timelines for extended follow-up data to be available to Kite/Gilead from ZUMA-1?

As outlined above 2-year follow-up data from the ZUMA-1 study will be presented at the American Society of Haematology (ASH) in December 2018. No further follow-up data beyond this will be collected with the exception of some safety analyses.

3. ***Appropriate extrapolation for overall survival in axicabtagene ciloleucel treatment arm***

   Median OS was not reached in the ZUMA-1 trial so OS needs to be extrapolated over the model time horizon. The company's mixture cure model extrapolating OS from the ZUMA-1 trial was presented to consultees as part of the technical engagement, along with the ERG alternative 'hybrid' approach. Clinical, patient and commissioning were asked about the plausibility of both scenarios. Experts agreed survival for patients with progressed disease is likely to be limited to a few months. They noted it would therefore be reasonable to use the cure fraction estimated from progression free survival (PFS) for the extrapolation of survival in the axicabtagene ciloleucel arm. Kite/Gilead have suggested it is plausible a minority of patients who received axicabtagene ciloleucel but have progressed may have some clinical benefit from the persistence of CAR-T and have prolonged survival. However, the ERG highlight the immaturity of the data and the retreatment of patients with axicabtagene ciloleucel as a potential confounder for survival in patients with progressed disease.

   Given the comments from the technical engagement around the company's extrapolation of overall survival in the axicabtagene ciloleucel arm please consider providing an alternative scenario for modelling survival in patients treated with axicabtagene ciloleucel.

Apart from the company base case approach of modelling axicabtagene ciloleucel survival (i.e. mixture cure model for OS and standard parametric curves for PFS), mixture cure models for PFS were also performed as requested by the ERG after the initial NICE submission. The resulting ICER using mixture cure model for PFS (gamma) was [redacted] (see Table 15 in company's responses to ERG clarification questions). No other alternative scenario is considered suitable for modelling OS for axicabtagene ciloleucel based on the available ZUMA-1 data.

4. ***Long-term survivors risk of excess mortality compared to the general population***
   Consultees noted it may be appropriate to use general population mortality for long term survivors. However, clinical and commissioning experts agreed excess mortality related to toxicities of previous chemotherapy treatment and cardiovascular and immunosuppression side effects would be expected to persist for several years. Please provide sensitivity analyses where patients in the pre-progression state revert to age-matched general population mortality after 3-5 years.

The company base case uses the mixture cure model methodology to model axicabtagene ciloleucel OS. The underpinning assumption behind this approach is that the population is split into two distinct patient groups: cured and uncured. The survival for these two distinct groups are modelled separately from time zero, with the cured proportion following age-matched general population mortality (from time zero) and the uncured proportion following survival as modelled using parametric survival curves (also from time zero). The modelling of OS using mixture cure model is not dependent on whether patients are in the pre-progression health states or post-progression states. Therefore, the request to use age-matched general population mortality for patients in pre-progression state after 3-5 years is not compatible to the mixture cure model approach and not possible to be implemented within the mixture cure model approach. Please note, in the model, the majority of uncured patients (>99%) will have been dead by 2-3 years, therefore the mixture cure model for axicabtagene ciloleucel is similar to assuming that all alive patients follow age-matched general population mortality after around 3 years (because all alive patients are cured patients in the model after around 3 years).

5. ***Storage and administration of CAR-T therapy in the NHS***
   There is uncertainty around the requirement for storage for CAR-T therapy. Consultees agreed that equipment required for the administration of axicabtagene ciloleucel is currently available at recognized centres, but the capacity of these centres to accommodate CAR-T without new equipment is unclear. Please provide sensitivity analyses to include costs of additional storage and thawing equipment assuming that current clinical equipment is not available because it is used at full capacity for SCT patients.

An additional scenario analysis is performed. For storage, a cost of £10,000 was assumed to represent the cost of a medical freezer. The assumption was based on the average costs from a large range of costs identified for this equipment. For the costs of thawing equipment, the cost of a 2-litre water bath was derived from ThermoFisher Scientific (https://www.thermofisher.com/order/catalog/product/TSGP02), which was £452. It was

assumed that these costs would be accrued for each centre, therefore, assuming 10 patients per centre, £10,452 was divided by 10 to derive an estimate of the cost per patient (£1,045) which was applied in the model as one-off cost at the beginning of the model for the axicabtagene ciloleucel arm.

It should be noted that this can be considered an extremely conservative scenario as we anticipate every centre will require additional equipment.

Table 3 shows the ICER for this additional scenario and the percentage change in ICER compared to the base case.

Table 3: Costs of storage and administration of CAR-T therapy

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base case	[redacted]	[redacted]	[redacted]	
Inclusion of storage and thawing costs	[redacted]	[redacted]	[redacted]	0.4%

6. ***Implementation of CAR-T therapy in the NHS – training requirements***
   Consultees all agreed administration of axicabtagene ciloleucel will require a large multidisciplinary team to administer the therapy and support patients who experience adverse events. The company state training costs have been included in the cost-effectiveness model, but other consultees and the ERG believe this could be a substantial underestimate. Please provide sensitivity analyses including the training of additional health care professionals (5-10 per centre) who will make up the MDT.

In the model base case, it is assumed that one health care professional (HCP) will undergo training over a 2-day period. Table 4 presents the ICER for two additional scenario analyses where five and ten HCPs will undergo training.

Table 4: Costs of training requirements

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base case	[redacted]	[redacted]	[redacted]	
Number of HCPs requiring training per centre: 5	[redacted]	[redacted]	[redacted]	0.1%
Number of HCPs requiring	[redacted]	[redacted]	[redacted]	0.3%

training per centre: 10				

7. ***Implementation of CAR-T therapy in the NHS – ambulatory care close to the hospital post infusion***
   After infusion with axicabtagene ciloleucel people are likely to remain in hospital for a period of time during which they are monitored and treated for AEs. After patients are discharged they are required to remain in close proximity to the treatment centre for 1 month following infusion. All consultees suggested the pre-existing NHS model of allogenic stem cell transplant would be an appropriate example on which to base the costs of axicabtagene ciloleucel ambulatory care. Clinical and commissioning experts note that the provision of hospital hotel facilities for a proportion of patients should be included in the costing of axicabtagene ciloleucel. Please provide sensitivity analyses including the cost of ambulatory care (suggested cost of £150 per day for a hospital hotel for 1 patient and family member who are required to remain in close proximity for 1 month following infusion)

Two additional scenario analyses are performed, assuming a cost of £150 per day for a hospital hotel over a 1-month period for all axicabtagene ciloleucel patients (scenario 1) or 50% of axicabtagene ciloleucel patients (scenario 2). Table 5 shows the ICER for these scenarios and the percentage changes compared to the base case.

It should be noted that the scenario assuming that 100% of patients will require a hospital hotel should be considered an extremely conservative scenario.

Table 5: Costs of ambulatory care

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base case	[redacted]	[redacted]	[redacted]	
Proportion requiring hospital hotel: 100%	[redacted]	[redacted]	[redacted]	1.6%
Proportion requiring hospital hotel: 50%	[redacted]	[redacted]	[redacted]	0.8%

8. ***Implementation of CAR-T therapy in the NHS – ICU bed availability***
   The cost of intensive care hospitalisation is included in the economic model. However, the period of time spent on average by a patient admitted to ICU is unclear between the clinical study report and the original evidence submission by Kite/Gilead. Please confirm the length of time used to model ICU stay in the cost-effectiveness model and provide updated results if any discrepancies are found.

In this additional scenario analysis, the cost-effectiveness model has been updated to assume a length of stay of 4 days for ICU stays, in line with the assumption used in the ERG base case. The ICER of this scenario analysis and percentage change compared to the base case is shown in Table 6.

Table 6: Costs of ICU stay

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base case	[redacted]	[redacted]	[redacted]	
ICU length of stay: 4 days	[redacted]	[redacted]	[redacted]	0.2%

9. ***Innovation***
   All consultees agreed axicabtagene ciloleucel is a step change in treatment for patients with DLBCL offering a potential cure to patients who have very limited curative treatment options available to them currently. However, long term survival is the overall goal of treatment. No evidence has been presented for substantial benefits not captured in the QALYs. We have noted that axicabtagene ciloleucel is provided as a single infusion compared to multiple cycles of conventional chemotherapy and committee will discuss the use of the alternative discount rate and its view on the acceptability of axicabtagene ciloleucel as a cost-effective use of NHS resources during the first committee meeting.

Please see our previous responses to the TER regarding the innovation of axicabtagene ciloleucel.

10. Long term usage and costs of IVIG treatment - real world experience

Given the uncertainty surrounding the potential duration of IVIG treatment, please present additional scenario analyses assuming patients require IVIG treatment for 0 months, 3 years, 5 years and a lifetime.

The model base case assumes IVIG therapy is given over a 12-month period. Two additional scenario analyses were performed to assume the duration of IVIG therapy is 0 months, 3 years, 5 years and lifetime. Table 7 shows the ICERs and percentages changes compared to the base case for these scenarios.

Table 7: Costs of IVIG treatment

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base case	[redacted]	[redacted]	[redacted]	
Duration of IVIG therapy: 0 months	[redacted]	[redacted]	[redacted]	-0.5%
Duration of IVIG therapy: 3 years	[redacted]	[redacted]	[redacted]	0.6%
Duration of IVIG therapy: 5 years	[redacted]	[redacted]	[redacted]	1.2%
Duration of IVIG therapy: lifetime	[redacted]	[redacted]	[redacted]	5.9%

11. Cost of chemotherapy administration

Consultees note that the company assumes the comparator chemotherapy is given as an inpatient, but 3 of the 4 regimes used in the company model can be given as day cases. Please provide a scenario analyses where patients are given conventional chemotherapy as outpatients. The unit cost should be derived from NHS reference costs (currency codes SB14Z and SB15Z).

The assumption that the treatment of BSC is given in an outpatient setting was already included in the ERG's additional analyses (see Table 37 in the ERG report). The description of the analysis provided in the ERG report was: "A monthly cost for outpatient visits for chemotherapy administration is applied to BSC patients, instead of a one-off inpatient admission cost as per company submission. The unit cost is derived from NHS reference costs (currency codes SB14Z and SB15Z) and applied to the number of cycles per month of the BSC blended comparator." (see Table 41 in the ERG report).

This scenario analysis uses the same approach as the ERG. The ICER and percentage change compared to base case of this scenario are shown in Table 8.

Table 8: Costs of chemotherapy administration

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base case	[redacted]	[redacted]	[redacted]	
Outpatient administration costs for chemotherapy	[redacted]	[redacted]	[redacted]	1.4%

12. Cancer Drugs Fund

The technical team and the committee chair consider axicabtagene ciloleucel to be a potential candidate for use in the CDF if the committee considers axicabtagene ciloleucel has the plausible potential for cost-effectiveness. In response to the technical engagement consultees all agreed the results from ZUMA-1 are very encouraging, but were concerned about the limited follow up data available. It was suggested collecting data on overall survival and disease progression after axicabtagene ciloleucel treatment would help to address the uncertainties around the survival benefit in the axicabtagene ciloleucel treatment arm. Clinical and commissioning experts suggested a period of 12 months incorporating a minimum follow up of 24 months for all patients should be explored. Please provide an update on the company's position on the cancer drugs fund.

Kite/Gilead is committed to making axicabtagene ciloleucel available to patients in England and Wales.

Kite/Gilead has submitted a simple discount commercial offer to demonstrate our commitment to making axicabtagene ciloleucel a cost-effective treatment option for patients with DLBCL. We believe that with the implementation of the simple discount commercial offer, axicabtagene ciloleucel represents a cost-effective use of NHS resources and should subsequently be recommended for baseline commissioning.

Should the Appraisal Committee take the decision that axicabtagene ciloleucel is a candidate for use in the CDF, Kite/Gilead remain committed to making axicabtagene ciloleucel available for patients via this funding route.

Kite/Gilead has engaged with relevant stakeholders (CDF, NHS England and NICE) in preliminary discussions around the commercial access agreement and data collection requirements should axicabtagene ciloleucel be made available via the CDF. We are committed to ensuring that all necessary arrangements are in place should the committee decide this is the most appropriate route.

Company responses (with commercial offer applied)

The following tables present the cost-effectiveness model results for the company base case and additional scenario analyses implemented with a commercial offer of [redacted] applied to axicabtagene ciloleucel drug cost.

Q1: Adjustment of SCHOLAR-1 cohort for comparative effectiveness estimates

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Results based on commercial offer	[redacted]	[redacted]	[redacted]	
SCHOLAR-1 excluding SCT patients	[redacted]	[redacted]	[redacted]	-16.6%

Q3: Appropriate extrapolation for overall survival in axicabtagene ciloleucel treatment arm

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Results based on commercial offer	[redacted]	[redacted]	[redacted]	
STM approach	[redacted]	[redacted]	[redacted]	29.4%

Q5: Storage and administration of CAR-T therapy in the NHS

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Results based on commercial offer	[redacted]	[redacted]	[redacted]	
Inclusion of storage and thawing costs				0.4%

Q6: Implementation of CAR-T therapy in the NHS – training requirements

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Results based on commercial offer	[redacted]	[redacted]	[redacted]	
Number of HCPs requiring training per centre: 5	[redacted]	[redacted]	[redacted]	0.1%
Number of HCPs requiring training per centre: 10	[redacted]	[redacted]	[redacted]	0.3%

Q8: Implementation of CAR-T therapy in the NHS – ICU bed availability

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Results based on commercial offer	[redacted]	[redacted]	[redacted]	
ICU stay: 4 days	[redacted]	[redacted]	[redacted]	0.2%

Q10: Long term usage and costs of IVIG treatment - real world experience

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Results based on commercial offer	[redacted]	[redacted]	[redacted]	
Duration of IVIG therapy: 0 months	[redacted]	[redacted]	[redacted]	-0.5%
Duration of IVIG therapy: 3 years	[redacted]	[redacted]	[redacted]	0.7%
Duration of IVIG therapy:	[redacted]	[redacted]	[redacted]	1.4%

5 years				
Duration of IVIG therapy: lifetime	[redacted]	[redacted]	[redacted]	6.9%

Q11: Cost of chemotherapy administration

Scenario	**Incremental costs**	**Incremental QALYs**	**ICER**	**% change from base-case ICER**
Results based on commercial offer	[redacted]	[redacted]	[redacted]	
Outpatient administration costs for chemotherapy	[redacted]	[redacted]	[redacted]	1.7%

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Addendum to the NICE submission: results presented with and without commercial in confidence commercial offer

Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell non-Hodgkin lymphoma [ID1115]

July 2018

The following document presents the base case model results for the cost-effective analysis of axicabtagene ciloleucel (axi-cel) versus best support care (BSC) with and without the commercial in confidence commercial offer of [redacted] applied to axi-cel drug cost.

Base-case incremental cost-effectiveness analysis results

The discounted base-case results for axi-cel versus BSC are shown in Table 1 at the list price for axi-cel, and in Table 2 with the commercial offer price for axi-cel.

At the list price, axi-cel is associated with [redacted] incremental life years gained (LYG), [redacted] incremental quality-adjusted life years (QALYs), and incremental costs of [redacted] per patient, compared with BSC. The incremental cost-effectiveness ratio (ICER) is [redacted] per additional QALY gained.

With the commercial in confidence commercial offer, axi-cel is associated with incremental [redacted] LYG, [redacted] incremental QALYs, and incremental costs of [redacted] per patient, compared with BSC. The ICER is [redacted] per additional QALY gained.

Table 1: Base-case results without commercial offer

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

Table 2: Base-case results with commercial offer

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

Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 3 and Table 4 show the disaggregated costs by category without and with the commercial offer respectively.

Table 3: Summary of costs by category – without commercial offer

	BSC	Axi-cel	Incremental

Axicabtagene ciloleucel costs	[redacted]	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]	[redacted]
Medical resource use costs	[redacted]	[redacted]	[redacted]
SCT costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Training costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Table 4: Summary of costs by category – with commercial offer

	BSC	**Axi-cel**	**Incremental**
Axicabtagene ciloleucel costs	[redacted]	[redacted]	[redacted]
BSC costs	[redacted]	[redacted]	[redacted]
Medical resource use costs	[redacted]	[redacted]	[redacted]
SCT costs	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Training costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was carried out to explore the sensitivity in the deterministic base-case model results when all model parameters were varied simultaneously. Each parameter was varied according to its associated distribution 10,000 times, and mean model results were recorded. These mean model results were then used to inform a PSA scatter plot and a cost-effectiveness acceptability curve (CEAC).

The PSA scatter plots without and with commercial offer are presented in Figure 1 and Figure 2, respectively.

Figure 1: PSA scatter plot at a £50,000 threshold without commercial offer

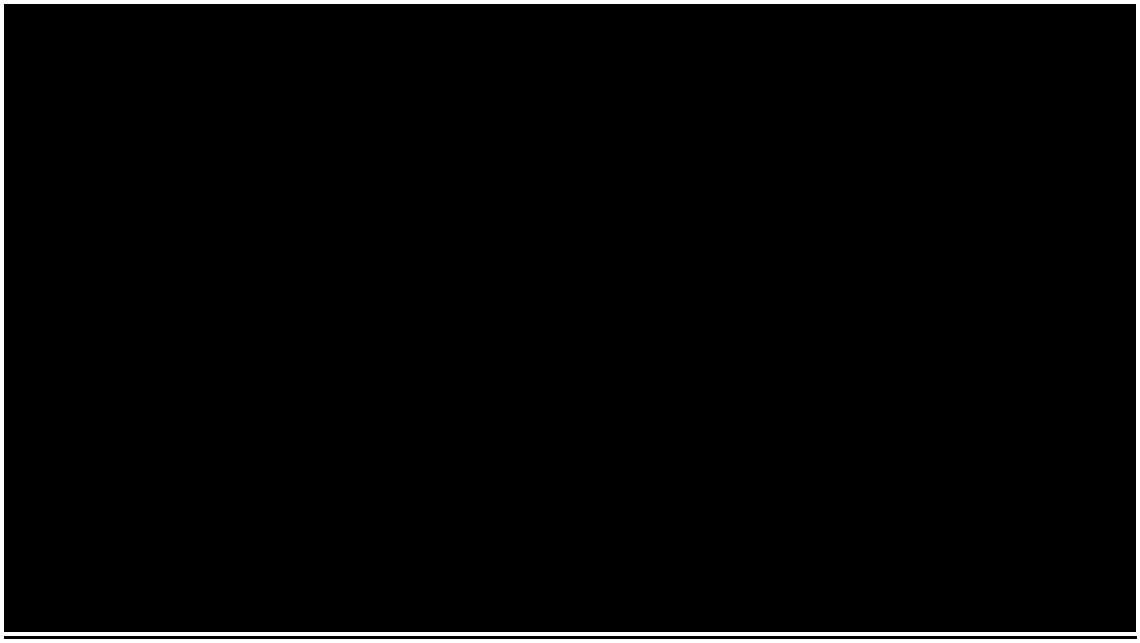
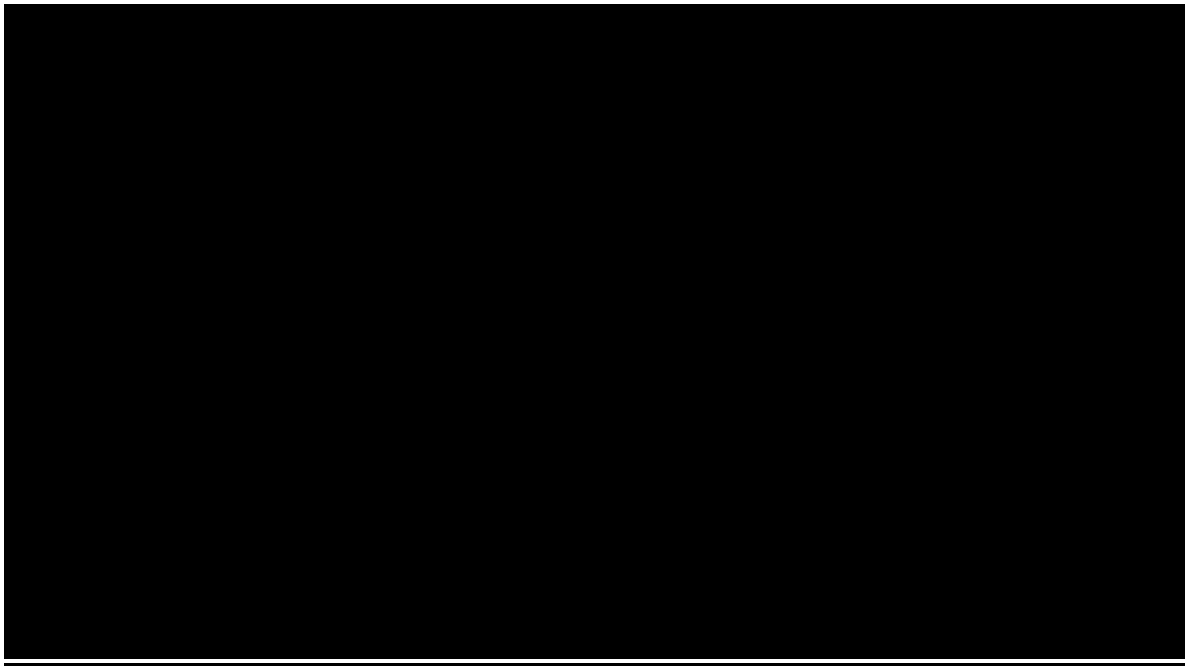


Figure 2: PSA scatter plot at a £50,000 threshold with commercial offer



The CEAC is presented for without and with commercial offer in Figure 3 and Figure 4, respectively. At the list price, the probability of axi-cel being the most cost-effective treatment is 0.5% for a willingness-to-pay (WTP) threshold of £50,000. With commercial offer, the probability of axi-cel being the most cost-effective treatment is 11.7% for the £50,000 threshold.

Figure 3: Cost-effectiveness acceptability curve without commercial offer

Figure 4: Cost-effectiveness acceptability curve with commercial offer

At the list price, the average incremental costs over the PSA simulated results were [redacted], and the average incremental QALYs were [redacted], giving a probabilistic ICER of [redacted]. This is relatively congruent with deterministic results of changes in costs and QALYs of [redacted] and [redacted], respectively, and resulted in a difference in ICER of approximately <1% between PSA and deterministic results. The probabilistic

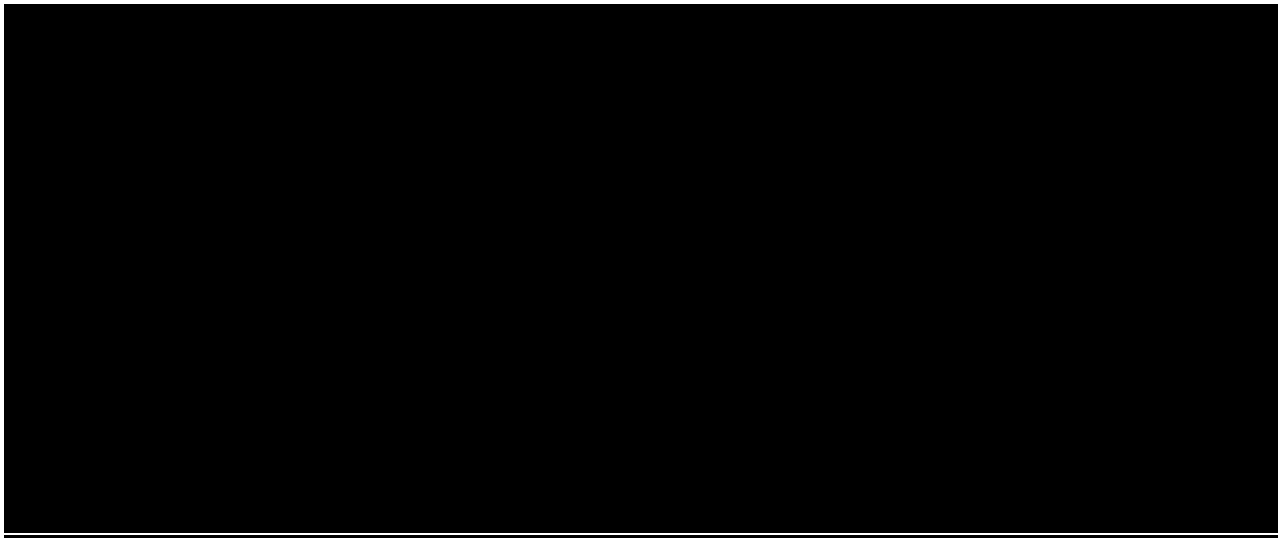
ICER at the commercial offer price was also similar to the deterministic ICER which are estimated to be [redacted] and [redacted], respectively.

Deterministic one-way sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to explore the sensitivity in the deterministic base-case model results when one parameter is varied at a time. Each parameter was set to its lower and upper bound, and the deterministic model results were recorded. The top ten influential parameters on the ICER are presented as a tornado diagram for without and with commercial offer in Figure 5 and Figure 6, respectively.

Figure 5: One-way sensitivity analysis: Tornado diagram without commercial offer

Figure 6: One-way sensitivity analysis: Tornado diagram with commercial offer



As shown in the tornado diagram, the three most influential parameters on the model result were the mean cure fraction (pi) used in the mixture cure model for modelling axi-cel OS, the constant coefficient for modelling axi-cel PFS, and the constant coefficient used for modelling BSC OS.

Scenario analysis

Scenario analyses were performed to analyse the effect of alternative model assumptions, model settings and data sources compared to the base-case model results. The scenarios that were explored are listed below:

- Time horizon: 10- and 20-year time horizons were explored
- Discounting: costs and outcomes were discounted at 1.5%
- Model type for axi-cel OS: alternative gamma mixture-cure model
- Model type for BSC OS:
    - Alternative single parametric curves (exponential, gamma, loglogistic, lognormal and Weibull)
    - Alternative Weibull, gamma and lognormal mixture-cure models
- Axi-cel PFS distribution: gamma parametric curve, as it provides the second best statistical fit
- BSC PFS:
    - 100% of time spent alive in the BSC arm is spent in the pre-progression state

    - 100% of time spent alive in the BSC arm is spent in the post-progression state
- SCHOLAR-1 dataset to be explored, with the choice of the following:
    - Unadjusted, full population, Gompertz parametric curve
    - Propensity score adjusted, full population, Gompertz parametric curve
    - Crude adjustment, excluding ECOG 2–4 and post-refractory SCT, Gompertz parametric curve
- Utility source: utilities of 0.76 for the pre-progression health state and 0.68 for the post-progression health state, as were used in the Pixantrone submission
- Assuming additional mortality of “not cured” patients (HR = 1.1) for axi-cel using mixture-cure model
- Utility for patients who have been in PFS for more than 2 years to be 90% of age-matched general population mortality

The results of the scenario analyses, when the list and commercial offer price were used, are presented below in Table 5.

Table 5: Scenario analysis results

Scenario	Base case	ICER at list price	ICER at commercial offer price

Base-case		[redacted]	[redacted]
Time horizon = 10 years	44 years	[redacted]	[redacted]
Time horizon = 20 years		[redacted]	[redacted]
Discount rates = 1.5%	3.5%	[redacted]	[redacted]
Mixture cure model used for BSC	PSM with single curves	[redacted]	[redacted]
100% progression-free in BSC arm	Based on ZUMA-1 OS/PFS ratio	[redacted]	[redacted]
100% progressed in BSC arm		[redacted]	[redacted]
Unadjusted, all	Unadjusted, excl. ECOG 2–4	[redacted]	[redacted]
Unadjusted, excl. ECOG 2–4 and SCT		[redacted]	[redacted]
Propensity score adjusted		[redacted]	[redacted]
Utility from literature (pixantrone)	ZUMA-1 safety population	[redacted]	[redacted]
AC PFS distribution: gamma	Gompertz	[redacted]	[redacted]
BSC OS distribution: exponential	Gompertz	[redacted]	[redacted]
BSC OS distribution: gamma		[redacted]	[redacted]
BSC OS distribution: loglogistic		[redacted]	[redacted]
BSC OS distribution: lognormal		[redacted]	[redacted]
BSC OS distribution: Weibull		[redacted]	[redacted]
AC OS distribution (MCM): Gamma	Weibull	[redacted]	[redacted]
Multiplier for DLBCL/PMBCL/TFL patients in long-term remission (general population utility values): 0.9	1	[redacted]	[redacted]
Multiplier for DLBCL/PMBCL/TFL patients in long-term remission (life tables): 1.1	1	[redacted]	[redacted]

ICERs from the scenario analyses ranged between [redacted] and [redacted] at the list price and [redacted] and [redacted] at the commercial offer price. The results demonstrate that the most influential scenario on the model results was the reduced time horizon of 10 years. The scenario resulted in an 107% increase in ICER compared to the base case without and with commercial offer. Additional to this, only two other scenarios resulted in an increased ICER of greater than 10%. These were

the use of the gamma distribution to model axi-cel PFS, and the use of a 20-year time horizon.

Using a discount rate of 1.5% rather than 3.5% reduces the ICER by 22% without and with commercial offer. Notably, the ICER is below the £50,000 threshold with commercial offer when 1.5% discount rate is applied. In treatments that can have a potential long-term benefit (in this case a significant proportion of patients treated with axi-cel is expected to have long-term remission), and have high upfront costs, it is reasonable to consider using a lower discount rate. We believe this scenario analysis is very relevant to this decision problem. Other commercial offer scenarios which result in an ICER below £50,000 threshold include the assumption of 100% progression in the BSC arm, the use of SCHOLAR-1 excluding ECOG 2-4 and SCT for the comparator arm and using different distributions to extrapolate BSC OS (exponential, loglogistic, lognormal or Weibull).